Real-world studies of biological treatment in severe asthma

Population-based registries, prediction of response and patient-tailored outcomes

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Chapter 1

General introduction

GENERAL INTRODUCTION

This thesis focuses on real-world outcomes of biological treatment in severe asthma. In this introduction, we firstly introduce severe asthma. Then we discuss the biologics for severe asthma, their mechanisms of action, and how real-world evidence is collected for these biologics. Lastly, we identify knowledge-to-care gaps in the clinical practice of biological treatment for severe asthma.

Severe asthma

Asthma is a heterogeneous, inflammatory airway disease, characterized by symptoms of coughing, wheezing and shortness of breath. The symptoms are caused by variable airway obstruction, airway hyperresponsiveness and mucus hypersecretion. Around 339 million people worldwide suffer from asthma. Most patients with asthma are adequately treated with inhaled medication, focusing on inflammation reduction and airway smooth muscle relaxation.(1) However, 3% to 10% of the patients with asthma have severe asthma. These patients require high dosage inhaled corticosteroids (ICS) with long-acting beta agonists (LABA) to control the disease or are uncontrolled despite high dose ICS-LABA. Severe asthma must be distinguished from difficult-to-treat asthma due to suboptimal inhalation therapy, inhalation technique or treatment of comorbidities as there are different treatment implications for severe asthma and difficult-to-treat asthma. Many of these patients with severe asthma experience asthma exacerbations and rely on high dose systemic corticosteroids to reduce asthma symptoms.(1-3)

Oral corticosteroids exert a broad effect, including suppression of airway inflammation, reduction of airway mucus production, upregulation of β2-adrenergic receptors and reduction of endothelial barrier leakage, resulting in a reduction of asthma symptoms.(4,5) Despite being very effective in reducing asthma symptoms, there are severe side effects associated with the use of (long-term) systemic corticosteroids. Examples of these side effects are depression, adrenal insufficiency, osteoporosis and obesity, further decreasing the already impaired quality of life. (6-9) Studies found that side effects to systemic corticosteroids are associated with the cumulative systemic corticosteroid dose.(10,11) Due to these side effects, there is a major interest in oral corticosteroid-sparing treatment options to maintain or achieve asthma control.

Phenotypes and types of inflammation

For a long time, oral corticosteroids were a fundamental part of the treatment of severe asthma. However, a lot has changed in the new millennium regarding

severe asthma care. Different asthma phenotypes have been identified based on clinical, functional or inflammatory parameters.(12) These phenotypes encompass heterogeneity in the age of asthma onset (as a child or as an adult), presence of allergy, severity of airflow limitation, exacerbation frequency, response to treatment and prognosis.(13,14) These different subtypes are related to the different inflammatory pathways that can lead to severe asthma. Two main types of inflammation are recognized: type 2-high and type 2-low inflammation (Figure 1). Type 2-high inflammation is characterized by the presence of type 2 cytokines (Interleukin (IL)-4, IL-5 and IL-13), resulting in eosinophilia, elevated Fractional exhaled Nitric Oxide (FeNO) or elevated Immunoglobulin E (IgE). On the other hand, there is a group of patients without evident type 2 inflammation, so-called type 2-low inflammation. The pathophysiological features of type 2-low inflammation still need to be elucidated, but it is known that type 2 low inflammation often encompasses neutrophilic or paucigranulocytic airway inflammation.(14) The majority of patients with severe asthma show biomarkers associated with type 2-high inflammation.(15) Distinguishing these different subtypes led to the development of new targeted treatment options in the form of monoclonal antibodies.(14)

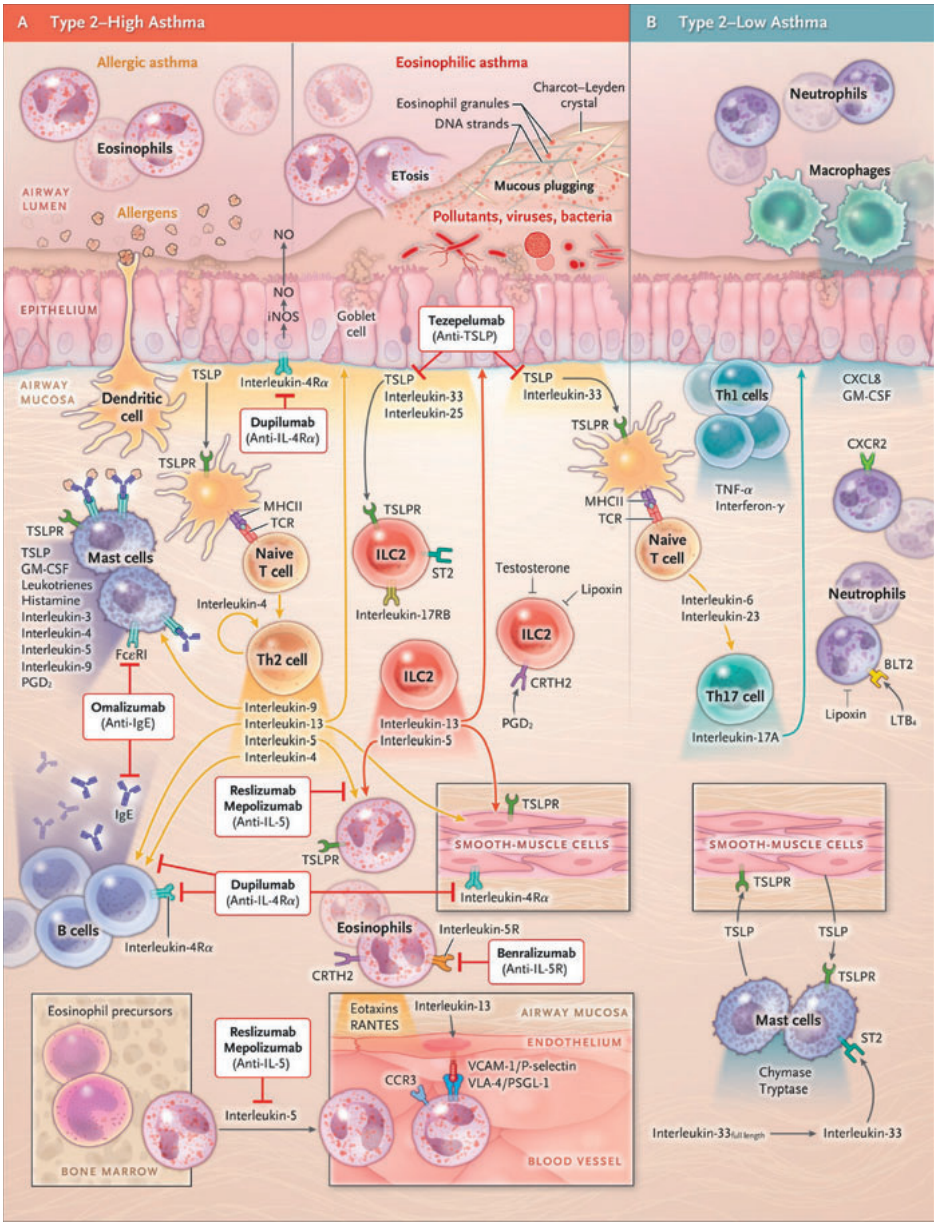

Figure 1: Airway inflammation in severe asthma and targets of biological treatment. Reproduced with permission from Brusselle et al. (14), Copyright Massachusetts Medical Society.

Biologics for severe asthma

Monoclonal antibodies, or biologics, are a relatively new class of drugs, finding their way into clinical practice since the late 1990's and early 2000's.(16) These immunoglobulins consist of two heavy and two light chains, forming a Y-shaped structure with two antigen binding sites (Figure 2).

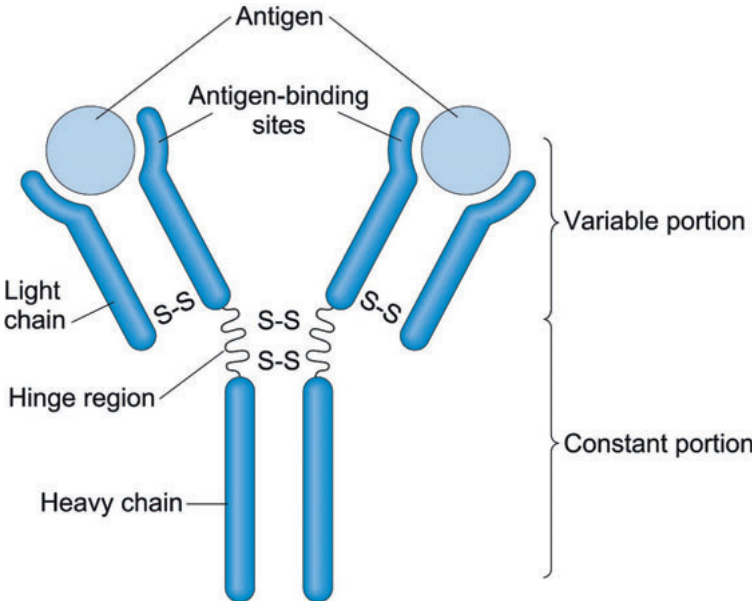

Figure 2: General structure of an IgG antibody.(17)

Biologics are heavy proteins (~150 kDa), and therefore differ greatly from small-molecule drugs in both pharmacokinetic and pharmacological properties.(18,19) Due to their size, the biologics do not undergo renal clearance. Instead, biologics are primarily cleared by proteolytic catabolism and intracellular degradation after binding to the biologic's target. These processes are relatively slow, leading to long half-lives of up to 4 weeks.(20,21) Biologics generally have a wide therapeutic range. Whether to dose based on body weight or independent from body weight is established in phase I and early phase II dose-finding trials.(21-23) However, post-approval pharmacokinetic trials seeking optimal biologic dosing, have led to changes in dose regimen for several biologics.(24,25) As a more personalized dosing sometimes leads to better treatment outcomes, these post-approval trials are an important complement to the initial posology.

At the end of 2022, six biologics are approved in the European Union (EU) for the treatment of severe asthma, five targeting type 2-high inflammation and one targeting both type 2-high and type 2-low inflammation (Figure 1, Table 1).(14) They have shown to markedly reduce asthma exacerbations and oral corticosteroid (OCS) use, as well as to improve asthma symptoms, lung function and quality of life.(26-29)

In 2003 omalizumab was registered for the treatment of moderate-to-severe allergic asthma. Omalizumab binds IgE, preventing its function in binding and activating the FcεRI on mast cells.(30-32)

In 2015 mepolizumab was registered for the treatment of severe eosinophilic asthma.(33-35) Mepolizumab binds free serum Interleukin (IL)-5, preventing it from binding and activating the alpha chain of the IL-5 receptor complex on eosinophils. (36) Reslizumab was registered in 2016 and has a similar mechanism of action as mepolizumab.(37-39)

In 2018, the third IL-5 targeting biologic, benralizumab, was registered, which binds the alpha chain of the IL-5 receptor on eosinophils, preventing IL-5 binding and subsequently eosinophil activation.(40-42) Furthermore, the constant heavy chain 2 part of the Fc-region of benralizumab lacks fucose sugar residue, greatly enhancing its affinity to the FcyRIIIa receptors on natural killer (NK)-cells and macrophages, leading to antibody-dependent cell-mediated cytotoxicity, depleting the number of eosinophils.(43,44)

Dupilumab is the fifth biologic, registered in 2019 for severe eosinophilic asthma with type 2 inflammation.(45,46) Dupilumab binds the alpha subunit of the IL-4 receptor, preventing the function of both IL-4 and IL-13.(47)

The field of severe asthma care is rapidly changing and new treatment options are on the horizon. At the time of writing this introduction, the anti-thymic stromal lymphopotein (TSLP) biologic tezepelumab received market authorization in the EU for the treatment of severe uncontrolled asthma. By inhibiting the function of TSLP, tezepelumab acts at the top of the inflammatory cascade.(48) Tezepelumab is being presented as the only biologic for severe asthma with no phenotype or biomarker limitations, but its place in the treatment of severe asthma among the other biologics remains to be determined.

Table 1: Biologics for severe asthma.

Biologic	Year of introduction	Mechanism of action	Criteria of prescription(1)	Dosing, interval and mode of administration
Omalizumab (49)	2003	Anti-IgE	Exacerbations in last year High serum IgE Allergen sensitization	75-600 mg every 2-4 weeks, SC
Mepolizumab (50)	2015	Anti-IL-5	Exacerbations in last year Elevated serum eosinophils	100 mg every 4 weeks, SC
Reslizumab (51)	2016	Anti-IL-5	Exacerbations in last year Elevated serum eosinophils	3 mg/kg every 4 weeks, IV
Benralizumab (52)	2018	Anti-IL-5Rα	Exacerbations in last year Elevated serum eosinophils	**Loading phase:** 30 mg every 4 weeks, SC **Maintenance phase:** 30 mg every 8 weeks, SC
Dupilumab (53)	2019	Anti-IL-4Rα	Exacerbations in last year Elevated serum eosinophils and/or raised FeNO	Based on comorbidities or OCS maintenance treatment: **Loading phase:** 600 mg or 400 mg, SC **Maintenance phase:** 300 mg or 200 mg every 2 weeks, SC
Tezepelumab (54)	2022	Anti-TSLP	Exacerbations in last year	210 mg every 4 weeks, SC

Abbreviations: FeNO: Fractional exhaled Nitric Oxide, IgE: Immunoglobuline E, IL: Interleukin, IV: Intravenous injection, SC: Subcutaneous injection, TSLP: Thymic stromal lymphopotein.

Real-world evidence

Randomized controlled trials (RCTs) are the gold standard of evidence-based medicine.(55) The controlled environment, strict inclusion and exclusion criteria, randomization and comparison to a placebo arm prove a valid tool to assess the effectiveness of an intervention, minimizing bias and confounders. Despite the evident advantages of RCTs, the strict inclusion and exclusion criteria limit the applicability of RCTs in the real-world. Clinical practice is not a controlled environment, and the population that will receive an intervention after its effectiveness was proven in RCTs, is often more heterogeneous than the population enrolled in the RCTs.(56) This phenomenon has been described as the 'gap' between RCTs and the real-world.(57)

Therefore, real-world evidence, or medicine-based evidence, is an important addition to knowledge derived from RCTs.(58,59) Real-world data help to confirm the findings from RCTs, enable post-market safety monitoring and provide insight in rare adverse events. While RCTs have a limited follow-up period, real-world evidence provides an opportunity to study long-term effects of an intervention. Depending on the method of data collection, larger populations can be included in real-world studies than in RCTs at relatively low costs.(56) Real-world studies also have their shortcomings. The lack of a controlled environment makes the findings susceptible to selection bias and confounding. Furthermore, real-world studies are usually observational in design, data are inconsistently collected and subject to missing data limiting the conclusions that can be drawn from these studies.(56)

In conclusion, while both RCTs and real-world studies have their advantages and shortcomings, both are important in the medical decision making, with real-world evidence being recognized as an important complement to the RCTs. In the current age of digitalization, data from large real-world populations are often collected in population-based registries.(57)

Population-based registries in severe asthma

In the early days after their approval in The Netherlands, the biologics were mostly prescribed in specialized severe asthma centres by experienced pulmonologists. These pulmonologists recognized the need to collect longitudinal real-world data concerning the new biologics. However, severe asthma is a relatively rare disease and the number of patients is limited. To study large numbers of patients and improve clinical practice in a meaningful way, the pulmonologists founded the Dutch Registry of Adult Patients with Severe Asthma for Optimal DIsease management, or RAPSODI. Initially, three severe asthma centres contributed to this registry, but

this number expanded over the years, leading to a collaboration of 21 hospitals in The Netherlands and Switzerland (Davos Dutch Asthma Centre) and including more than a thousand patients at the time of writing this introduction.(60)

The RAPSODI registry strives to include patients with severe asthma and collects follow-up annually. The data are collected in concordance with the new General Data Protection Regulation. In addition to the annual follow-up, the patients are asked to fill in commonly used questionnaires every 3 months using PatientCoach, a dedicated self-management tool for patients with asthma, COPD, high blood pressure and diabetes mellitus.(61)

The idea of a nationwide severe asthma registry was not unique. Multiple countries in Europe founded their own registries, leading to several populations with similar data.(62) Unfortunately, each single country usually has a limited number of included patients, restricting the ability to deliver generalizable evidence and answer important research questions. The European Respiratory Society (ERS) saw the necessity to combine the data of these populations and founded the Severe Heterogeneous Asthma Registry, Patient-centered (SHARP).(63) One of the ambitious goals of this Clinical Research Collaboration (CRC) is combining pan-European data of patients treated with the biologics.(64) However, due to the General Data Protection Regulation (GDPR), these data cannot leave each respective country. In addition, discrepancies between the data collection models make it difficult to combine data. To this end, an objective of SHARP is the development of a federated analysis platform, using the open-source Common Data Model from the Observational Medical Outcomes Partnership, in order to connect and harmonize these nationwide registries in a privacy-proof manner and pave the way for real-world studies involving thousands of patients across Europe.(64,65)

Knowledge-to-care gaps and outline of this thesis

The novel biologics have been proven to be effective in the treatment of severe asthma by reducing exacerbations and the use of maintenance oral corticosteroids, and improving pulmonary function and quality of life in the RCTs leading to approval of the biologics.(14) However, not all patients respond equally well to the biologics. This, in light of the high treatment costs (approximately €15.000,- per patient per year) and high disease burden of severe asthma, warrants that the response to the biologics is evaluated and, if possible, optimized.

The Global INitiative for Asthma (GINA) guidelines suggest that the treatment is evaluated after 4-6 months and switched or discontinued if needed.(1) There is

however a need for clear consensus on what response is, as just like each patient is different, response also differs between patients. There is a need for studies that focus on what parameters to take into account when evaluating response and what the optimal moment for evaluating response is.(14,66) Other examples of knowledge-to-care gaps are criteria for discontinuation or switching of the biologics, the effects on the cumulative oral corticosteroid exposure, the applicability of serum drug levels measurements and therapeutic drug monitoring, the prevalence of anti-drug-antibody development, criteria for interval adjustments based on adequate or inadequate response, evidence on specific patient-populations, and the occurrence of rare adverse events. In addition, it has been widely recognized that predictive parameters, predicting an individual's chance of long-term response to the biologics, are lacking and prove an important objective for clinical studies. Lastly, due to the limited duration of RCTs, long-term outcomes of the biologics are lacking. Real-world studies could contribute to answering these knowledge-to-care gaps.

In light of these knowledge-to-care gaps, the overall objective of this thesis is to gain insight in real-world outcomes of biological treatment for severe asthma. To this end, we performed several studies with a variety of study designs.

Part I. Population-based registries

In order to gain insight in the real-world long-term outcomes to anti-IL-5 treatment in severe asthma, in **chapter 2** we studied the prevalence of super-, partial-, and non-responders, the prevalence of switches between the anti-IL-5 biologics and residual disease manifestations after two years of anti-IL-5 treatment. In **chapter 3**, we studied the real-world effectiveness of reslizumab, both in biologic-naive patients and patients switching to reslizumab treatment. The RCTs that led to the approval of the anti-IL-5 biologics focused on the reduction of asthma exacerbations and the maintenance OCS dose. However, OCS-related adverse events are more related to the cumulative OCS exposure. Therefore, in order to gain insight in the real-world long-term cumulative OCS exposure before and after anti-IL-5 initiation, we performed the study presented in **chapter 4**. The studies in chapters 2, 3 and 4 included a nationwide population from the Dutch RAPSODI registry.

In addition to these nationwide studies, we also performed pan-European studies within the SHARP CRC. **Chapter 5** describes the experiences with development and implementation of the federated analysis platform, which can be used to perform studies across different countries and nationwide registries in a privacy-proof manner. The first study using this platform is described in **chapter 6**, in which

real-world data from patients initiating mepolizumab for severe asthma from 10 European countries are extracted and analyzed.

Part II. Prediction of response to the biologics used in severe asthma

In **chapter 7**, we explored the current state of response prediction of the currently registered biologics for severe asthma. A literature review was performed, assessing whether adequate response prediction is possible and what clinical or inflammatory parameters predict a patient's chance of being a responder. In **chapter 8**, we performed a single-centre study on early changes in patient-reported outcome measures and the chance of long-term mepolizumab response. This study led to the initiation of a study on the prediction of long-term benralizumab response in a larger population, discussed in **chapter 9**. In this study, we aimed to combine baseline characteristics and patient-reported outcome measures at three months to predict benralizumab response at one year. In this nationwide study, data from the Dutch RAPSODI registry were used and complemented.

Part III. Patient-tailored approaches

The biologics for severe asthma are generally applied in fixed dose intervals. However, in clinical practice, some patients feel that their dose interval is not optimal, sometimes leading to a patient-tailored treatment with shortened or prolonged dose intervals. In **chapter 10** we studied whether this perceived need for the next administration is related to omalizumab serum levels. In order to further study the phenomenon of waning of biological effect towards the end of the dose interval, we performed the study in **chapter 11**. In this study, we developed a questionnaire based on patient-interviews and performed a single-centre, cross-sectional analysis of the patient-perceived waning of biological effect. Lastly, in **chapter 12**, we describe the case of a patient receiving benralizumab treatment while admitted to the intensive care unit for a COVID-19 infection.

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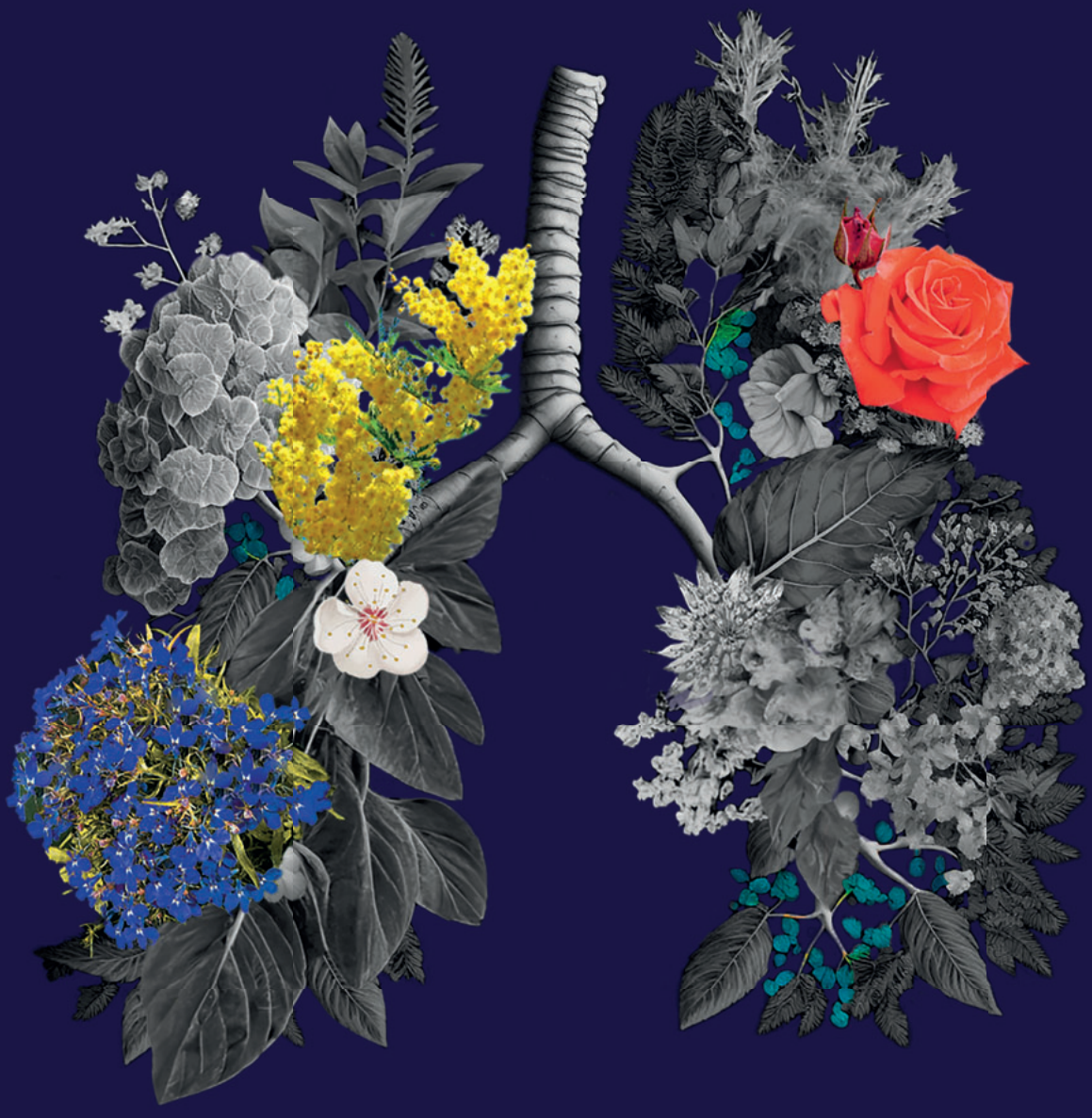
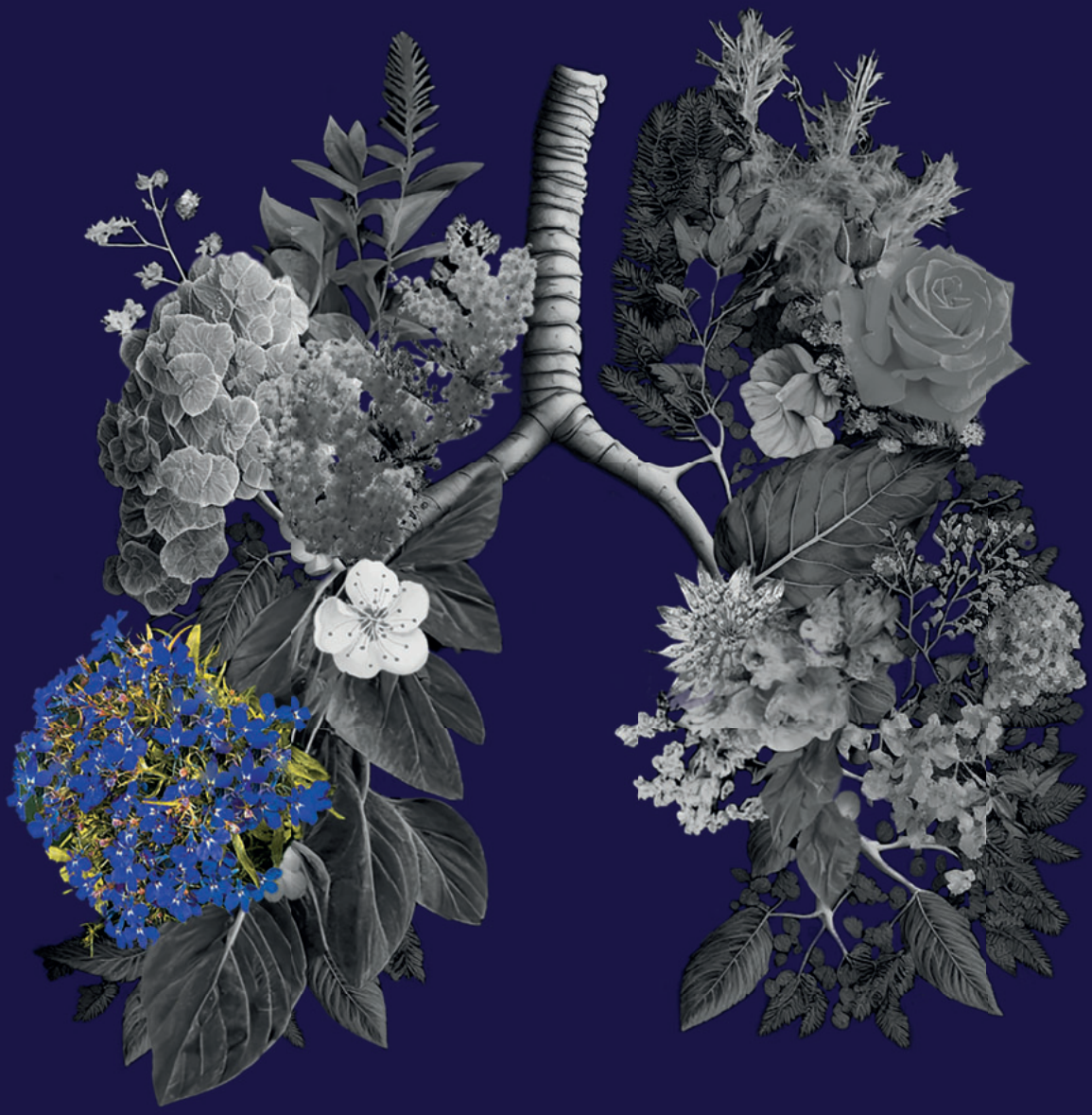


Part I

Population-based registries



Chapter 2

Long-term therapy response to anti-interleukin-5 biologics in severe asthma – a real-life evaluation

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ABSTRACT

Background

Patients with severe eosinophilic asthma show different responses to various anti-interleukin (IL)-5 biologics, ranging from super- to non-response. Residual disease manifestations observed in partial responders may prompt physicians to switch between biologics. More data on response, switches, and residual disease manifestations are needed to improve personalized treatment.

Objective

To assess; (1) prevalences and predictors of super-, partial- and non-responders to long-term anti-IL-5 treatment, (2) frequency and reasons for switches between anti-IL-5 biologics, (3) nature of residual disease manifestations.

Methods

In this 2-years follow-up study, patients with severe asthma were included who initiated an anti-IL-5 biologic (mepolizumab, reslizumab, benralizumab) (n=114). Patient characteristics (clinical, functional, inflammatory) and co-morbidities were collected at baseline and 2-years follow-up. Definitions: "super-responders" showed no residual disease manifestations at 2-years follow-up; "partial responders" experienced residual disease manifestations, and "non-responders" discontinued anti-IL-5 treatment <2yr because of clinical worsening.

Results

After 2-years anti-IL-5 treatment 14% of patients were super responders, 69% partial responders, and 11% non-responders. Super-response was predicted by shorter asthma duration and higher FEV_1, and tended to be associated with adult-onset asthma, absence of nasal polyps and lower BMI. Switches between anti-IL-5 biologics occurred frequently (41%). After 2-years treatment most common residual disease manifestations included impaired lung function (59%), uncontrolled sino-nasal disease (58%) and uncontrolled asthma symptoms (48%).

Conclusion

After 2 years of anti-IL-5 treatment, a favorable response was found in 83% of patients with severe asthma, including a super-response in 14%. Most partial responders show impaired lung function or uncontrolled sino-nasal disease, causing physicians to switch between biologics.

INTRODUCTION

Severe asthma is a debilitating disease associated with persistent symptoms, poor quality of life, and frequent use of oral corticosteroids (OCS) that are known to increase the risk of co-morbidities.[1,2] Fortunately, the new steroid-sparing biologics for severe asthma targeting interleukin (IL)-5 (mepolizumab and reslizumab) or IL-5 receptor (benralizumab) have a large positive impact on the lives of many patients.[3–5]

However, the response to these anti-IL-5 biologics does not seem to be equal in every patient. Some patients reach complete asthma control ("super-responders"), while others experience residual disease manifestations ("partial responders"), or show no improvement or even clinical worsening ("non-responders").[6–8] The underlying mechanisms of these different responses are not yet known. Moreover, responses may vary between the different anti-IL-5 biologics, which may be due to differences in target, mode of administration, or dosing (interval). Perhaps that is why clinicians in real-life may decide to switch between treatments in those patients who have an incomplete response in order to achieve optimal disease control.[9]

At present, there are limited data about long-term effects of anti-IL-5 treatment in patients with severe asthma in real-life.[6,7,10,11] Many questions about responders and non-responders, predictors of response and residual disease after blocking the IL-5 pathway are still unanswered. Answers to these questions could help to better understand the pathophysiology of severe asthma, and thus further improve personalized treatment.

The aims of the present study were first, to assess the prevalence of "super-responders", "partial responders", and "non-responders" to long-term (2 years) anti-IL-5 treatment; second, to assess predictors of non- and super-response; third, to evaluate the proportion of patients who had switched between anti-IL-5 biologics and why; and fourth, to characterize residual disease manifestations in partial responders. We used prospective real-life data from a multicenter cohort of 114 patients with severe eosinophilic asthma treated with different anti-IL-5 biologics (mepolizumab, reslizumab, benralizumab) for more than 2 years.

METHODS

Design and patient selection

Patients with severe asthma visiting the pulmonary outpatient clinics from two Dutch asthma expertise centers (Amsterdam University Medical Center (AMC) and Medical Center Leeuwarden (MCL)) were asked to participate in this study. Patients were diagnosed with severe asthma according to ERS/ATS guideline criteria[12] and were included in the Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI) or a similar registry running in MCL, after having provided informed consent. For inclusion in the present study, patients had to be treated with one or more biologics against IL-5 (mepolizumab and/or reslizumab and/or benralizumab) and had to have started anti-IL-5 treatment in the period April 2016-December 2017. Patients were excluded if they were lost to follow-up, if they had interrupted anti-IL-5 treatment for >3 months during the follow-up period, or if they had previously received anti-IL-5 treatment in a trial. At baseline and at 2-years follow-up clinical, functional, inflammatory and comorbidity data were derived from the registries and supplemented with data from electronic patient files.

Measurements

Clinical characteristics: demographics, asthma duration, asthma control questionnaire (ACQ)-6 item score[13].

Surrogate inflammatory markers/anti-inflammatory treatments*:* peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO, NIOX System, Aerocrine, Sweden)[14], maintenance dose of OCS, OCS bursts or episodes of doubling the OCS maintenance dose ³3 days in the last 3 months, immunoglobulin E (IgE).

Lung function: forced expiratory volume in 1 second (FEV_1) measured according to standardized methods[15].

Co-morbidities*:* chronic rhinosinusitis (CRS), and presence of nasal polyps (NP) or chronic otitis was diagnosed by an ENT specialist; allergic rhinoconjunctivitis was diagnosed by elevated specific IgE testing combined with a history of allergic symptoms; and atopic dermatitis was diagnosed based on patient's history and physical examination. Adrenal insufficiency (AI) confirmed by low morning cortisol levels (<150 nmol/L) or inability to lower OCS dose due to severe AI symptoms such as severe fatigue and nausea.

Changes in anti-IL-5 treatments*:* frequency of switches between anti-IL5 treatments, reasons for switches (e.g. persistent asthma or sino-nasal symptoms including exacerbations, persistent airflow limitation, inability to taper or stop OCS, adverse effects), or discontinuation of anti-IL-5 treatments.

Definitions of responders

Super-responders were defined as patients with complete control of asthma after 2 years of anti-IL-5 treatment, as shown by: no chronic OCS use, no OCS bursts in the past 3 months, ACQ <1.5, FEV_1 ≥80% predicted, FeNO <50ppb, and complete control of co-morbidities (CRS, NP, chronic otitis, allergic rhinoconjunctivitis and atopic dermatitis).

Non-responders were defined as patients who discontinued anti-IL-5 treatment <2 years because of clinical worsening with either increased symptoms, decreased FEV_1 or increased OCS use.

Partial responders were defined as patients who did not fulfill the criteria of non-responders or super-responders after 2 years of anti-IL-5 treatment.

Analyses

First, the prevalences of super-responders, partial responders and non-responders were calculated. Patient characteristics of the three responder groups at baseline were evaluated using descriptive statistics. Blood eosinophil levels (expressed as cells*10^9/L) in patients on chronic OCS therapy were corrected for the daily maintenance OCS dose (mg/day) with the following calculation: (eosinophils)*$(1.07)^{(OCS\ dose)}$.[16] Differences between non-responders or super-responders versus the other patients were analysed by using Mann-Whitney U, Chi square or Fisher exact tests when applicable. Differences in patient characteristics with a p-value <0.15 from this analysis were tested in a binary logistic regression analysis to assess whether these variables were predictors of non- or super-response adjusted for age and sex.

Second, the prevalence of patients who switched between anti-IL-5 biologics was assessed, both for the entire cohort as well as for the various responder groups separately. Next, the proportions of the different categories of reasons for these switches were evaluated. Descriptive statistics at 2-years follow-up were used to evaluate residual disease manifestations in partial responders.

Differences were considered significant if p-values were <0.05. SPSS software (IBM SPSS Statistics, version 26, IBM Corporation) was used to perform the statistical analyses.

RESULTS

Patient selection

Of 141 patients with severe asthma in the registries who had initiated anti-IL-5 treatments (mepolizumab, reslizumab, benralizumab) in the period April 2016-December 2017, 2 patients were lost to follow-up, 19 patients were participants of previous anti-IL-5 trials and 6 patients had interruptions in anti-IL-5 treatment >3 months during the 2-year period. The 114 patients included in the analyses were mostly middle-aged, had an adult-onset asthma, a high prevalence of sino-nasal disease, a high ACQ score, and 2/3rd of patients used OCS maintenance therapy at baseline (Table I, left panel).

Prevalence of super-responders, partial responders and non-responders

After 2 years of anti-IL-5 treatment, 95 of 114 patients (83%) still used anti-IL-5 biologics and 19 patients (17%) had discontinued this treatment. Sixteen patients (14%) met the definition of super-responder, 79 (69%) were partial responders and 12 (11%) were non-responders (Figure 1). Non-responders had received a median of 8 administrations of an anti-IL-5 biologic (interquartile range (IQR) 4-15). Anti-IL-5 treatment was discontinued for other reasons in 7 patients (6%), 3 of which discontinued because of adverse effects.

Predictors of response to long-term anti-IL-5 therapy

Baseline characteristics of super-responders, partial responders and non-responders to 2 years anti-IL-5 treatment are shown in Table I. Non-responders could not be distinguished from the other groups by any of the baseline characteristics, although there was a trend towards lower blood eosinophils (p-value 0.183) and more frequent asthma that started below 18yrs of age (p-value 0.135). In a regression analysis no significant predictors of non-response could be identified. Super-responders however showed a significantly shorter duration of asthma (p-value 0.009) and a higher FEV_1 % predicted (p-value 0.024) as compared to the other patients, and tended to have a lower BMI (p-value 0.091), more frequently asthma that had started in adulthood (p-value 0.104) and less often nasal polyps (p-value 0.112). After adjustment for age and gender, FEV_1 % predicted and asthma duration were predictors of super-response with an OR of 3.7 and 3.5 respectively (Table II). Further adjustment for potential confounders was not possible due to the small number of super-responders.

Table I. Patient characteristics at baseline and 2 years follow-up

	All patients (n=114)	Non-responders (n=12)	Partial responders (n=79)		Super-responders (n=16)	
	Baseline	Baseline	Baseline	2yrs follow-up	Baseline	2yrs follow-up
Clinical characteristics						
age* - yr	55 (46-64)	53 (46-70)	56 (45-63)	-	53 (49 - 62)	-
male sex - %	54%	50%	51%	-	67%	-
body-mass index* - kg/m^2	27 (25-31)	27 (25-30)	28 (25-32)	-	25 (23-29)#	-
former smoker - %	43%	42%	43%	-	53%	-
duration of asthma* - yr	15 (5-30)	21 (8-38)	16 (6-34)	-	6 (4-12)#	-
asthma onset ≥18yr -%	70%	50%#	71%	-	93%#	-
ACQ-6*(n=75)	2.50 (1.50-3.17)	2.67 (2.10 -3.50)	2.50 (1.50-3.33)	1.33 (0.67-2.17)	2.33 (1.17-2.33)	0.17 (0.00-0.83)
ACQ-6 ≥1.5 - %	77%	89%	78%	48%	71%	0%
Surrogate inflammatory markers						
OCS maintenance therapy - %	68%	75%	70%	32%	63%	0%
OCS dose‡* - mg/day	10 (7.5-15)	7.5 (6.25-12.5)	10 (7.5-15)	10 (5-13.75)	10 (5-15)	n/a
≥1 OCS burst last 3 months - %	56%	56%	55%	24%	63%	0%
eosinophils* - 10^9/L	0.51 (0.27-0.96)¶	0.36 (0.19-0.69)¶	0.57 (0.28-1.04)¶	0.07 (0.02-0.10)	0.46 (0.25-0.53)¶	0.07 (0.02-0.12)
FeNO* - ppb	34 (24-52)	36 (19-65)	34 (25-56)	35 (23-54)	32 (22-40)	24 (11-35)
FeNO >50ppb - %	26%	33%	27%	26%	19%	0%
total IgE* - IU/ml (n=96)	114 (35-299)	95 (29-131)	116 (40-319)	n/a	147 (38-260)	n/a
Lung function						
FEV_1* - % predicted	76 (61-93)	76 (63-101)	74 (61-90)	73 (61-94)	94 (68-106)#	98 (90-113)
FEV_1 <80% - %	56%	58%	61%	59%	31%#	0%

Table I. Continued.

	All patients (n=114)	Non-responders (n=12)	Partial responders (n=79)		Super-responders (n=16)	
	Baseline	Baseline	Baseline	2yrs follow-up	Baseline	2yrs follow-up
Uncontrolled co-morbidities						
CRS – %	69%	67%	72%	57%	56%	0%
nasal polyps – %	23%	25%	26%	19%	6%[#]	0%
chronic otitis – %	12%	8%	14%	12%	6%	0%
atopic dermatitis – %	6%	0%	9%	7%	0%	0%
allergic rhinoconjunctivitis – %	26%	33%	26%	23%	19%	0%
adrenal insufficiency - %	n/a	n/a	n/a	10%	n/a	0%

[*]Median (interquartile range); [‡]OCS dose is provided as prednisone-equivalent for patients on chronic OCS therapy; [¶]eosinophil levels in patients on chronic OCS therapy are corrected for OCS dose[16], [#]p-value <0.15 (super-responders or non-responders vs other patients). Abbreviations: *ACQ-6*, asthma control questionnaire–6 item score; *CRS*, chronic rhinosinusitis; *FeNO*, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second1; *IgE*, immunoglobulin E; *IQR*, interquartile range; *n/a* not applicable or not available; *OCS*, oral corticosteroids.

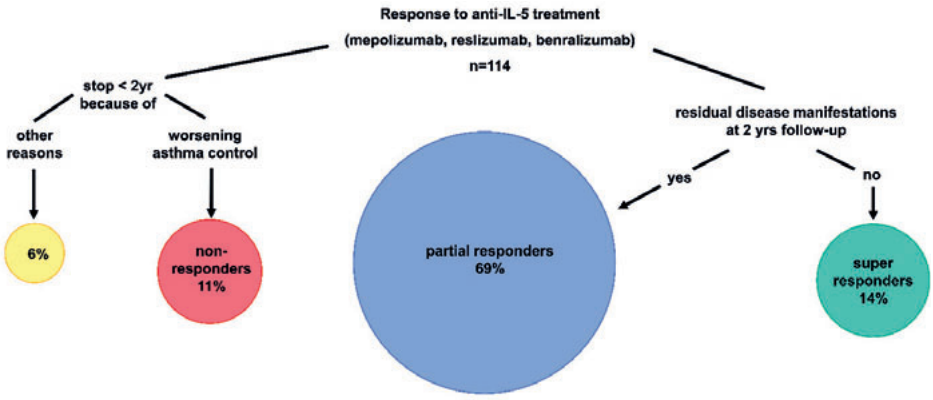

Figure 1. Prevalence of super-responders, partial responders and non-responders after 2 years of treatment with anti-IL-5 biologics for severe eosinophilic asthma. In this observational cohort study 11% of patients could be labelled as non-responders, 69% as partial responders and 14% as super-responder after 2 years of anti-IL-5 treatment for severe eosinophilic asthma. 6% of patients discontinued anti-IL-5 treatment <2 years for other reasons.

Table II. Predictors of super-response to long-term anti-IL-5 biologics

	Adjusted OR*	95% CI	p-value
Asthma onset ≥18yr	5.961	0.706-50.311	0.101
Absence of nasal polyps	5.950	0.721-49.082	0.098
FEV_1 ≥80% predicted	3.708	1.120-12.284	0.032
Asthma duration <10 years	3.572	1.093-11.673	0.035
BMI <25 kg/m²	2.675	0.820-8.719	0.103

*OR adjusted for age and sex. Abbreviations: CI, confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

Switches between anti-IL-5 biologics

Of the 114 included patients 67 (59%) did not switch between anti-IL-5 biologics during the study period, 39 (34%) switched to another anti-IL-5 and 8 (7%) made 2 switches. The frequency of switches was not significantly different between super-, partial or non-responders (p-value 0.670, Figure 2). Persistent asthma or sino-nasal symptoms, including exacerbations, were the most frequently reported reasons for switching between anti-IL-5 biologics (53%), followed by inability to taper or stop OCS (28%), or persistent airflow limitation (17%). Only a small percentage of patient switched because of adverse effects (5%).

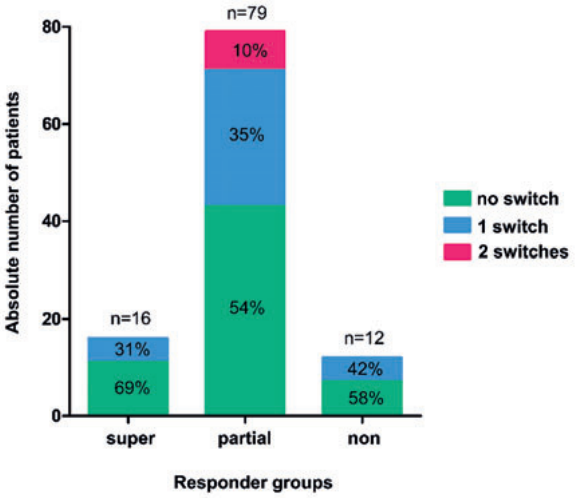

Figure 2. Frequency of switches between anti-IL-5 treatments in the different response groups. Figure 2 shows the number of switches between anti-IL-5 treatments in super-responders, partial responders and non-responders. There was no significant difference in the number of switches between the different responder groups (p-value 0.670).

Residual disease manifestations in partial responders after 2 years anti-IL-5 treatment.

The residual disease manifestations in partial responders are summarized in Figure 3. The most prevalent residual conditions were persistent airflow obstruction (59%), symptoms of ear-nose-throat (ENT) pathology including CRS, nasal polyps or chronic otitis (58%), and uncontrolled asthma symptoms (48%). After 2 years treatment 32% of patients still used maintenance OCS, of which about 1/3rd were diagnosed with adrenal insufficiency by their treating physician. More detailed information on outcomes in both partial and super-responders, including ACQ-6 scores, FeNO levels and FEV_1 % predicted values, can be found in Table I.

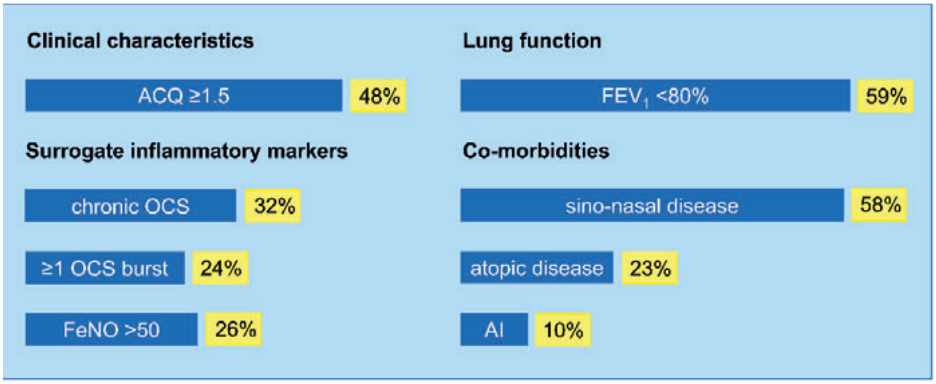

Figure 3. Residual disease manifestations in partial responders after 2 years anti-IL-5 treatment. OCS bursts were recorded <3 months before 2-years follow-up. Sino-nasal disease is uncontrolled chronic rhinosinusitis, or presence of nasal polyps or chronic otitis. Atopic disease is uncontrolled allergic rhinoconjunctivitis or atopic dermatitis. Abbreviations: *ACQ-6*, asthma control questionnaire–6 item score; *AI*, adrenal insufficiency; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *OCS*, oral corticosteroids.

DISCUSSION

In this real-life study 83% of patients with severe eosinophilic asthma had a favorable response to long-term (2 year) anti-IL-5 treatment, although frequent switches between biologics occurred. Super-response was observed in 14% of patients and was predicted by shorter asthma duration and higher FEV_1, and tended to be associated with adult-onset asthma, absence of nasal polyps and lower BMI. Partial responders (69%) experienced residual disease manifestations even after 2 years treatment, including inadequately controlled symptoms of asthma or rhinosinusitis, persistent airflow limitation, or OCS dependency. Only 11% of patients qualified as non-responders.

After 2 years of anti-IL-5 treatment 14% of patients were completely free of any disease manifestation which we labeled "super-responders". Other studies focusing on super-responders found higher rates (20-28%), but this can be explained by the less stringent criteria of super-response in these studies.[6,7] For example, we found that many patients with a favorable response regarding OCS use or asthma exacerbations, still suffered from (severely) impaired lung function or uncontrolled sinus disease, even after 2 years of treatment.

Several studies have looked at predictors of (super-)response to anti-IL-5 treatment, but here again response was mostly defined in terms of reduction of exacerbations

or OCS use.[17,18] For these outcome parameters higher eosinophil counts or higher exacerbation rates seem to be the best predictors. However, despite the small numbers in our study, we may carefully suggest that the profile of a true super-responder to long-term anti-IL-5 biologics is an adult with a relatively short duration of eosinophilic asthma, without nasal polyps, chronic airflow limitation or overweight. Further research in larger cohorts is needed to confirm these findings.

The observed heterogeneity of response to anti-IL-5 treatments can have several causes. First, it may be related to the medication itself. Individual differences in pharmacokinetics and resulting plasma drug levels are currently not taken into account, while therapeutic drug monitoring is common practice in other chronic conditions treated with monoclonal antibodies.[19] In addition, monoclonal antibodies in general can induce immunogenicity with subsequent formation of anti-drug antibodies (ADA), which in theory could lead to secondary loss of response.[20,21] Moreover, dosing of medication is not tailored to the degree of inflammation in the airways, which may lead to under-dosing in patients with the most severe inflammation.[9,22] Second, incomplete responses to anti IL-5 treatment could be due to irreversible remodeling of upper and lower airways or irreversible adrenal insufficiency after long-term OCS use.[23,24] Third, residual asthma symptoms without evidence of eosinophilic inflammation may be caused by co-morbidities such as dysfunctional breathing, obesity, deconditioning, bronchiectasis or cardiovascular disease. Lastly, the observed residual disease manifestations may result from ongoing activation of non-IL-5 driven inflammatory pathways, such as the IL-4/IL-13 pathway.[25–28] It is even conceivable that blocking one inflammatory pathway activates another.[29]

This study has strengths and limitations. Strengths include first, that it is a non-pharma-sponsored real-life study of a relatively large group of patients on long-term treatment with various anti-IL-5 biologics. Second, it is the only study with documentation of switches between treatments and reasons for switches. Third, we used a composite treatment response definition, covering all relevant asthma-related parameters.

The limitations of this study are those that generally apply to real-world studies; e.g. no standardized way of recording, possibility of incompleteness of data, etc. However, we believe that these limitations were relatively insignificant since patients were recruited in two centers that have extensive experience in performing drug trials in patients with severe asthma. Another limitation was that in this real-life study it was not possible to determine which anti-IL-5 biologic performed best, as

the order of introduction of the various anti-IL-5 biologics in the Netherlands was an important bias factor. Indeed, previous treatment with one biologic may have affected the response to the next biologic. A randomized head-to-head comparison would be more appropriate for this purpose.

An important clinical implication of our study is that although the anti-IL-5 biologics lead to an impressive clinical response in the majority of patients, physicians should realize that many are still left with unresolved disease manifestations such as impaired lung function, nasal polyposis or persistent OCS dependency, likely indicating active airway inflammation that may require additional local or systemic treatment.[30] It seems therefore advisable to evaluate the therapeutic response in a systematic way taking into account therapy adherence as well as all domains of disease including comorbidities and inflammatory biomarkers such as FeNO.[31,32]

In conclusion, this study shows that the vast majority of patients with severe asthma respond favorably to anti-IL-5 biologics after 2 years treatment, with 14% super-responders and only a small proportion non-responders. However, residual disease manifestations are common and vary from asthma exacerbations, OCS dependency, and persistent airflow limitation, to uncontrolled asthma-related co-morbidities. This incomplete response often causes physicians to switch between anti-IL-5 biologics in their patients, or switch to biologics targeting other pathways like the IL-4/IL-13 pathway. Presumably, new future asthma biologics that simultaneously block multiple inflammatory pathways will eventually provide a more complete resolution of severe asthma symptoms and co-morbidities.

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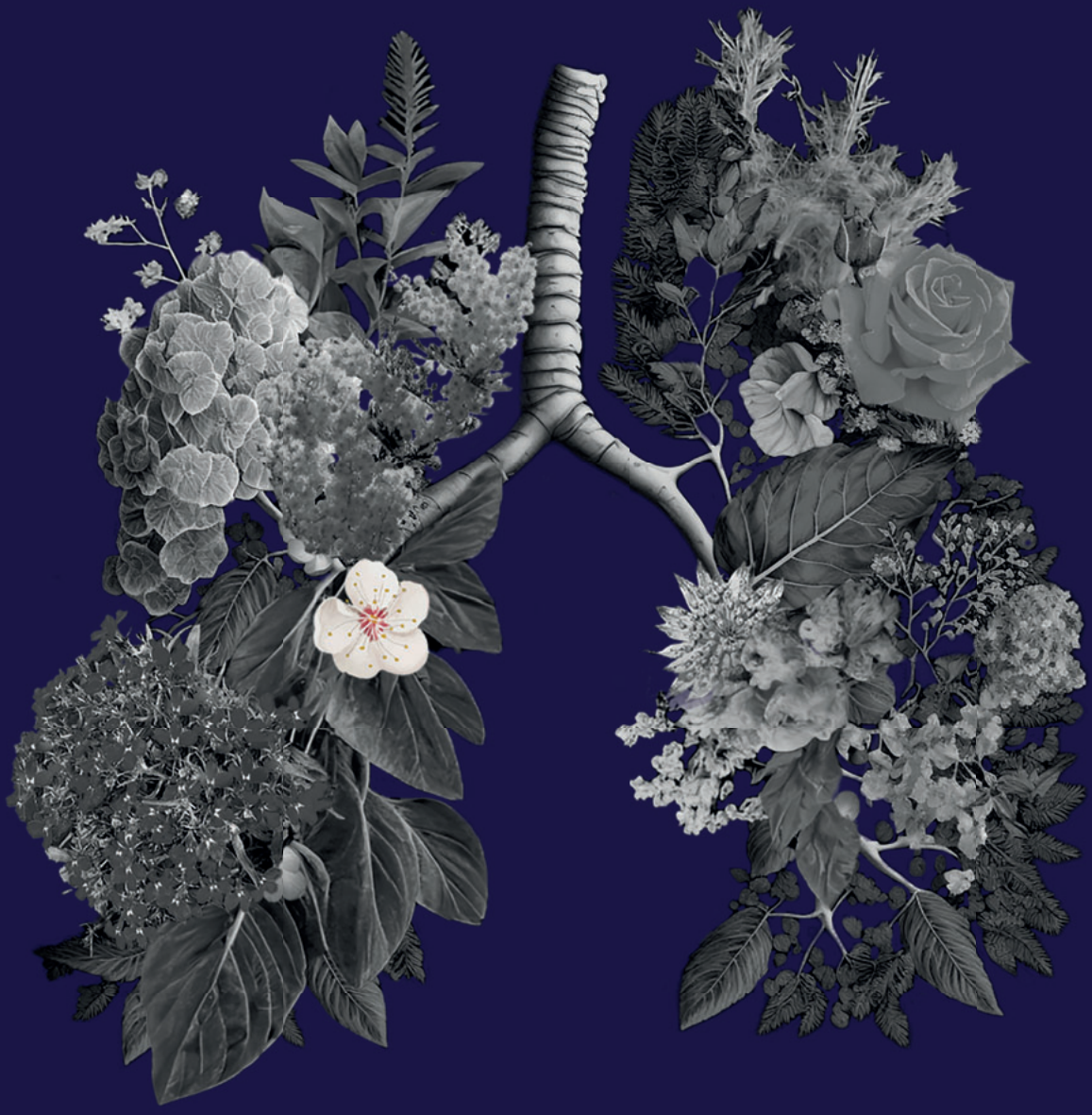

Chapter 3

Real-World Effectiveness of Reslizumab in Patients with Severe Eosinophilic Asthma – "First Initiators" and "Switchers"

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ABSTRACT

Background

Reslizumab, a biologic targeting interleukin-5 has been shown to reduce asthma exacerbations and maintenance oral corticosteroid (OCS) use in randomized controlled trials and pre-post studies in patients with severe eosinophilic asthma. However, real-world effectiveness data of reslizumab are scarce, and it is unknown whether reslizumab has added value after switching from another type 2 biologic.

Objective

To evaluate (1) real-world effectiveness of reslizumab on severe asthma exacerbations, maintenance OCS-use and overall treatment response, both in biologic naive patients who initiated reslizumab, and in patients who switched from another type 2 biologic; and (2) physicians' experience with reslizumab treatment.

Methods

This observational real-world study evaluated data from 134 adults with severe eosinophilic asthma included in the Dutch severe asthma registry (RAPSODI) who initiated reslizumab treatment (4-weekly infusions, 0.3 mg/kg) before April 2020 and had follow-up data ≥6 months. Clinical asthma experts completed surveys on their experience with reslizumab treatment.

Results

Overall, reslizumab reduced exacerbation rate (OR(95%CI): 0.10(0.05-0.21), p<0.001), oral corticosteroid use (OR(95%CI) 0.2(0.0-0.5), p<0.001) and maintenance dose, median(CI): 5.0(0.0-10.0) to 0.0(0.0-5.0), p<0.001), with comparable results in biologic-naive reslizumab initiators and switchers. The overall response to reslizumab was graded 'good' or 'excellent' in 59.2% of patients. The additive effectiveness of reslizumab after switching from another biologic was reflected in physicians' surveys.

Conclusion

Real-world data show that reslizumab reduces severe asthma exacerbations and oral corticosteroid use in patients with severe eosinophilic asthma, both in biologic-naive reslizumab initiators and in those who switched from another type 2 biologic. This additional value of reslizumab was recognized by clinical asthma experts.

INTRODUCTION

Severe asthma is a form of asthma that does not respond or responds insufficiently to the current inhaled preventer medication for asthma (1,2). Patients with severe asthma face a sizeable daily disease burden with persistent symptoms of dyspnea, coughing, mucus production, and impaired daily life activity (3,4). Moreover, these patients are at increased risk of severe, potentially fatal asthma exacerbations that can often only be prevented by frequent courses or the continuous use of oral corticosteroids (OCS), which is associated with serious long-term side effects (5,6,7).

Most patients with severe refractory asthma exhibit type 2 airway inflammation with elevated eosinophils in sputum and blood (8). For the add-on treatment of patients with this so-called "severe eosinophilic asthma" several biologics have become available in recent years targeting interleukin (IL)-5, a key cytokine responsible for the differentiation, maturation, recruitment and activation of eosinophils (9). In randomized clinical trials, these anti-IL-5 add-on treatments have been shown to effectively reduce the rate of asthma exacerbations, lower the dose of maintenance oral corticosteroids, and improve asthma symptoms, pulmonary function and quality of life in patients with severe eosinophilic asthma (10,11).

One such add-on treatment is reslizumab, an immunoglobulin G subclass 4 kappa monoclonal antibody targeting IL-5 and given intravenously to patients with severe eosinophilic asthma and blood eosinophils ≥400 cells/μL (12). The efficacy of reslizumab has been convincingly demonstrated in prospective, randomized clinical trials, but data on the real-life effectiveness of this antibody outside of clinical trials are scarce (13-17). It has been shown that in real-life patients receiving asthma biologics often switch between the currently available ones, but it is unclear why physicians decide to switch, or whether switching between biologics has any additional value or not (18).

In the present study we evaluated the real-world effectiveness of reslizumab on severe asthma exacerbations, maintenance OCS-users and maintenance OCS dose and overall quality of treatment response, both in patients who initiated reslizumab as their first asthma biologic and in those who had switched from another type 2 biologic. We also evaluated physicians' expectations and clinical experience with reslizumab treatment. For the analyses we used real-world longitudinal patient-level data from RAPSODI, the Dutch Registry of Patients with Severe asthma (19) and an anonymized online survey distributed among all Dutch physicians who had treated RAPSODI patients with reslizumab.

METHODS

Study population

The study population consisted of all adult patients with severe asthma included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI) who initiated reslizumab between 1 January 2017 and 1 April 2020 and had follow-up data available at least 6 months after reslizumab initiation. We distinguished two groups of patients: biologic naive reslizumab initiators ("biologic naive initiators") and patients who had switched from another type 2 biologic ("switchers"). Patients who participated in clinical trials at the time of reslizumab initiation were excluded. Figure 1 shows the flow-chart of inclusion.

The Medical Ethics Review Committee of the Academic Medical Center was consulted before the execution of this study (reference number W21_075 # 21.085).

Design

This was a multicenter observational registry-based study, involving the extraction and analysis of data from RAPSODI. We first identified patients who had their first initiation with reslizumab before 1 April 2020 and then selected patients who had used reslizumab for ≥6 months for the analysis. We used a pre-post approach, i.e. patient characteristics and treatment outcomes at 6 months (i.e. data collected at a time point closest to ≥6 months) post-reslizumab initiation were compared with data at the time of reslizumab initiation. If reslizumab treatment was preceded by another type 2 biologic we also evaluated the effect of the first biologic by comparing data at initiation of reslizumab with data at initiation of the previous biologic. Before the results of the present study were disclosed, a short anonymous survey was distributed to physicians who had treated RAPSODI patients with reslizumab about their clinical experience with this treatment.

Data source

Data from individuals with severe asthma from 19 Dutch hospitals were retrieved from the RAPSODI registry, which is based on two sources: annual electronic case report forms (eCRF, CASTOR EDC platform®, Amsterdam, The Netherlands) (20), and 3-monthly electronic patient questionnaires (PatientCoach®, Leiden University Medical Center, Leiden, The Netherlands) (21). The eCRF included sections related to the inclusion criteria for the study, demographics, asthma history, comorbidities, lung function, laboratory measures and medication. At each center, designated staff contributed to registration of data for eligible patients who provided written consent. The quality of the data was assessed and any necessary follow-up with the

centers was conducted. After data quality issues were resolved, data cleaning and preparation ensued, including identifying outlier values, labeling and formatting of variables, and creating new derived variables as required.

Patients included in RAPSODI were asked to complete every 3-months on a voluntary basis two standard questionnaires: Asthma Control Questionnaire (ACQ-6) (22) and Asthma-related Quality of Life Questionnaire (AQLQ) (23), and information about past asthma exacerbations through PatientCoach. Data from the PatientCoach platform were merged with data from Castor eCRF via the pseudonymized unique RAPSODI patient identifier.

For the physicians' opinion on reslizumab add-on therapy we used data from an anonymized survey completed by all physicians who had treated RAPSODI patients with reslizumab during the study period. The survey consisted of 7 questions (see supplementary files). Physicians were not aware of the study results at the time they completed the survey.

Study outcomes

Primary outcomes

Co-primary study outcomes included change in annualized exacerbation rate and change in maintenance OCS dose (mg/day) after at least 6 months reslizumab therapy for the whole group of reslizumab users.

Secondary outcomes

Secondary outcomes included change in proportion of patients using maintenance OCS after 6 months reslizumab initiation, unscheduled emergency visits, hospitalizations, intensive care unit (ICU) admissions and overall quality of response to reslizumab.

Subgroup analyses

Two pre-defined subgroups were analyzed separately: 1) biologic naive reslizumab initiators ("biologic naive initiators") and 2) patients who initiated reslizumab after having switched from another type 2 biologic ("switchers").

Physicians' opinions

Physicians' opinions about reslizumab add-on therapy included the degree of satisfaction with reslizumab given as first add-on biologic therapy or after switching from another type 2 biologic therapy. The physician's survey was written in Dutch;

an English translation and the complete results of the survey are available in the supplementary files.

Study Variables and Definitions

Study variables included: demographics, questionnaire scores (ACQ, AQLQ), pulmonary function (forced vital capacity (FVC), Forced Expiratory Volume in first second (FEV_1), comorbidities, inflammatory markers (blood eosinophils, Fraction of exhaled nitric oxide (FeNO) total and specific IgE), exacerbation rate, asthma medication use, OCS use, OCS maintenance dose, (reasons for) discontinuation of reslizumab or switch from or to another biologic.

Severe asthma exacerbations were defined by at least one of the following criteria: 1) patient-reported use of OCS courses (if not on maintenance OCS); 2) patient-reported doubling of maintenance dose of OCS for at least 3 days; 3) patient-reported unscheduled emergency visits or hospitalization for asthma.

Maintenance OCS dose before reslizumab initiation (or before initiation of a previous biologic) was defined as the median daily dose of prednisolone equivalent (mg/day) within a period <1 month prior to initiation. Maintenance dose post-reslizumab was defined as the daily dose of prednisolone equivalents collected at a time point closest to ≥6 months after reslizumab initiation.

Statistical Analyses

Comparison of clinical outcomes pre- and post reslizumab initiation

Continuous variables were expressed as mean with standard deviation or median and interquartile range when applicable. Categorical variables were expressed in absolute numbers and/or percentages.

Variables were compared between pre reslizumab initiation (“start-reslizumab”) and after at least 6 months of reslizumab treatment (“after ≥6 month follow-up”), and between pre-initiation of another previous biological treatment (“start first biologic”) and switch to reslizumab treatment (“switch to reslizumab). Comparisons of exacerbation rate categories, proportion of OCS users, unscheduled emergency visits, hospitalizations and ICU admissions were performed using mixed effect (ordinal) logistic regression analysis using all available data. Wilcoxon-signed paired analysis test was used for comparisons of OCS maintenance dose. P-values less than 0.05 were considered statistically significant (two-sided). Statistical analysis was performed using Stata software (version 16 (StataCorp LLC, College Station, Texas)

Estimation of the proportion of patients who were reslizumab (non)responders
The number and proportion of reslizumab responders was calculated and categorized into the following mutually exclusive and exhaustive groups (see table 1): 1) Excellent response; 2) Good response; 3) Partial response; 4) Non-response/ treatment failure. Counts and percentages were used to describe each component following reslizumab treatment initiation.

Table 1. Quality of response to reslizumab*

Category	Definition
Excellent response	• Zero to one asthma exacerbations within 6 months post-reslizumab initiation AND • No maintenance OCS at 6 months post reslizumab initiation
Good response	• Ineligible for category 1 ("excellent response") • Zero to one asthma exacerbations within 6 months post-reslizumab initiation AND • ≥50% reduction in average maintenance OCS dose (mg/day) at 6 months post reslizumab initiation
Partial response	• Ineligible for categories 1 or 2 ("excellent response" or "good response") AND • Two to five asthma exacerbations within 6 months post-reslizumab initiation OR • Any reduction in average maintenance OCS dose (mg/day)
No-response/ treatment failure	Any of the following: • More than 5 asthma exacerbations within 6 months post-reslizumab initiation OR • no reduction in maintenance OCS dose (mg/day) OR • Discontinuation due to adverse events (AEs) at any time

*In RAPSODI, exacerbation frequency was classified in 3 categories: 0-1 exacerbations, 2-5 exacerbations and >5 exacerbations over the past year

Physicians' survey

Counts and percentages were used to describe the answers to each of the questions of the survey.

RESULTS

Recruitment

One hundred forty-two out of 702 patients included in the RAPSODI registry at 1 April 2020 had ever initiated reslizumab treatment between 1 January 2017 and 1 April 2020. Eight (6%) patients did not fulfill inclusion criteria (*i.e.* follow-up data ≥6 months).

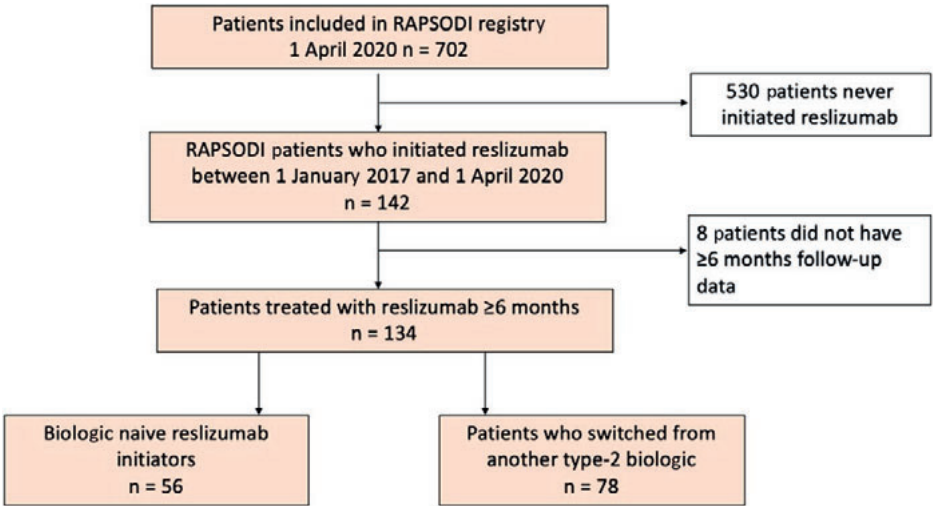

Figure 1. Flow chart. "Biologics naive reslizumab initiators" are patients who started reslizumab treatment as their first add-on biologic and "patients who switched from another type 2 biologic" are patients who started reslizumab treatment after cessation of another type 2 biologic.

Baseline characteristics

Table 2 summarizes baseline characteristics of 134 included patients at reslizumab initiation. Of note, 57.9% of reslizumab initiators used OCS on a daily base, 60% had used another type 2 biologic prior to reslizumab, 70.7% had adult-onset asthma, 42.5% were former smokers, and 92.5% had at least one comorbidity.

Table 2. Patients' baseline characteristics

Patient characteristics	Observations	
Age, mean (range)	134	53.4 (21-83)
Female sex, n (%)	134	65 (48.5)
BMI, mean (SD)	129	28.3 (5.9)
BMI<25	43	22.8 (1.9)
25≤BMI ≤30	45	27.4 (1.3)
BMI>30	41	35.0 (4.9)
Onset of asthma ≥18 yr, n (%)	133	94 (70.7)
Smoking status, n (%)	134	
Never smoker		77 (57.5)
Former smoker		57 (42.5)
Current smoker		0
Pack years, median (IQR)	127	0 (0-10)
High dose ICS,n (%)	131	111 (84.7)
LABA use,n (%)	131	126 (96.1)
LAMA use,n (%)	131	52 (39.6)
Anti-leukotriene use,n (%)	130	22 (16.9)
OCS exposure		
on OCS maintenance therapy, n (%)	133	77 (57.9)
OCS dose mg/day, median (IQR) (n=77)	74	10 (5-15)
Exacerbations (annual rate), n (%)	131	
0 to 1		52 (39.6)
2 to 5		51 (38.9)
More than 5		28 (21.4)
ICU admission previous year, n (%)	132	4 (3.0)
Hospital admission previous 3 months, n (%)	68	9 (13.2)
Unscheduled visits previous 3 months, n (%)	68	
0		57 (83.8)
1		9 (13.2)
2		2 (2.9)
ACQ score, mean (SD)	74	2.3 (1.2)
Well-controlled (ACQ ≤0.75)	74	6 (8.1)
Indeterminate (ACQ 0.76–1.49)		12 (16.2)
Not well-controlled (ACQ ≥1.50)		56 (75.7)
AQLQ score, mean (SD)	73	4.9 (1.3)
Pulmonary function		
FEV_1 in mL, mean (SD)	123	2452 (840)
FEV_1 %, mean (SD)		76.1 (21.2)
FVC in mL, mean (SD)	121	3910 (1165)
FVC in %, mean (SD)		97.8 (17.6)
FeNO in ppb, median (IQR)	107	35 (19-70)
Eosinophils, cells/µL, median (IQR)	120	305 (100-575)

Table 2. Continued.

Patient characteristics	Observations	
IgE kU/L, median (IQR)	97	135 (64-375)
Positive allergen specific IgE	82	43 (52.4)
Comorbidities	134	
Atopic dermatitis, n (%)		6 (4.5)
Allergic rhinoconjunctivitis, n (%)		14 (10.5)
Chronic rhinosinusitis, n (%)		51 (38.1)
Nasal polyposis, n (%)		37 (27.6)
Vocal cord dysfunction n (%)		3 (2.2)
Anxiety/depression, n (%)		14 (10.5)
Gastroesophageal reflux, n (%)		16 (11.9)
COPD, n (%)		0
Diabetes mellitus, n (%)		5 (3.7)
Chronic congestive heart failure, n (%)		1 (0.8)
Obstructive sleep apnea syndrome, n (%)		6 (4.5)
Obesity (BMI>30) n (%)		41 (30.5)
None of the above, n (%)		10 (7.5)
Biologics used prior to reslizumab	132	
Omalizumab, n (%)		3 (2.3)
Mepolizumab, n (%)		66(50)
Benralizumab, n (%)		8 (6.1)
Dupilumab, n (%)		1 (0.76)
none		54 (40.1)

Footnote Table 2: For unscheduled emergency visits, hospital admissions, asthma control questionnaire score (ACQ), and asthma related quality of life-score (AQLQ) data were missing because not all patients were able to enter data via the online platform PatientCoach. ICS=inhaled corticosteroids, LABA=long-acting beta-agonists, LAMA= long-acting muscarinic antagonist, OCS=oral corticosteroids. Definition for high dose ICS was ≥1000mcg/day fluticasone dipropionate equivalent.

Effect of reslizumab on exacerbation rate and maintenance OCS dose

The median (IQR) follow-up period after reslizumab initiation was 12 (12-14) months for all reslizumab initiators (n=134), 12 (12-12) months for biologic naive initiators (n=56) and 12 (12-15) months for patients who had used another type 2 biologic prior to reslizumab (n=78). This latter group had used their previous biologic type 2 treatment for at least 3 months (median (ICR) 9 (5-17) months) and had discontinued treatment after a lag time of 1.6 (1-5) months before initiating reslizumab. In all reslizumab initiators (n=134) reslizumab significantly reduced the annualized rate of exacerbations (OR (95%CI) 0.10 (0.05-0.21), p<0.001 (Figure 2A), as well as the median (95%CI) maintenance dose of OCS from 5.0 (0.0-10.0) to 0 (0.0-5.0) mg/day, p<0.001 (Table 3a). Significant effects in these variables were also observed in biologic naive reslizumab initiators (Figure 2B, Table 3b) and those who had switched from another biologic (Figure 2C, Table 3c).

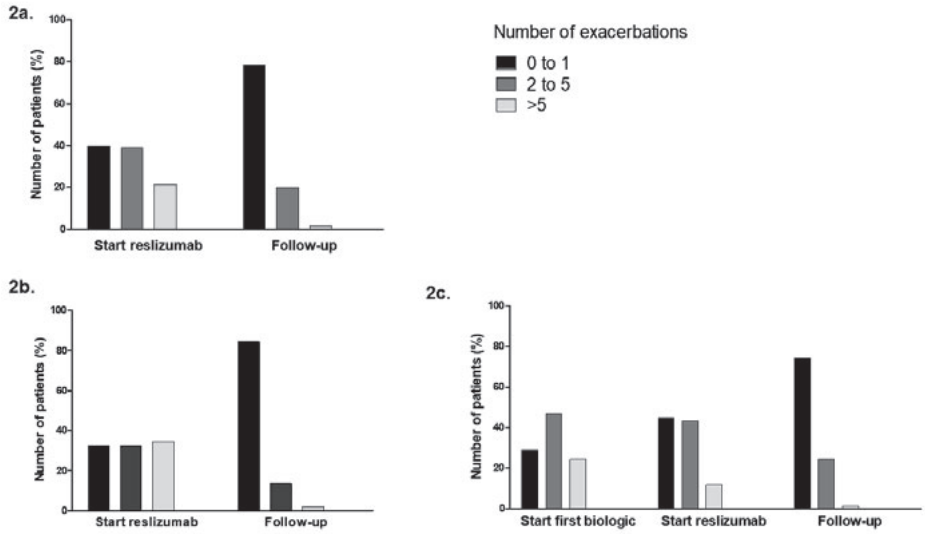

Figure 2. Effect of reslizumab on annualized exacerbation rate. The proportion of patients experiencing 0-1, 2-5 or >5 severe asthma exacerbations in all reslizumab users (Figure 2a), in the subgroup of patients who started with reslizumab as first biologic ("biologics naive reslizumab initiators") (Figure 2b), and in the subgroup of patients who started reslizumab after cessation of another type 2 biologic "switchers" (Figure 2c). Percentages are related to the number of patients in the same (sub)group.

Effect of reslizumab on OCS users, emergency visits, hospitalizations and ICU admissions

In all reslizumab initiators (n=134) the proportion of OCS-users decreased from 57.9% to 39.7% (OR (95%CI) 0.20 (0.08-0.48), p<0.001) (Table 3a). In biologic-naive reslizumab initiators (n=56) it decreased from 48.2% to 35.2% (0.11 (0.01-1.45), p=0.09) (Table 3b), and in switchers from another type 2 biologic (n=78) it decreased from 64.9% to 42.9% (0.23 (0.08-0.60), p=0.003) (Table 3c).

Unscheduled emergency visits and hospitalizations could only be analyzed in patients who filled out the online questionnaires (n=74). These patients appeared to have milder disease given the lower OCS maintenance dose, the lower exacerbation rate and the lower blood eosinophil count at reslizumab initiation (Table E1).

In these 74 patients the proportion with ≥1 unscheduled emergency visit decreased from 16.2% to 6.5% ((OR (95%CI) 0.06 (0.00-0.96), p=0.05) (Table 3a). Numbers of hospitalizations and ICU admissions were too small for reliable analyses. This was also true for secondary outcomes in the subgroups (Tables 3b, 3c)

Table 3a. Effect of reslizumab on exacerbation rate and OCS use

	Start reslizumab	After ≥6 months follow up	p-value
Exacerbations annual rate			p<0.001
0 to 1	52 (39.6)	98 (78.4)	
2 to 5	51 (38.9)	25 (20.0)	
More than 5	28 (21.4)	2 (1.6)	
Missing	3	9	
OCS maintenance dose (mg/day)			p<0.001
median (95%CI)	5.0 (0 -10.0)	0 (0 -5.0)	
Missing (n)	5	8	
On OCS maintenance therapy (%)			p<0.001
Yes, n (%)	77 (57.9)	52 (39.7)	
No, n (%)	56 (42.1)	79 (60.3)	
Missing (n)	1	3	
Unscheduled visits previous 3 months*			p=0.05
0	57 (83.8)	72 (93.5)	
1-2	11 (16.2)	5 (6.5)	
Missing (n)	66	57	
Patients hospitalized (previous 3 months)*			NS
Yes, n (%)	9 (13.2)	7 (9.1)	
No, n (%)	59 (86.8)	70 (90.9)	
Missing (n)	66	57	
Patients admitted to ICU (previous year)			NS
Yes, n (%)	4 (3.0)	2 (1.5)	
No, n (%)	128 (97.0)	128 (98.5)	
Missing (n)	2	4	

Footnote Table 3a: *only 74 of 134 patients filled out data in PatientCoach. ICU= Intensive Care Unit, NS= Not Significant, OCS=Oral Corticosteroids. Comparisons of exacerbation rate categories, proportion of OCS users, unscheduled emergency visits, hospitalizations and ICU admissions were performed using mixed effect (ordinal) logistic regression analysis using all available data. Wilcoxon-signed paired analysis test was used for comparisons of OCS maintenance dose.

Table 3b. Effect of reslizumab on primary outcomes in biologic naive reslizumab initiators (n=56)

	Start reslizumab	After ≥6 months follow up	p-value
Exacerbations annual rate			p<0.001
0 to 1, n (%)	18 (32.7)	43 (84.3)	
2 to 5, n (%)	18 (32.7)	7 (13.7)	
More than 5, n (%)	19 (34.6)	1 (2.0)	
Missing, n (%)	1	5	
OCS Maintenance dose (mg/day),			p=0.02
median (95 CI)	0 (0 - 10.0)	0 (0-5.0)	
missing, n	1	4	
On OCS maintenance therapy			p=0.09
Yes, n (%)	27 (48.2)	19 (35.2)	
No, n (%)	29 (51.8)	35 (64.8)	
Missing (n)	0	2	
Unscheduled visits previous 3 months*			NS
0	27 (90.0)	35 (97.2)	
1-2	3 (10.0)	1 (2.7)	
Missing (n)	26	20	
Patients hospitalized (previous 3 months)*			NS
Yes, n (%)	3 (10)	3 (8.3)	
No, n (%)	27 (90)	33 (91.7)	
missing, n	26	20	
Patients admitted to ICU (previous year)			NS
Yes, n (%)	2 (3.6)	1 (1.9)	
No, n (%)	54 (96.4)	52 (98.1)	
missing, n	0	3	

Footnote Table 3b: *only 34 of 56 patients filled out data in PatientCoach. ICU= Intensive Care Unit, NS= Not Significant, OCS=Oral Corticosteroids. Comparisons of exacerbation rate categories, proportion of OCS users, unscheduled emergency visits, hospitalizations and ICU admissions were performed using mixed effect (ordinal) logistic regression analysis using all available data. Wilcoxon-signed paired analysis test was used for comparisons of OCS maintenance dose.

Table 3c. Effect of reslizumab on primary outcomes in patients who had switched from another type 2 biologic (n=78)

	Start first biologic (B1)	"Switch" to reslizumab (B2)	6 months follow-up (FU)	p-value (B2-B1)	p-value (FU-B2)
Exacerbations annual rate				p<0.01	p<0.001
0 to 1, n (%)	19 (28.8)	34 (44.7)	55 (74.3)		
2 to 5, n (%)	31 (47.0)	33 (43.4)	18 (24.3)		
More than 5, n (%)	16 (24.2)	9 (11.8)	1 (1.3)		
Missing, n (%)	12	2	4		
OCS Maintenance dose (mg/day),				p=0.03	p<0.01
Median (95 CI)	10 (0 -15.0)	5.0 (0-10.0)	0 (0-5.5)		
Missing, n	19	4	4		
On OCS maintenance therapy				p=0.04	p<0.01
Yes, n (%)	54 (76.1)	50 (64.9)	33 (42.9)		
No, n (%)	17 (23.9)	27 (35.1)	44 (57.1)		
Missing (n)	7	1	1		
Unscheduled visits previous 3 months*				NS	p=0.07
0	17 (77.2)	30 (78.9)	37 (90.2)		
1-2	5 (22.7)	8 (21.1)	4 (9.8)		
Missing (n)	56	40	37		
Patients hospitalized (prev. 3 months)*				NS	NS
Yes, n (%)	2 (9.1)	6 (15.8)	4 (9.8)		
No, n (%)	20 (90.9)	32 (84.2)	37 (90.2)		
Missing, n	56	40	37		
Patients admitted to ICU (previous yr)				NS	NS
Yes, n (%)	7 (9.5)	2 (2.6)	1 (1.3)		
No, n (%)	67 (90.5)	74 (97.3)	76 (98.7)		
Missing, n	4	2	1		

Footnote Table 3c: *only 48 of 78 patients filled out data in PatientCoach. ICU= Intensive Care Unit, NS= Not Significant, OCS=Oral Corticosteroids. Comparisons of exacerbation rate categories, proportion of OCS users, unscheduled emergency visits, hospitalizations and ICU admissions were performed using mixed effect (ordinal) logistic regression analysis using all available data. Wilcoxon-signed paired analysis test was used for comparisons of OCS maintenance dose.

Effect of reslizumab on quality of treatment response

Table 4 and Figure 3 summarize the effect of reslizumab on quality of treatment response to reslizumab in all patients, biologic naive reslizumab initiators and switchers. Amongst biologic naive initiators 69.2% of patients showed good or excellent response and 9.6% did not improve; in the patients who had switched from another type 2 biologic 52.1% showed good or excellent response, and 16.4% showed no response. Comparison in treatment responses between the two subgroups showed a trend toward a worse response in switchers as compared to biologic naive initiators, OR (95%CI) 0.55 (0.28 – 1.09); p=0.09.

Table 4. Effect of reslizumab on quality of treatment response after ≥6 months

	All patients	**"Biologic naive initiators"**	**"Switchers"**
n	134	56	78
Treatment response			
Excellent, n (%)	65 (52.0)	31 (59.6)	34 (46.6)
Good, n (%)	9 (7.2)	5 (9.6)	4 (5.5)
Partial, n (%)	34 (27.2)	11 (21.2)	23 (31.5)
No response, n (%)	17 (13.6)	5 (9.6)	12 (16.4)
Missing, n	9	4	5

Footnote table 4: Excellent response: 0 to 1 clinical asthma exacerbations post-reslizumab initiation AND no maintenance OCS; Good response: Ineligible for category "Excellent response" AND 0 to 1 clinical asthma exacerbations AND ≥50% reduction maintenance OCS; Partial response: Ineligible for categories "excellent response" or "good response" AND 2 to 5 clinical asthma exacerbations OR any reduction OCS dose; No response: more than 5 clinical asthma exacerbations OR treatment discontinuation due to adverse events (AEs) OR no reduction OCS dose.

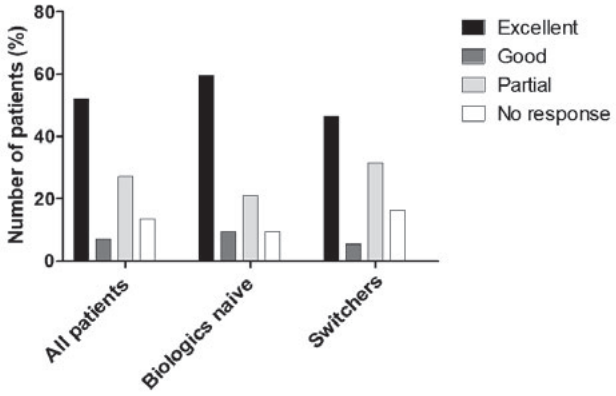

Figure 3. Effect of reslizumab on quality of treatment response after ≥6 months. Response to reslizumab treatment after ≥6-months of follow-up in all reslizumab users (n=134); in the subgroup of "biologics naive" reslizumab initiators (patients who started with reslizumab as their first add-on biologic, n=56) and in the subgroup of "switchers" (patients who started reslizumab after discontinuation of another type 2 biologic, n=78). Percentages relate to the number of patients in the same (sub)group. Excellent response: 0 to 1 clinical asthma exacerbations post-reslizumab initiation AND no maintenance OCS; Good response: Ineligible for category "Excellent response" AND 0 to 1 clinical asthma exacerbations AND ≥50% reduction maintenance OCS; Partial response: Ineligible for categories "excellent response" or "good response" AND 2 to 5 clinical asthma exacerbations OR any reduction OCS dose; "No response: more than 5 clinical asthma exacerbations OR treatment discontinuation due to adverse events OR no reduction OCS dose.

Results from physician's survey on reslizumab therapy

The survey responses are illustrated in Figures 4a-b, and E1-7. Ten (out of 13) physicians prescribing reslizumab as one of the five available type 2 add-on biologics for RAPSODI patients responded to the survey. None of the physicians prescribed reslizumab solely as first add-on treatment, 40% prescribed reslizumab solely as second or third add-on biologic, and 60% prescribed reslizumab both as first and second/third add-on biologic (Fig. E2). As a reason for prescribing reslizumab, 50% responded that they expected their patients to respond better to reslizumab than to the other type 2 biologics (Fig. 4a and E3). 90% of physicians were 'satisfied' or 'very satisfied' with reslizumab (Fig E5), and 80% found reslizumab to be of added value over the other biologics (Fig. 4b and E6).

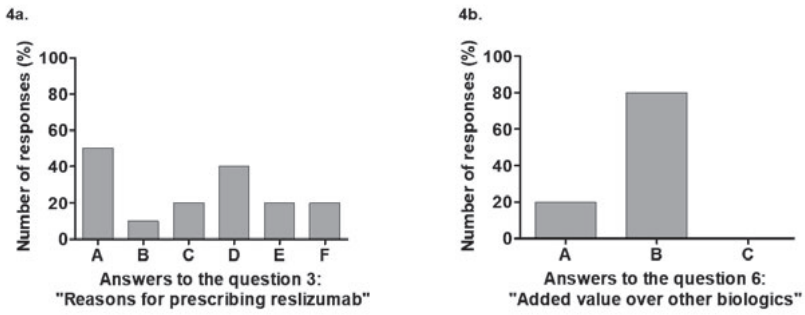

Figure 4. Physicians' experience with reslizumab use (anonymous survey). (A) Answers provided by the doctors to the question "What were your reasons for prescribing reslizumab?", multiple answers were possible. A: Compared to other biologicals, I expected a greater effect on prednisone withdrawal and/or exacerbations; B: Compared to other biologicals, I expected a greater effect on chronic sinusitis and nasal polyps; C: Compared to other biologicals, I expected fewer side effects; D: I found intravenous administration to be more reliable than subcutaneous administration; E: I wanted to gain experience with this drug; F: Other reason. (B) Answers provided by the doctors to the question "Do you think reslizumab has any added value over other asthma biologics?" A: No, not at all; B: Yes, a little; C: Yes, very much.

DISCUSSION

This real-world study in patients with severe eosinophilic asthma shows that reslizumab add-on treatment significantly reduced the rate of asthma exacerbations, the proportion of patients on maintenance OCS, as well as the dose of maintenance OCS. These beneficial effects were not only evident in patients receiving reslizumab as their first add-on biologic therapy, but also in those who previously failed on another type 2 biologic and switched to reslizumab. This additional beneficial effect of reslizumab over other type 2 biologics was confirmed by an anonymous survey among Dutch asthma experts treating patients with severe eosinophilic asthma. The included patients in this study were at the extreme end of asthma severity and complexity, given that the majority (58%) were OCS dependent and almost all (92%) suffered from comorbidities. Yet, only a small minority of patients (13.6%) did not improve with this therapy at all.

The present real-world study confirms and extends the results from randomized controlled trials and pre-post studies in patients with eosinophilic asthma (13,14) which showed that reslizumab reduces asthma exacerbations and oral corticosteroid use, and improves asthma control, lung function and rescue medication use.

Beneficial effects of reslizumab were also observed in two real-world studies. One such study reported results from 26 patients treated with reslizumab who were followed for 2 years (16). The study showed a sustained improvement in ACQ, a decrease in exacerbations rate and a reduction in OCS maintenance dose from reslizumab therapy. Another real-world study conducted in the US among 215 patients who initiated reslizumab showed a significant reduction in asthma symptoms, exacerbation rate, pulmonary function, and health care utilization after 6 months, with half of OCS-dependent patients being able to eliminate OCS after 10 months (17). Our study slightly differs from these studies because it not only included patients who received add-on therapy with reslizumab as their first type 2 biologic (biologic-naive patients) but also patients who were previously treated with another type 2 biologic but had to discontinue that treatment because of insufficient response or a serious adverse event. Remarkably, reslizumab treatment in the latter group showed an additional improvement in the rate of exacerbations and oral corticosteroid use, suggesting that reslizumab offered added value over previous type 2 biologics, including those targeting IL-5 in half of our patients.

Apart from the beneficial effects of reslizumab on exacerbation rate and OCS use our study shows some noteworthy results. First, many patients included in this real-world study had characteristics that differed from patients in the phase 3 trials, which would have precluded participation in these trials. For example, patients in our study could have a history of heavy smoking, serious comorbidities like cardiovascular diseases, maintenance OCS dosing above 30 mg/day, eosinophil counts <400 cells/μL or recent use of other type 2 biologics. Despite these differences in asthma population, the beneficial effects of reslizumab in the real world were largely comparable to those of the phase 3 trials. This suggests that in the real-world, reslizumab is effective even if the strict inclusion criteria of phase-3 trials are not entirely met.

Another noteworthy finding of this study is that patients who were prescribed reslizumab in the real-world appeared to have more severe asthma than those included in the phase-3 trials. For example, in our study 48% of patients receiving reslizumab as first add-on biologic therapy and 65% who used it as second or third add-on biologic used daily maintenance OCS versus only 12% and 19% in the two phase 3 trials (13). Of the 78 patients who had switched from another asthma biologic before initiating reslizumab, only 4 out of 78 (5%) patients had been able to stop OCS, while after switching to reslizumab an additional 21 (27%) patients could completely eliminate OCS. Also exacerbation rates and OCS maintenance dose were significantly further reduced after switching to reslizumab therapy. This suggests

that switching from another asthma biologic to reslizumab, even if targeting the same cytokine may be beneficial in some patients. Interestingly enough, this was also the opinion of 70% of the asthma experts regarding the effectiveness of reslizumab compared to other type 2 biologics. However, no definitive judgment can be made on differences in effectiveness between asthma biologics until head-to-head trials have been conducted.

Our study showed that patients who initiated reslizumab as their first biologic had better overall outcomes at ≥6 months compared to patients who had switched from another biologic. The most plausible explanation is that patients who switched were more likely to be OCS-dependent than biologically-naive patients, given the higher percentage of patients on maintenance OCS at the time of starting reslizumab treatment as well as the higher median maintenance doses of OCS, while the number of exacerbations was lower (Table E2).

Our study is unique in several respects. First, data in the multicenter Dutch RAPSODI registry are collected longitudinally in a standard way both by physicians and patients themselves, making this registry probably the best existing data source to conduct prospective real-world research on patients with severe asthma in the Netherlands. Second, we analyzed data from all 134 patients from this registry who ever initiated reslizumab and were followed for at least 6 months before the beginning of the COVID-19 pandemic. Since more than half of these patients had received reslizumab as second or third add-on asthma treatment, we were able to investigate whether or not switching from treatment with another asthma biologic to reslizumab would lead to further clinical improvement. Third, we added an anonymized physician survey to our study to verify whether asthma experts' real-world clinical experience with reslizumab was consistent with our study results. We considered this an important addition to a real-world study so that physicians' clinical impressions could be related to objective research data.

Our study also has several limitations that are inherent to the observational registry-based design of the study, such as the lack of a control group and possible hidden confounders. Further, for patient-reported outcomes many data were missing, which is not surprising, since patients were asked to enter this data themselves on a voluntary base via the PatientCoach platform. Therefore, although the numbers in the subgroups followed trends in the group as a whole, ultimately there were insufficient data to draw reliable conclusions regarding these patient-reported outcomes.

The findings of our study and the accompanying survey have both clinical and research implications. The observed additional effect of reslizumab as a second or third add-on treatment suggests that it may be worthwhile to switch patients who do not respond adequately to one specific type 2 biologic to a second add-on biologic, even if this second biologic acts on the same molecular pathway. Further research will have to determine whether an improved response after switching from one anti-IL-5 biologic drug to another is due to greater drug potency, better dosing, pharmacodynamics or pharmacokinetics, the type of antibody or target, or whether it is merely a consequence of a longer-term inhibition of the inflammatory process in the airways with equally effective agents.

In conclusion, this study has shown that also in a real-world setting, reslizumab is effective in reducing exacerbations and OCS use in patients with severe eosinophilic asthma. When given after switching from another asthma biologic, even if it targets the same cytokine, reslizumab appears to produce additional clinical improvement, which is also recognized by asthma specialists according to an anonymous survey.

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SUPPLEMENTARY MATERIALS

Supplementary file 1. Physicians' survey

Question 1: Have you ever prescribed reslizumab (Cinqaero) to your patients with severe asthma?
Yes -> proceed to question 2
No -> end of survey

Question 2: For which indication have you prescribed reslizumab for your patients?
a) Only as first choice add-on biologic
b) Only as 2nd or 3rd choice add-on biologic
c) Both first and 2nd or 3rd choice supplement biologic

Question 3: What were your reasons for prescribing reslizumab? *(Multiple answers possible)*
Compared to other biologicals, I expected a greater effect on prednisone withdrawal and/or exacerbations
Compared to other biologicals, I expected a greater effect on chronic sinusitis and nasal polyps
Compared to other biologicals, I expected fewer side effects
I found intravenous administration to be more reliable than subcutaneous administration
I wanted to gain experience with this drug
Other reason, namely…

Question 4: How satisfied were you with the overall effect of reslizumab as an add-on treatment?
Very dissatisfied
Dissatisfied
Neutral
Satisfied
Very satisfied

Question 5: How satisfied were/are your patients with reslizumab as an add-on treatment?
Very dissatisfied
Dissatisfied
Neutral
Satisfied
Very satisfied

Question 6: Do you think reslizumab has any added value over other asthma biologics?
No, not at all
Yes, a little
Yes, very much

Question 7: Will you be prescribing more reslizumab in the future?
Yes, most likely
No, most likely not

This is the end of the survey. Thank you for your cooperation!

Supplementary figures E1-E7. Physicians' experience with reslizumab use (all questions from the anonymous survey)

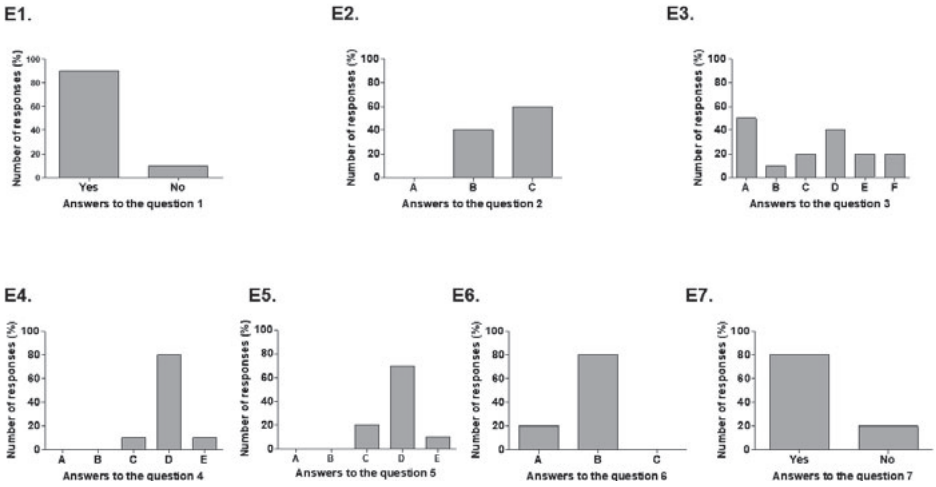


Figure E1. Answers provided by the doctors to the question "Have you ever prescribed reslizumab (Cinqaero) to your patients with severe asthma?". A: Yes; B: No. Figure E2. Answers provided by the doctors to the question "For which indication have you prescribed reslizumab for your patients?" A: Only as first choice add-on biologic; B: Only as 2nd or 3rd choice add-on biologic; C: Both first and 2nd or 3rd choice supplement biologic. Figure E3. Answers provided by the doctors to the question "What were your reasons for prescribing reslizumab?", multiple answers were possible. A: Compared to other biologicals, I expected a greater effect on prednisone withdrawal and/or exacerbations; B: Compared to other biologicals, I expected a greater effect on chronic sinusitis and nasal polyps; C: Compared to other biologicals, I expected fewer side effects; D: I found intravenous administration to be more reliable than subcutaneous administration; E: I wanted to gain experience with this drug; F: Other reason. Figure E4. Answers provided by the doctors to the question "How satisfied were you with the overall effect of reslizumab as an add-on treatment?" A: Very dissatisfied; B: Dissatisfied; C: Neutral; D: Satisfied; E: Very satisfied. Figure E5**.** Answers provided by the doctors to the question "How satisfied were/are your patients with reslizumab as an add-on treatment?" A: Very dissatisfied; B: Dissatisfied; C: Neutral; D: Satisfied; E: Very satisfied. Figure E6. Answers provided by the doctors to the question "Do you think reslizumab has any added value over other asthma biologics?" A: No, not at all; B: Yes, a little; C: Yes, very much. Figure E7. Answers provided by the doctors to the question "Will you be prescribing more reslizumab in the future?" A: Yes, most likely; B: No, most likely not.

Supplementary table E1. Patient characteristics of the whole group (n = 134) and of patients who entered data in PatientCoach (n = 74).

PATIENT CHARACTERISTICS	Whole group n=134		Patient-Coach n=74	
	Observations		Observations	
Age, mean (range)	134	53.4 (21-83)	74	53.7 (23-78)
Female sex, n (%)	134	65 (48.5)	74	36 (48.7)
BMI, mean (SD) –> n= 129	129	28.3 (5.9)	74	29.2 (6.1)
Onset of asthma ≥18 yr, n (%)	133	94 (70.7)	74	49 (66.2)
Smoking status, n (%)	134		74	
Never smoker		77 (57.5)		42 (56.8)
Former smoker		57 (42.5)		32 (43.2)
Current smoker		0		0
Pack years, median (IQR)	127	0 (0-10)	70	0 (0-10)
Exacerbations (annual rate) n (%)	131		73	
0 to 1		52 (39.6)		27 (37.0)
2 to 5		51 (38.9)		28 (38.4)
More than 5		28 (21.4)		18 (24.7)
ICU admission previous year, n (%)	132	4 (3.0)	74	3 (4.1)
Hospital admission previous 3 months, n (%)	68	9 (13.2)	66	8 (12.1)
ER visits last 3 months n (%)	68		66	
0		57 (83.8)		55 (83.3)
1		9 (13.2)		9 (13.6)
2		2 (2.9)		2 (3.03)
ACQ score, mean (SD)	74	2.3 (1.2)	74	2.8 (1.2)
Well-controlled (ACQ ≤0.75)	74	6 (8.1)	74	6 (8.1)
Indeterminate (ACQ 0.76–1.49)		12 (16.2)		12 (16.2)
Not well-controlled (ACQ ≥1.50)		56 (75.7)		56 (75.7)
AQLQ scores, mean(SD)	73	4.9 (1.3)	71	4.8 (1.3)
Pulmonary function				
FEV_1 in mL, mean (SD)	123	2452 (840)	71	2374 (830)
FEV_1 %, mean (SD)		76.1 (21.2)		74 (21.8)
FVC in mL, mean (SD)	121	3910 (1165)	70	3916 (1146)
FVC in %, mean (SD)		97.8 (17.6)		97.9 (16.7)

Supplementary table E1. Continued.

PATIENT CHARACTERISTICS	Whole group n=134		Patient-Coach n=74	
	Observations		Observations	
FeNO in ppb, median (IQR)	107	35 (19-70)	63	31 (19-55)
Eosinophils, cells/µL, median (IQR)	120	305 (100-575)	72	250 (90-560)
IgE kU/L, median (IQR)	97	135 (64-375)	58	129 (64-366)
Positive allergen specific IgE	82	43 (52.4)	45	24 (53.3)
Comorbidities	134		74	
Atopic dermatitis, n (%)		6 (4.5)		4 (5.4)
Allergic rhinoconjunctivitis, n (%)		14 (10.5)		10 (13.5)
Chronic rhinosinusitis, n (%)		51 (38.1)		31 (41.9)
Nasal polyposis, n (%)		37 (27.6)		22 (29.7)
Vocal cord dysfunction n (%)		3 (2.2)		2 (2.7)
Anxiety/depression, n (%)		14 (10.5)		7 (9.5)
Gastroesophageal reflux, n (%)		16 (11.9)		10 (13.5)
COPD, n (%)		0		0
Diabetes mellitus, n (%)		5 (3.7)		3 (4.1)
Chronic congestive heart failure, n (%)		1 (0.8)		1 (1.4)
Obstructive sleep apnea syndrome, n (%)		6 (4.5)		4 (5.4)
Obesity n (%)		12 (9.0)		8 (10.8)
None of the above, n (%)		10 (7.5)		3 (4.1)
OCS exposure	133		74	
on maintenance therapy, n (%)	129	77 (57.9)	74	39 (52.7)
dose mg/day, median (IQR)		5 (0-10)		1.25 (0-10)

Supplementary table E1. Continued.

PATIENT CHARACTERISTICS	Whole group n=134		Patient-Coach n=74	
	Observations		Observations	
Biologics used prior to reslizumab	132		74	
Omalizumab, n (%)		3 (2.3)		2 (2.7)
Mepolizumab, n (%)		66 (50)		33 (44.6)
Benralizumab, n (%)		8 (6.1)		5 (6.7)
Dupilumab, n (%)		1 (0.76)		1 (1.4)
none		54 (40.1)		33 (44.6)

Abbreviations: ACQ, Asthma Control Questionnaire; IQR, interquartile range; OCS, oral corticosteroids.

Supplementary table E2. Baseline characteristics of biologic-naive reslizumab initiators and switchers.

PATIENT CHARACTERISTICS	n	Naive initiators	n	Switchers
Age, mean (range)	56	53.9 (1.60)	78	52.8 (1.67)
Female gender, n (%)	56	29 (51.8)	78	36 (46.2)
BMI, mean (SD) –> n= 129	56	28.9 (0.75)	73	27.9 (0.71)
BMI<25		15 (26.8)		28 (38.4)
25≤BMI ≤30		17 (30.4)		28 (38.4)
BMI>30		24 (42.8)		17 (23.2)
Onset of asthma ≥18 yr, n (%)	56	38 (67.9)	78	56 72.7)
Smoking status, n (%)	56		78	
Never smoker		29 (51.8)		48 (61.5)
Former smoker		27 (48.2)		30 (38.5)
Current smoker		0		0
Pack years, median (IQR)	56	0 (0-12)	78	0 (0-12)

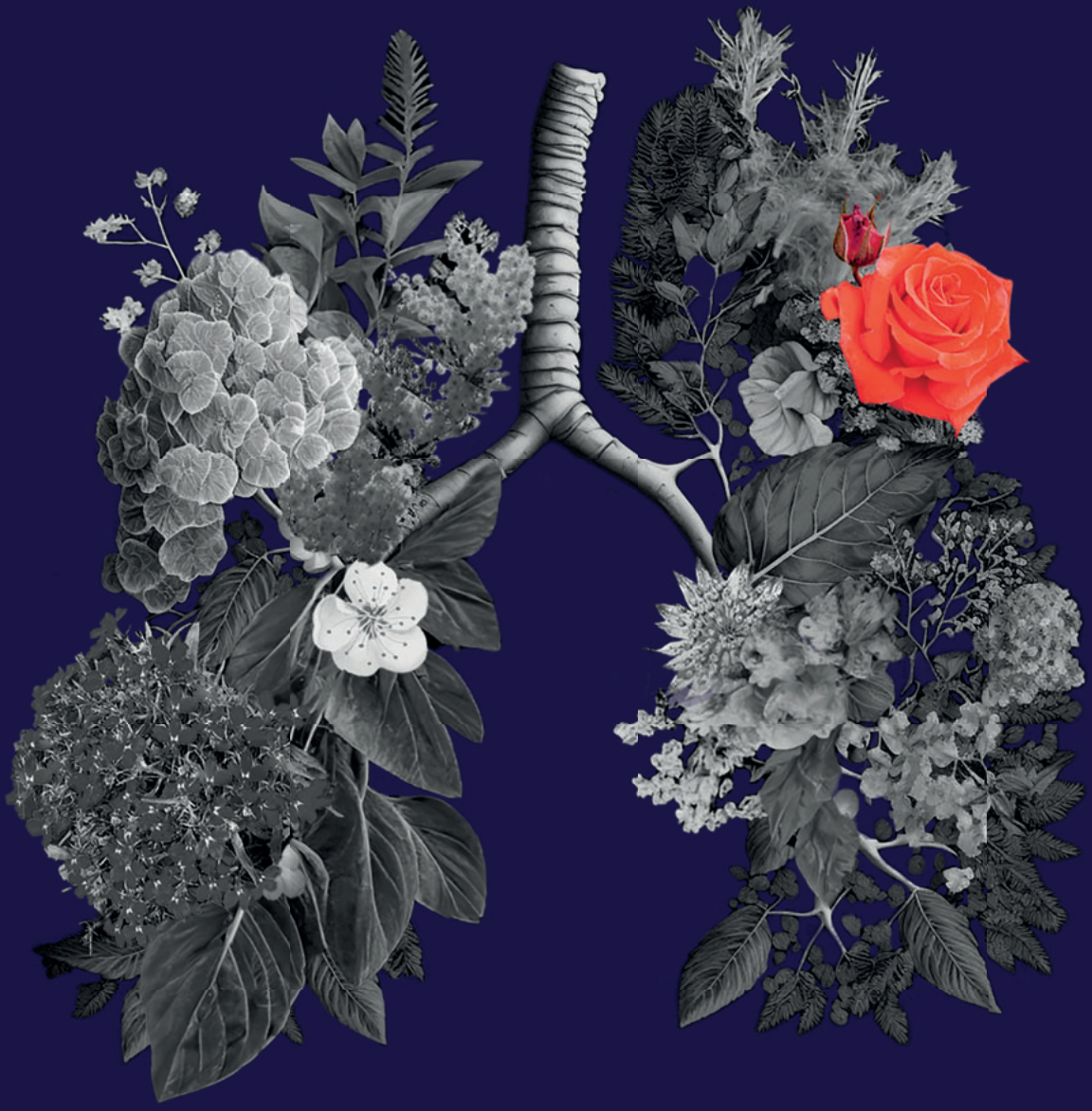
Supplementary table E2. Continued.

PATIENT CHARACTERISTICS	n	Naive initiators	n	Switchers
High dose ICS	55	45	76	66
LABA use	55	53	76	73
LAMA use	55	21	76	31
Anti-leukotriene use	55	11	75	11
Exacerbations (annual rate) n (%)	55		76	
0 to 1		18 (32.7)		34 (44.7)
2 to 5		18 (32.7)		33 (34.4)
More than 5		19 (34.6)		9 (11.8)
ICU admission previous year, n (%)	56	2 (3.57)	76	2 (2.63)
Hospital admission previous 3 months, n (%)	56	3 (10)	76	6 (15.8)
ER visits last 3 months n (%)	56		76	
0		27 (90)		30 (79.0)
1		3 (10)		6 (15.8)
2		0		2 (5.26)
ACQ score, mean (SD)	34	2.14 (0.19)	40	2.39 (0.21)
Well-controlled (ACQ ≤0.75)	34	2 (5.9)	40	4 (10)
Indeterminate (ACQ 0.76–1.49)		6 (17.7)		6 (15)
Not well-controlled (ACQ ≥1.50)		26 (76.5)		30 (75)
AQLQ scores, mean(SD)	31	4.93 (0.21)	42	4.83 (0.15)
Pulmonary function	55		68	
FEV_1 in mL, mean (SD)		2486 (802)		2428 (874)
FEV_1 %, mean (SD)	54	78.5 (21.2)	67	74.1 (21.11)
FVC in mL, mean (SD)		3998 (1179)		3840 (1158)
FVC in %, mean (SD)		101.2 (17.2)		95.0 (17.5)
FeNO in ppb, median (IQR)	50	30 (18-64)	57	42(26-80)

Supplementary table E2. Continued.

PATIENT CHARACTERISTICS	n	Naive initiators	n	Switchers
Eosinophils, cells/µL, median (IQR)	54	455 (250-620)	66	165 (40-400)
IgE kU/L, median (IQR)	53	135 (55-366)	44	130 (71-378)
Positive allergen specific IgE, n (%)	47	25 (53)	35	18 (51%)
Comorbidities	56		78	
Atopic dermatitis, n (%)		6 (10.7)		6 (7.6)
Allergic rhinoconjunctivitis, n (%)		21 (37.5)		15 (19.2)
Chronic rhinosinusitis, n (%)		38 (67.8)		49 (62.8)
Nasal polyposis, n (%)		28 (50.0)		37 (47.4)
Vocal cord dysfunction n (%)		1 (1.7)		1 (1.2)
Anxiety/depression, n (%)		6 (10.7)		14 (17.9)
Gastroesophageal reflux, n (%)		12 (21.4)		15 (19.2)
COPD, n (%)		0 (0)		0 (0)
Diabetes mellitus, n (%)		2 (3.5)		5 (6.4)
Chronic congestive heart failure, n (%)		1 (1.7)		0 (0)
Obstructive sleep apnea syndrome, n (%)		5 (8.9)		8 (10.2)
Obesity (BMI>30), n (%)		24 (42.8)		17 (23.2)
None of the above, n (%)		7 (12.5)		10 (12.8)
OCS exposure	56		77	
on maintenance therapy, n (%)	55	27 (48.2)	74	50 (64.9)
dose mg/day, median (IQR)		10 (5-10)		10 (5-15)

Abbreviations: ACQ, Asthma control questionnaire; BMI, body mass index; IQR, interquartile range.
For unscheduled emergency visits, hospital admissions, ACQ, and Asthma-Related Quality of Life score data were missing because not all patients were able to enter data via the online platform (PatientCoach). The definition for high-dose inhaled corticosteroids was ≥1,000 µg/d fluticasone dipropionate equivalent.



Chapter 4

Cumulative Corticosteroid Sparing Effect Of Anti-Interleukin-5/5Ra In Eosinophilic Asthma.

J.A. Kroes, S.W.J. Zielhuis, K. de Jong, S. Hashimoto, J.K. Sont, S.W. Zielhuis, E.N. van Roon, E.H. Bel, A. ten Brinke, on behalf of the RAPSODI consortium

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ABSTRACT

Introduction

Anti-interleukin-5/5Ra therapy has shown to reduce maintenance oral corticosteroid dose in severe eosinophilic asthma. However, the effect on cumulative oral corticosteroid exposure is currently unknown. Neither is it known how prior oral corticosteroid exposure affects response to anti-interleukin-5/5Ra treatment. We aimed primarily to compare the cumulative oral corticosteroid exposure over a 2-year period before and after anti-interleukin-5/5Ra initiation, and secondarily to investigate whether duration and cumulative oral corticosteroid exposure prior to anti-interleukin-5/5Ra influence the ability to discontinue oral corticosteroids within 2 years of anti-interleukin-5/5Ra therapy.

Methods

This real-world nationwide observational registry-based study evaluated all dispensed oral corticosteroids from 389 adults with severe eosinophilic asthma included in the Dutch severe asthma registry (RAPSODI) 2 years before and 2 years after initiating anti-interleukin-5/5Ra. Wilcoxon-signed rank test and multivariable regression analyses were used.

Results

Median (IQR) cumulative oral corticosteroid exposure in the 2 years before and after anti-interleukin-5/5Ra initiation decreased from 2.715 g (1.150-5.539) to 1.050 g (0.300-3.640), $p<0.001$. Fifty-two percent of patients were able to discontinue oral corticosteroids within 2 years anti-interleukin-5/5Ra therapy, which was independently predicted by lower and shorter prior oral corticosteroid exposure.

Conclusion

This real-world study showed that anti-interleukin-5/5Ra therapy leads to a significant reduction in cumulative oral corticosteroid exposure over a 2-year period. Patients with lower and shorter oral corticosteroids exposure were more likely to completely eliminate oral corticosteroids. Since cumulative exposure increased progressively prior to anti-interleukin-5/5Ra initiation, our data suggest that early intervention leads to a better long-term prognosis in patients with severe eosinophilic asthma.

INTRODUCTION

Severe asthma is a debilitating form of asthma that is refractory to regular inhaled preventer therapy.[1,2] The majority of patients with severe asthma present with an eosinophilic phenotype, which is characterized by extensive eosinophilic inflammation in the airways[3], associated with ongoing asthma symptoms, poor quality of life and severe and potentially fatal exacerbations that can only be controlled by recurrent or daily use of oral corticosteroids (OCS).[4-6] Since its introduction in the early 1950's the long-term use of systemic glucocorticoids is known to be associated with a multitude of serious adverse effects including diabetes, cardiovascular disease and immunosuppression.[7] These co-morbidities are associated with increased morbidity and mortality rates and high costs for the society.[8] Studies have shown that OCS-related adverse effects are dose dependent and associated with the cumulative OCS exposure rather than the mean daily dose of OCS.[9,10]

After decades of unsuccessful searches for oral corticosteroid-sparing treatments, a breakthrough has finally come in recent years with the availability of biologics, in particular biologics targeting Interleukin (IL)-5, the major cytokine responsible for recruitment and activation of eosinophils.[11] Three biologics targeting the IL-5/5Ra pathway (mepolizumab, reslizumab and benralizumab) are currently approved for treatment of patients with severe eosinophilic asthma, resulting in significant reductions in the rate of severe asthma exacerbations and the daily maintenance dose of OCS.[12-17]

Randomized controlled trials evaluating the effect of anti-IL-5/5Ra biologics on OCS use have evaluated the effect on the daily maintenance dose of OCS at 24-28 weeks.[13,16] Recently, the PONENTE trial demonstrated the effectiveness of anti-IL-5Ra in safely reducing the maintenance OCS using a personalized algorithm.[18] However, the cumulative OCS dose over a longer period before and after anti-IL-5/5Ra initiation is unknown. Also, the pattern and course of OCS exposure before starting anti-IL-5/5Ra treatment has never been explored. Finally, while the predictive value of mean baseline OCS dose on the response to anti-IL-5Ra has been previously established, it is not known whether the duration and extent of OCS use prior to biologic initiation influence the ability to completely eliminate the use of OCS.[19] Answering these questions is important, as it can help doctors predict whether biologics treatment will be effective for a particular patient with severe asthma or not, and it can inform patients what to expect from such treatment.

The present real-life study used patient data from the Dutch Severe Asthma Registry RAPSODI, included between 1 December 2015 and 1 January 2019 with 2 year follow-up data. The primary aim of the study was to compare the cumulative exposure of OCS over a 2-year period prior to and after initiation of treatment with anti-IL-5/5Ra biologics for a nationwide population. Secondarily we studied the cumulative OCS exposure in patients with different durations of previous OCS use and investigated whether the duration of previous OCS use and cumulative exposure predict the ability to stop OCS within 2 years after starting treatment with biologics.

METHODS

Study design and patient population

This was a nationwide, multicentre observational registry-based real-world population study. The study population consisted of patients with severe asthma included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI) which contains patient-level data on patients with severe asthma from 19 Dutch hospitals. We selected and included all patients who initiated an anti-IL-5/5Ra biologic (mepolizumab, reslizumab or benralizumab) between 1 December 2015 and 1 January 2019 and who were followed for at least 24 months after initiation of this anti-IL-5/5Ra biologic. Inhaled medication doses and inhaler technique were optimized before initiating anti-IL-5/5Ra treatment, in concordance with the Dutch Severe Asthma Guidelines.[20] Patients were excluded if they were lost to follow-up or if they had inflammatory comorbidities (e.g. Crohn's disease, Rheumatoid Arthritis) to ensure that all OCS were prescribed for the treatment of severe asthma, preventing possible confounding. Informed consent for this study was collected at registry-enrolment. A medical ethics committee approved the study. The study was registered in the Netherlands Trial Register (registration number: NL9041).

Measurements

Baseline characteristics at the moment of anti-IL-5/5Ra initiation were collected from the RAPSODI registry. Baseline data included: Clinical characteristics (patient demographics, asthma duration, smoking history, year of anti-IL-5/5Ra initiation), surrogate inflammatory markers (peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO), receiving OCS maintenance treatment, OCS maintenance dose, number of exacerbations in 12 months before anti-IL-5/5Ra initiation), lung function measurements (FEV_1), and comorbidities (nasal polyposis, adrenal insufficiency).

In addition, dispensing data of systemic corticosteroids (ATC-code H02AB) during 24 months before and 24 months after anti-IL-5/5Ra initiation were requested from each patient's pharmacy. Dutch pharmacies have access to all dispensed medication for reasons of medication surveillance and reimbursement. To ensure that medication possibly dispensed at other pharmacies was captured, researchers made sure the patient consented to the Dutch National Exchange Point.[21] OCS exposure was expressed in prednisone equivalents. In the Netherlands, medication is dispensed for a maximum period of 3 months, therefore, in addition to the total OCS exposure over 24 months, the cumulative OCS exposure was expressed in 3-months periods.

To study cumulative OCS exposure in patients with different durations of OCS use, patients were divided into 3 subgroups: 1) patients with first OCS dispensed <12 months before initiation of an anti-IL-5/5Ra biologic, 2) patients with first OCS dispensed between 12 and 21 months before initiation of an anti-IL-5/5Ra biologic and 3) patients with first OCS dispensed >21 months before initiation of an anti-IL-5/5Ra biologic. To investigate what proportion of patients was able to completely eliminate OCS after initiation of an anti-IL-5/5Ra biologic, patients were subdivided into 2 subgroups: those with and those without any OCS dispensed during the 18-24 months after initiating an anti-IL-5/5Ra biologic.

Statistical analysis

Continuous variables were expressed as medians (IQR) and categorical variables as percentages. Normality was assessed using the Kolmogorov-Smirnov test. The cumulative OCS exposures over 24 months prior to and after initiating anti-IL-5/5Ra treatment were compared using the Wilcoxon signed-rank test. Bar charts were used to illustrate cumulative OCS exposure over 24 months and cumulative OCS exposures in 3 monthly-periods in all patients, and in subgroups of patients with different duration of OCS exposure (≤12 months, 12-21 months and >21 months). To visually compare the patterns of cumulative OCS use over time between these subgroups, we standardized the cumulative 3-monthly OCS doses to those of 100 patients.

The reduction of cumulative OCS exposure after initiating anti-IL-5/5Ra was calculated as percentage change from the exposure 0-3 month prior to anti-IL-5/5Ra initiation. OCS exposure post anti-IL-5/5Ra initiation was calculated per 3-month period, and illustrated in a line-chart.

To explore baseline variables associated with complete elimination of OCS within 2 years after anti-IL-5/5Ra initiation, binary logistic regression analysis was used. First univariately associated factors (P-value <0.1) were entered into a multivariable logistic regression model. Second, non-significant variables (P-value ≥0.05) were removed using backward elimination. Factors independently associated with discontinuation of OCS within 2 years were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). In the analysis, the following contrasts were considered: Blood eosinophils <0.150*10^9cells/L, ≥0.150-0.300*10^9cells/L, ≥0.300-0.450*10^9cells/L, ≥0.450*10^9cells/L, FeNO <25 ppb, 25-50 ppb and ≥50 ppb, FEV_1 predicted pre-bronchodilator <80% and ≥80%, Start year of anti-IL-5/5Ra treatment 2015-2016, 2017 and 2018, first OCS exposure before anti-IL-5/5Ra ≤12 months, 12-21 months and >21 months, receiving OCS maintenance and without OCS maintenance before anti-IL-5/5Ra initiation. The cumulative OCS dose 2 years before anti-IL-5/5Ra was divided into quartiles ranging from lowest (quartile 1) to highest (quartile 4) OCS dose. The cumulative OCS dose 3 months before anti-IL-5/5Ra initiation was similarly analysed using quartiles.

All study-eligible patients in the registry were enrolled in the data-analysis. Therefore, no sample size calculation was performed.

A P-value <0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 26.0.

RESULTS

Patients

Of the RAPSODI registry containing 878 patients on 1st January 2021, 462 patients initiated anti-IL-5/5Ra biologic (mepolizumab, reslizumab or benralizumab) before 1st January 2019 and were followed for ≥2 years. Data from 389 patients were used in the analysis, as shown in Figure 1.

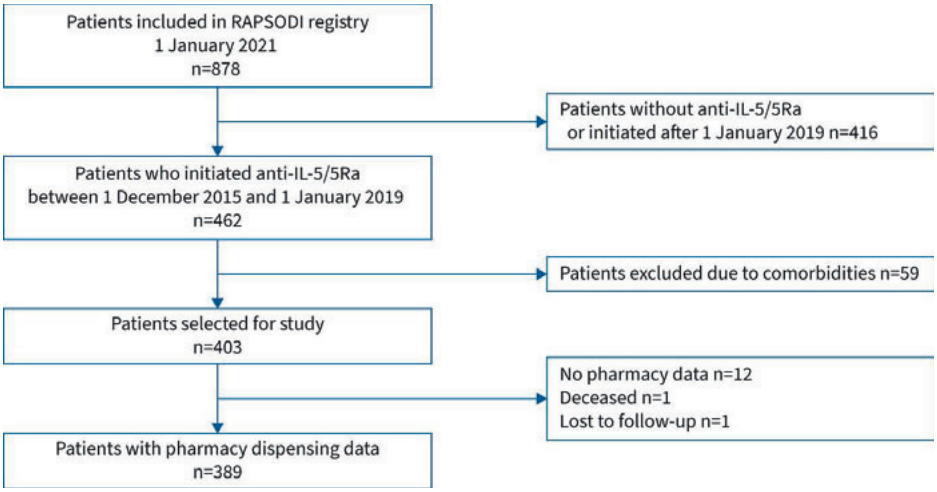

Figure 1: Flow chart of selected patients.

The characteristics of included and excluded patients are compared in Supplementary Table S1. These groups did not differ. Table 1 shows the characteristics of the patients at anti-IL-5/5Ra initiation. Of note, 75.6% of the patients developed asthma as an adult, 41.9% were former smokers, and 57.8% received maintenance OCS treatment. Information on comorbidities is demonstrated in Supplementary Table S2.

Table 1. Patients' baseline characteristics

Patient characteristic	**N=389**
Age (y)*	57 (48-64)
Gender; male, %	45.5
Body mass index (kg/m²)*	27.3 (24.3-29.9)
Former smoker, %	42
Pack years (y)*	10 (5-20)
Age of onset of eosinophilic asthma (y)*	44 (23-53)
Late onset asthma, %	75.6
Non-atopic asthma, %	53.4
Nasal polyposis, %	50.6
Adrenal insufficiency, % †	1.5
Number of exacerbations in previous year, %	
0-1 Exacerbations	23.4
2-5 Exacerbations	56.1
>5 Exacerbations	20.5
OCS maintenance, %	57.8

Table 1. Continued.

Patient characteristic	N=389
OCS maintenance dose (mg/day)*	10 (6.3-15)
Blood eosinophils (*10^9/L)*	0.42 (0.20-0.67)
Blood eosinophils in categories (*10^9/L), %	
<0.150	20.6
≥0.150-0.300	13.6
≥0.300-0.450	18.7
≥0.450	47.1
FeNO (ppb)*	40 (24-76)
FEV_1 (%predicted)*	76 (61-90.5)
Cumulative OCS 2 years before anti-IL-5/5Ra (g)*	2.7 (1.2-5.5)
Cumulative OCS 3 months before anti-IL-5/5Ra (g)*	0.45 (0.013-0.90)
Start year of anti-IL-5/5Ra therapy, %	
2015-2016	28.3
2017	33.7
2018	38.0
First OCS exposure before anti-IL-5/5Ra therapy, %	
≤12 months	16.7
12-21 months	28.0
>21 months	55.3

Abbreviations: FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, IQR: interquartile range, OCS: Oral corticosteroids (prednisone equivalents) *: median (IQR), †: underreported in this study.

Change in cumulative OCS exposure

Overall cumulative OCS exposure standardized to 100 patients over 24 months before and 24 months after initiating anti-IL-5/5Ra add-on treatment is illustrated in Figure 2. The median (IQR) cumulative OCS dose in the 2 years before and after anti-IL-5/5Ra initiation decreased from 2.715 g (1.150-5.539) to 1.050 g (0.300-3.640) respectively, p<0.001.

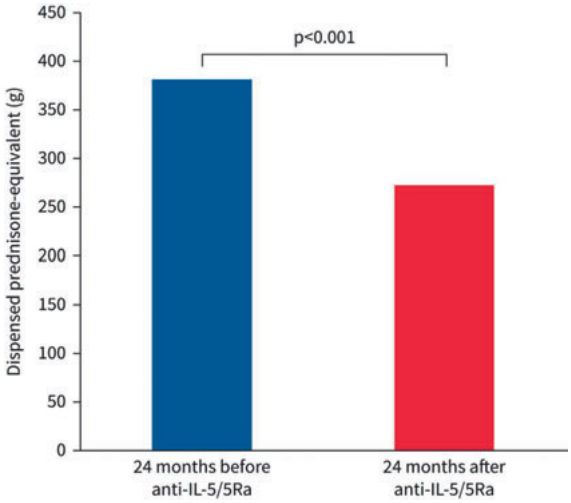

Figure 2: Cumulative oral corticosteroid exposure 24 months before and after initiating anti-interleukin-5/5Ra. This figure shows the cumulative oral corticosteroid exposure standardized to 100 patients (N=389) expressed in dispensed prednisolone equivalents in grams over the 2 years before and after anti-interleukin-5/5Ra initiation. The exposure decreased significantly, p<0.001.

Figure 3 illustrates OCS exposure standardized to 100 patients for 24 months before and 24 months after initiation of anti-IL-5/5Ra add-on therapy, expressed as dispensed prednisone equivalents (in grams) per 3 month periods. In the years prior to initiating anti-IL-5/5Ra therapy, OCS exposure steadily increased. A rapid and significant reduction of OCS exposure was observed after initiating anti-IL-5/5Ra therapy, but OCS exposure was not eliminated in all patients.

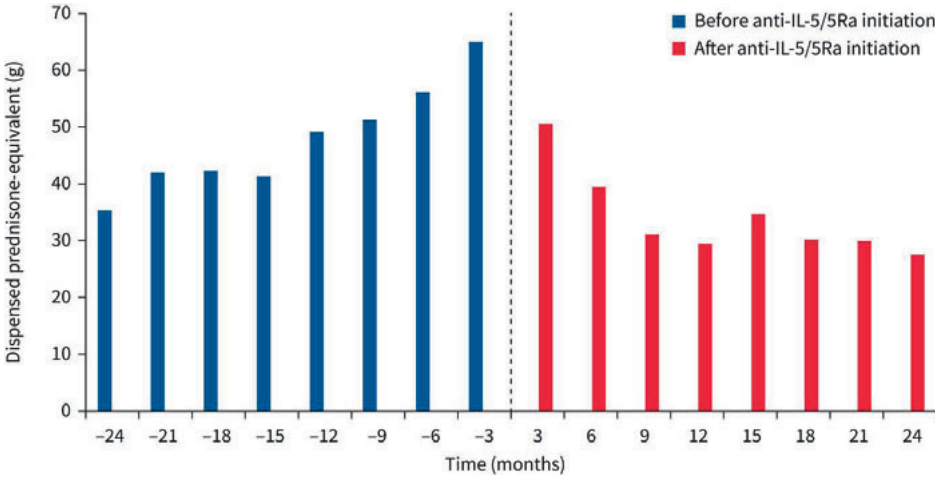

Figure 3: Course of cumulative oral corticosteroid exposure 24 months before and after initiating anti-interleukin-5/5Ra**.** This figure shows the cumulative oral corticosteroid exposure in dispensed prednisolone equivalents in grams 24 months before and after initiating anti-interleukin-5/5Ra (dotted line), expressed per 3 months, standardized to 100 patients (N=389). Over the 24 months pre anti-interleukin-5/5Ra initiation, the oral corticosteroid dose per 3 months increases by 84%. An oral corticosteroid maintenance dose of 5 mg/day equals 0.45 g per 3 months, a 7 day oral corticosteroid course equals 0.21 g.

Figure 4 A-C illustrates OCS exposure for 24 months before and 24 months after initiation of anti-IL-5/5Ra add-on therapy, expressed as dispensed prednisone equivalents (in grams) per 3-month periods in 3 subgroups with different OCS exposure times: <12 months, 12-21 months and >21 months before initiation of an anti-IL-5/5Ra biologic. OCS exposures were standardized to groups of 100 patients for reasons of comparability between groups. The data show that the longer the period of OCS exposure, the higher the 3-month cumulative OCS exposure. In addition, it shows that the longer and higher the exposure before initiation of anti-IL-5/5Ra therapy, the higher the cumulative OCS use after 2 years of anti-IL-5/5Ra therapy. The proportion of patients requiring OCS dispensing after initiating anti-IL-5/5Ra, subdivided in duration subgroups, is displayed in Supplementary Figure 1.

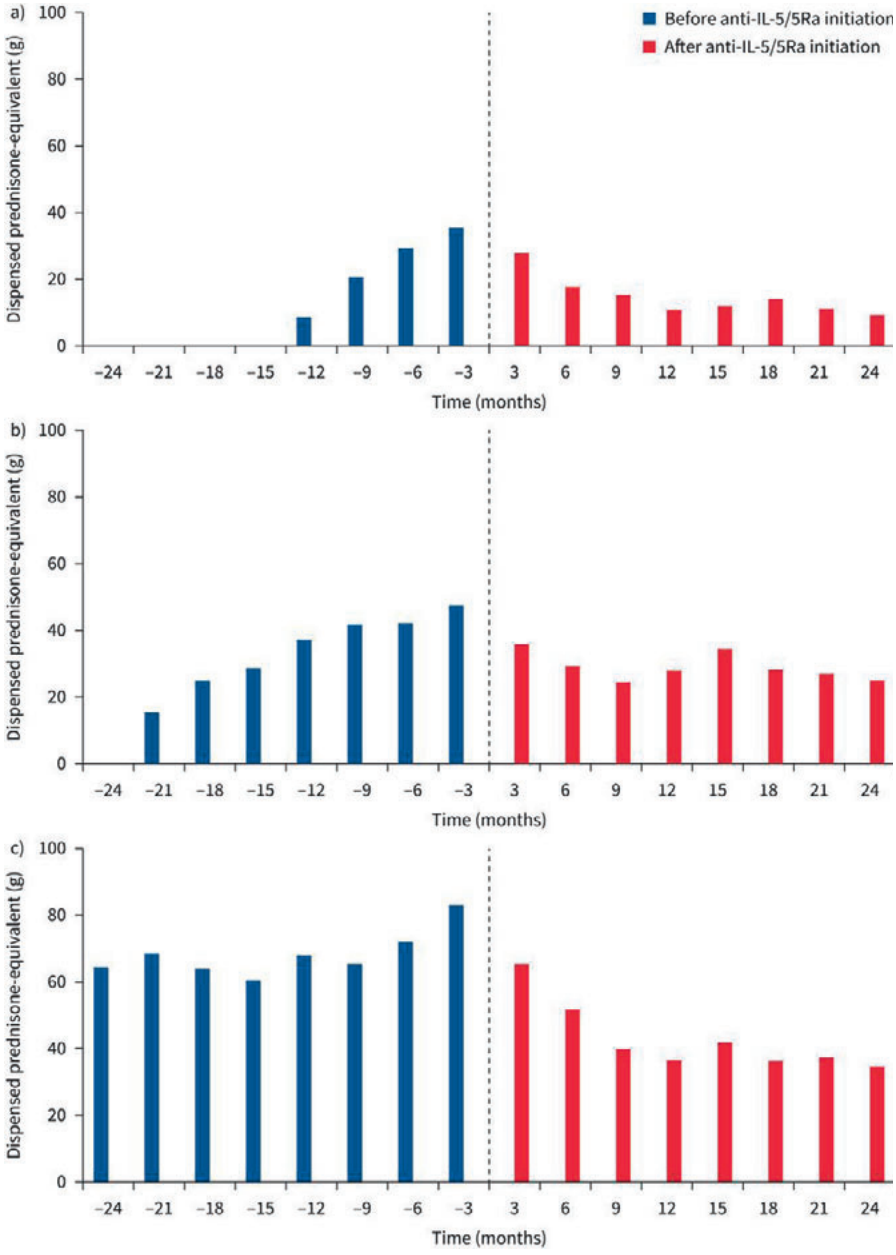

Figure 4: Cumulative oral corticosteroid (OCS) exposure in dispensed prednisolone-equivalent 24 months before and after initiating anti-IL-5/5Ra (dotted line), expressed per 3 months, standardised to 100 patients: patients with first OCS exposure a) ≤12 months (n=65), b) >12–21 months (n=109) and c) >21 months (n=215) before anti-IL-5/5Ra.

Ability to stop OCS after initiating anti-IL-5/5Ra therapy

Figure 5 shows the median change (%) in cumulative OCS dose after anti-IL-5/5Ra initiation compared to the 3 months before anti-IL-5/5Ra initiation. Six months after anti-IL-5/5Ra initiation, the median OCS exposure per 3-month period was reduced to 0.126 g (IQR 0-0.591), a reduction of 66% compared to the 3-months period before initiation of anti-IL-5/5Ra ($p<0.001$). Beyond 6 months, the median reduction continued and reached 100% after 15 months. Fifty-two percent of the population (202 patients) were able to discontinue OCS within 2 years of anti-IL-5/5Ra therapy. The baseline median OCS maintenance dose did not differ between patients able or unable to discontinue OCS within 2 years of anti-IL-5/5Ra treatment (10 (7.5-15) mg/day *vs.* 10 (5-11.3) mg/day, p=0.132)

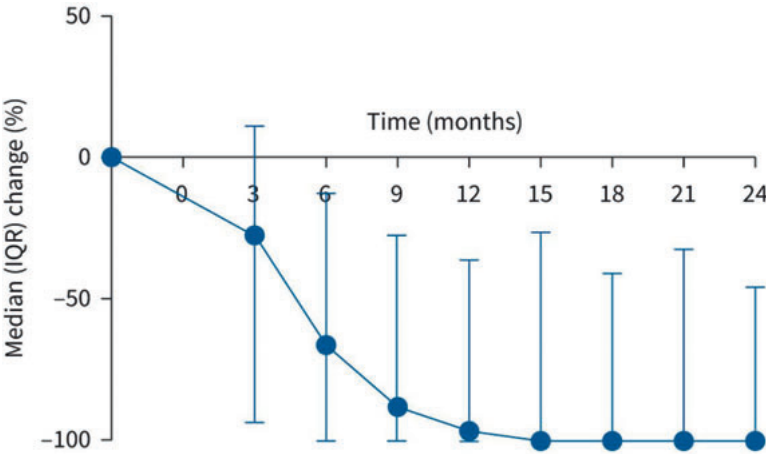

Figure 5. Change in cumulative dose of oral corticosteroid expressed in 3-monthly periods. Median (IQR) change (%) in oral corticosteroid exposure after anti-interleukin-5/5Ra initiation (T=0), per 3 months, compared to 3 months before anti-interleukin-5/5Ra (N=389).

Predictors of ability to stop OCS use

Univariate and multivariable significant predictors of OCS discontinuation within 2 years are described in Table 2. All variables that were examined are described in Supplementary Table S3. Three variables independently predicted the ability of OCS-discontinuation: 1) lower total OCS exposure over 24 months before anti-IL-5/5Ra initiation, 2) shorter duration of OCS exposure, and 3) later year of starting anti-IL-5/5Ra therapy.

Table 2: Significant factors associated with complete elimination of OCS after 2 years of anti-IL-5/5Ra.

	Univariate analysis			Multivariable analysis		
Risk factor	OR	95%CI	P-value	OR	95%CI	P-value
Cumulative OCS dose during 2 years before anti-IL-5/5Ra therapy			<0.001			<0.001
Quartile 1 (≤1.1g)	1			1		
Quartile 2 (1.1-2.7g)	0.4	(0.22-0.75)	0.004	0.45	(0.23-0.88)	0.02
Quartile 3 (2.7-5.5g)	0.25	(0.13-0.46)	<0.001	0.27	(0.13-0.53)	<0.001
Quartile 4 (≥5.6g)	0.11	(0.06-0.21)	<0.001	0.11	(0.052-0.24)	<0.001
First OCS exposure before anti-IL-5/5Ra therapy			<0.001			0.018
≤12 months	1			1		
12-21 months	0.3	(0.15-0.59)	<0.001	0.42	(0.20-0.88)	0.022
>21 months	0.29	(0.16-0.54)	<0.001	0.83	(0.40-1.7)	0.62
Starting year of anti-IL-5/5Ra therapy			<0.001			0.004
2015-2016	1			1		
2017	1.8	(1.1-3.0)	0.032	1.7	(0.99-3.1)	0.056
2018	2.9	(1.8-4.9)	<0.001	2.6	(1.5-4.5)	<0.001
OCS maintenance therapy prior to anti-IL-5/5Ra therapy						
Yes	0.37	(0.25-0.57)	<0.001			NS
FEV_1 (%pred)						
Continuous	0.99	(0.98-1.0)	0.052			NS
FEV_1 (%pred)						
≥80%	0.7	(0.46-1.1)	0.088			NS
FeNO (ppb)						
Continuous	1.006	(1.000-1.011)	0.045			NS

Table 2: Continued.

	Univariate analysis			Multivariable analysis		
Risk factor	OR	95%CI	P-value	OR	95%CI	P-value
FeNO (ppb)			0.094			NS
<25	1					
25-50	0.89	(0.48-1.7)	0.70			
≥50	1.6	(0.89-2.8)	0.12			
OCS dose during 3 months prior to anti-IL-5/5Ra therapy			<0.001			NS
Quartile 1 (≤0.03g)	1					
Quartile 2 (0.04-0.45g)	0.55	(0.30-0.98)	0.044			
Quartile 3 (0.45-0.9g)	0.4	(0.22-0.72)	0.002			
Quartile 4 (≥0.91g)	0.21	(0.11-0.39)	<0.001			
Blood eosinophils in categories (10^9/L)			0.023			NS
<0.150	1					
≥0.150-0.300	1.5	(0.72-3.1)	0.284			
≥0.300-0.450	2.2	(1.1-4.2)	0.025			
≥0.450	2.3	(1.3-4.0)	0.003			

Abbreviations: FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, OCS: Oral corticosteroids, OR: Odds Ratio, NS: Non-significant in backward stepwise regression analysis.

DISCUSSION

This real-world study shows that anti-IL-5/5Ra add-on treatment for severe eosinophilic asthma leads to a significant reduction in cumulative OCS exposure in the majority of patients. Furthermore, OCS exposure increases progressively in the years prior to anti-IL-5/5Ra initiation, and declines rapidly after initiating anti-IL-5/5Ra therapy. More than half of the patients are able to completely eliminate OCS within 2 years of initiating anti-IL-5/5Ra therapy. This is especially true for patients with shorter OCS exposure and lower cumulative OCS doses, suggesting that early introduction of anti-IL-5/5Ra therapy leads to better therapeutic results.

The results of our study confirm and are an important extension of previous findings from controlled trials and real-world studies with anti-IL-5/5Ra biologics. Most placebo-controlled studies focused on the daily OCS maintenance dose and found approximately 50% dose reduction relative to placebo after 24 weeks of treatment with anti-IL-5/5Ra biologics, which is comparable to the findings in our study.[13][16] However, unlike our study, these studies did not examine the effect on cumulative OCS dose, which is a better predictor of OCS-related side effects than the daily dose at some point in the disease.[9] Our findings regarding discontinuation of OCS after initiation of anti-IL-5/5Ra was also observed in 3 other studies. The recently published PONENTE study provided detailed information on how to safely reduce OCS after initiation of anti-iL-5Ra using a personalized OCS reduction algorithm. In this study, the majority of patients was able to eliminate OCS and nearly all patients achieved a daily maintenance dose of ≤5mg per day.[18] An Australian real-world study examining the effect of mepolizumab in 309 patients found a reduction in the proportion of patients requiring OCS (maintenance and/or bursts) from 97% to 67% after 12 months of treatment.[22] Yet another study based on insurance claims in the USA including 527 patients found an increase in the proportion of patients without OCS use from 6.6% to 20.3% after 12 months mepolizumab treatment.[23] Our study included a longer observation period of 2 years before and 2 years after initiation of anti-IL-5/5Ra therapy, which allowed us not only to calculate cumulative OCS exposure, but also to determine the course of OCS exposure before and after starting anti-IL-5/5Ra therapy, and to demonstrate that longer duration and higher total exposure to OCS predicted a poorer response to anti-IL-5/5Ra therapy.

Our large nationwide study is unique in that it provides insight into the use of OCS for 2 years prior to initiation of anti-IL-5/5Ra treatment. To our knowledge, this has never been done before and provides important information about the course of severe eosinophilic asthma. Data on OCS use were collected by directly contacting

the patients' pharmacies. Dutch pharmacies have access to all dispensed medication for reasons of medication surveillance and reimbursement. The Dutch National Exchange Point prevented that medication dispensed at other pharmacies during the study period was missed in the analysis. This guaranteed a complete overview of the OCS exposure and prevented possible recall bias. While randomized controlled trials and subsequent real-world studies only evaluated the effect of anti-IL-5/5Ra biologics on the daily maintenance dose of OCS, in our study we could accurately calculate the cumulative OCS exposure over several years. This will allow a better estimate of the effect of anti-IL-5/5Ra on the long-term adverse effects of OCS that are primarily related to the cumulative OCS exposure.

Our study has some limitations as well. First, there are the usual limitations inherent of a real-world intervention study like the lack of a control group. The registry did not allow for a control group, since patients without a biologic were not included and the number of patients firstly starting a non-anti-IL-5/5Ra biologic were limited. A second limitation of this study is that dispensing medication does not imply that the patient actually takes the medication. Due to the retrospective character of our study, it was not possible to verify that the medication was taken as prescribed. However, given the severity of the disease and the eventual dependence on OCS, it seems likely that all medications have been used. Third, we did not have access to data on systemic corticosteroid use during hospital admissions. However, as this may have led to an underestimation of OCS use, especially in the pre-initiation period of anti-IL-5/5Ra therapy, this would only further augment the effects found in our study. Furthermore, our selection of patients might have influenced the observed progression prior to anti-IL-5/5Ra initiation because patients with OCS progression might be more likely to be deemed anti-IL-5/5Ra eligible. On the other hand, the reduction in OCS exposure might have been influenced by so-called regression to the mean due to the possible selection of patients initiating anti-IL-5/5Ra therapy at a time when they experienced more severe symptoms, which would also have spontaneously improved after starting therapy. Although unlikely given the prolonged pre-treatment observation period, we cannot fully exclude this possibility.

We found a progressive course of OCS exposure in the 2 years before anti-IL-5/5Ra initiation, which was especially evident in patients with relatively short OCS exposure. This suggests that severe eosinophilic asthma, which is known to usually start in adulthood, has a progressive course in the first years with a rapid increase in the need for OCS. Such a rapidly progressive disease course might be related to the formation of immunogenic Charcot-Leyden Crystals, the activation

of airway autoantibodies or the autocrine production of IL-5/5Ra by eosinophilic granulocytes leading to a self-reinforcing inflammation requiring treatment with ever higher doses of OCS.[24][25][26] If future studies confirm the progressive course of eosinophilic asthma, this will have a major impact on the management of this severe condition.

We showed that the ability to completely eliminate the use of OCS within 2 years after anti-IL-5/5Ra initiation is associated with lower and shorter OCS exposure before initiating anti-IL-5/5Ra, which is not surprising. But how to explain that a later start year of anti-IL-5/5Ra therapy influenced the ability to eliminate OCS? The most likely explanation is that the first patients prescribed anti-IL-5/5Ra therapy were those with the most severe illness and highest OCS exposure, who had waited the longest time for health authorities to approve this add-on therapy. In later years, anti-IL-5/5Ra treatment became more accessible to patients with milder disease and lower OCS exposure, which may be an explanation why the effect of treatment was greater in those patients and why they could more easily discontinue OCS altogether. The suggestion that initially patients with more severe asthma were included could also be inferred from their baseline characteristics showing that nearly 58% used maintenance OCS, 42% were former smokers and 50.6% were diagnosed with nasal polyposis. These numbers are higher compared to patients in the Severe Asthma Research Program (SARP) in the United States and European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED).[27,28] Therefore, it would be interesting to make a comparison with other severe asthma cohorts in order to better estimate the generalisability of our findings.

Our study showed, that even after 2 years of anti-IL-5/5Ra therapy only half of our patients were able to discontinue the use of OCS. This can have several explanations. For example, there may still be active airway inflammation, which cannot be completely suppressed by anti-IL-5/5Ra. Possible contributing factors are an inadequate serum concentration or insufficient tissue concentration of anti-IL-5/5Ra, or involvement of another pathophysiological pathway in the inflammatory process, *e.g.* the IL-4/IL-13 pathway.[29,30] Another possible explanation for the residual OCS exposure is adrenal insufficiency which is a major side effect of long-term OCS use.[31] Adrenal insufficiency was not systematically assessed in the study population, which has likely led to an underreporting of adrenal insufficiency. The recent PONENTE trial found that 60% of patients had any form of adrenal insufficiency at the time treatment with the anti-IL-5Ra biologic benralizumab was initiated.[18] Studies like the PONENTE trial show that adrenal insufficiency is underrecognized in the Dutch severe asthma population. The need to systematically

examine adrenal insufficiency has been highlighted by the PONENTE trial and should lead to a major change in current clinical practice. Estimates about the influence of the duration and extent of OCS exposure on the occurrence of adrenal insufficiency are currently lacking. This remains a topic for future studies in patients with severe eosinophilic asthma.

An important clinical implication of our findings is that physicians treating patients with severe eosinophilic asthma should consider initiating anti-IL-5/5Ra treatment early in the disease process, when their patients require relatively low doses of OCS to control their asthma. Furthermore, clinicians and patients should be aware of possible residual OCS exposure despite anti-IL-5/5Ra treatment and pursue further treatment optimization either through individualized OCS taper schedules as suggested in the PONENTE study, or by switching to add-on therapies targeting different inflammatory pathways. Furthermore, due to the observed progressive course of the OCS dose, our results indicate that there is an unmet need to get more insight into the natural course of severe eosinophilic asthma.

In conclusion, this real-world study showed that anti-IL-5/5Ra therapy leads to a significant reduction in cumulative OCS exposure over a two-year period. Patients who develop severe eosinophilic asthma appear to have a rapid progression of cumulative OCS exposure associated with an increased risk of adverse events. The lower and shorter the OCS exposure, the more patients might benefit from anti-IL-5/5Ra add-on treatment and achieve complete elimination of OCS use. These data suggest that early intervention with anti-IL-5/5Ra biologics in patients with severe eosinophilic asthma leads to a better long-term prognosis.

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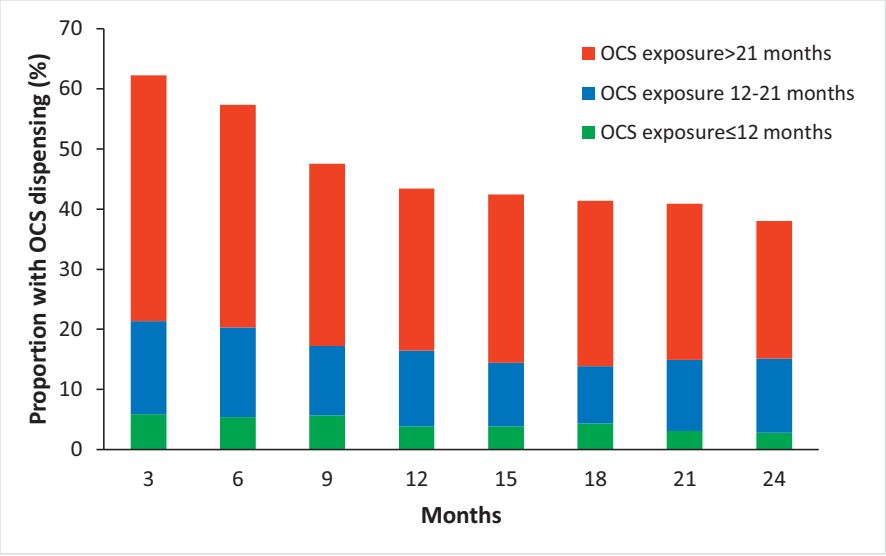
SUPPLEMENTARY MATERIALS

Supplementary figure 1. Proportion of patients requiring OCS dispensing after initiating anti-IL-5/5Ra.



Supplementary Figure 1: Proportion of patients with an OCS dispensing.

Legend to Supplementary Figure 1: This figure shows the percentage of patients with an OCS dispensing after initiating anti-IL-5/5Ra per 3 months period. The bars represent the total population and are built up by patients with first OCS exposure ≤12 months (green), 12-21 months (blue) or >21 months (red) before anti-IL-5/5Ra initiation. After initiating anti-IL-5/5Ra, the proportion of patients with an OCS dispensing gradually decreases.

Abbreviations: IL= Interleukin, OCS = Oral corticosteroids.

Supplementary table S1: Comparison included *vs.* excluded patients.

	Included (N=389)	**Excluded (N=59)**	**P-value**
Age (y)*	57 (48-64)	57 (46-64)	0.614
Gender; male, %	45.5	42.4	0.676
Body mass index (kg/m²)*	27.3 (24.3-29.9)	28.8 (24.1-32.2)	0.095
Former smoker, %	42.0	42.4	0.926
Pack years in smokers (y)*	10 (5-20)	12 (7-25)	0.291
Age of onset of eosinophilic asthma (y)*	44 (23-53)	39 (19-49)	0.216
Late onset asthma, %	75.6	69.5	0.336
Non-atopic asthma, %	53.4	60.6	0.504
Nasal polyposis, %	50.6	45.7	0.207

*: median (IQR).

Supplementary Table S2. Comorbidities.

Comorbidity	**N=389**
Atopic dermatitis (%)	10.6
Allergic Rhinoconjunctivitis (%)	20.4
Chronic Rhinosinusitis (%)	69.2
Nasal polyposis (%)	50.6
Aspirin intolerance (%)	10.6
Depression (%)	10.1
Gastroesofageal reflux disease (%)	17.5
Bronchiectasis (%)	18
Obstructive sleep apnea (%)	11.1
Skin abnormality (%)*	12.9
Weight gain (%)*	27.6
Osteoporosis (%)*	12.6
Hypertension (%)*	5.4
Cataract (%)*	2.3
Diabetes mellitus (%)*	4.1
Adrenal insufficiency (%)*	1.5

* Possibly related to the use of OCS.

Abbreviation: OCS = Oral corticosteroids.

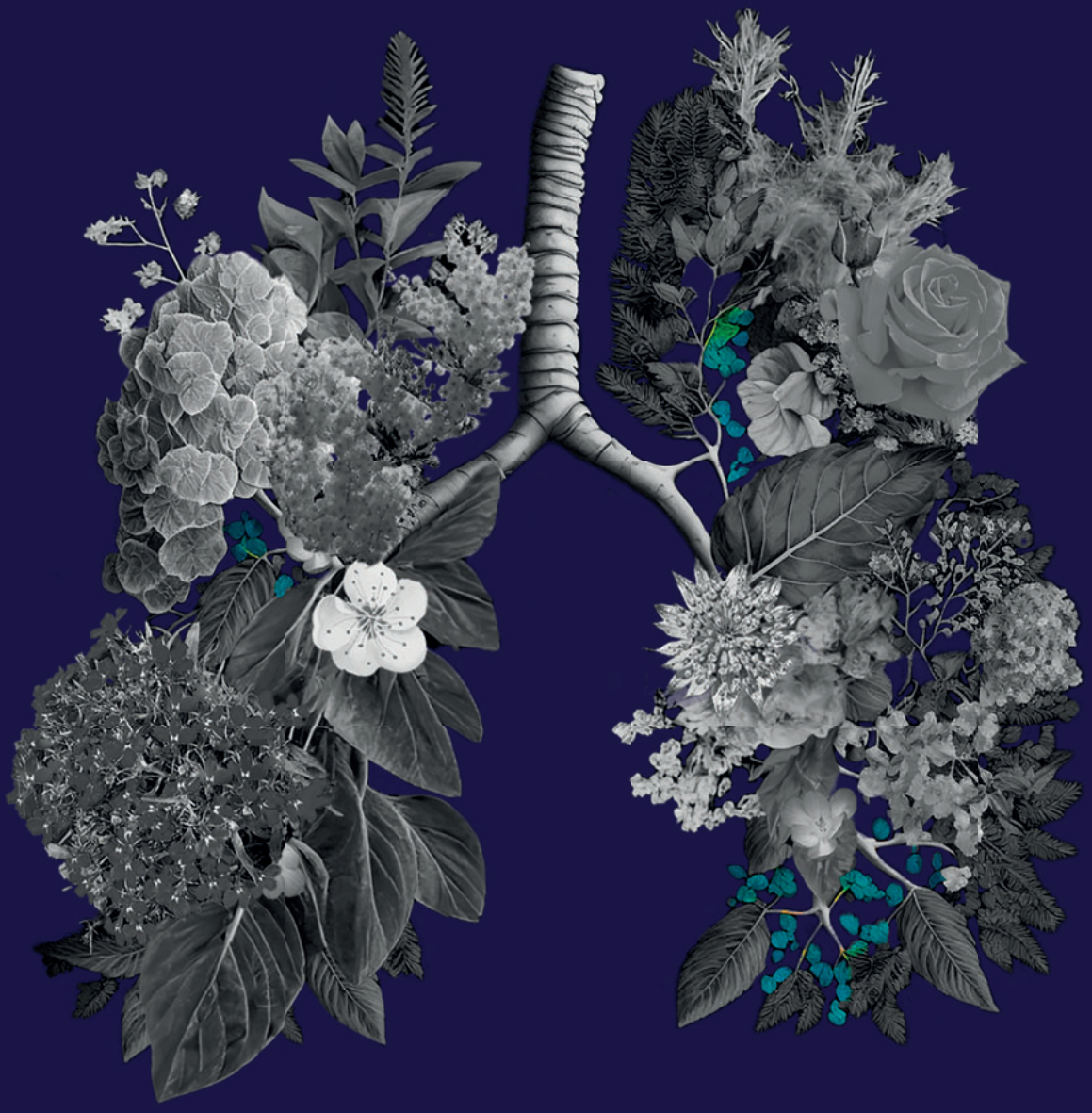
Supplementary Table S3. Univariate binary logistic regression analysis assessing associations between baseline variables and complete OCS elimination after 2 years of anti-IL-5/5Ra.

Risk factor		OR Univariate	95%CI	P-value
Age		1.0	(1.0-1.1)	0.125
Gender				
	Male	1.1	(0.73-1.6)	0.671
Body mass index		0.98	(0.94-1.0)	0.258
Former smoker				
	Yes	1.4	(0.92-2.1)	0.115
Pack years		0.99	(0.97-1.0)	0.485
Age of onset of eosinophilic asthma		1.0	(0.99-1.0)	0.132
Type of asthma onset				
	Late onset	0.79	(0.49-1.2)	0.307
Type of asthma				
	Non-atopic	0.91	(0.60-1.4)	0.653
Nasal polyposis				
	Yes	1.2	(0.75-1.8)	0.517
Number of exacerbations in previous year				0.219
	0-1 Exacerbations	1		
	2-5 Exacerbations	0.77	(0.47-1.3)	0.316
	>5 Exacerbations	0.60	(0.31-1.1)	0.081
OCS maintenance therapy prior to anti-IL-5/5Ra therapy				
	Yes	0.37	(0.25-0.57)	<0.001
OCS maintenance dose (mg/day)		0.99	(0.96-1.03)	0.754
Blood Eosinophils (10^9/L)		1.3	(0.86-2.0)	0.203
Blood eosinophils in categories (10^9/L)				0.023
	<0.150	1		
	≥0.150-0.300	1.5	(0.72-3.1)	0.284
	≥0.300-0.450	2.2	(1.1-4.2)	0.025
	≥0.450	2.3	(1.3-4.0)	0.003
FeNO (ppb)		1.006	(1.000-1.011)	0.045
FeNO (ppb)				0.094
	<25	1		
	25-50	0.89	(0.48-1.7)	0.701
	≥50	1.6	(0.89-2.8)	0.116
FEV_1 (%pred)		0.99	(0.98-1.0)	0.052
FEV_1 (%pred)				
	≥80%	0.7	(0.46-1.1)	0.088

Supplementary Table S3. Continued.

Risk factor	OR Univariate	95%CI	P-value
Cumulative OCS dose at 2 years before anti-IL-5/5Ra therapy			<0.001
Quartile 1 (≤1.1g)	1		
Quartile 2 (1.1-2.7g)	0.40	(0.22-0.75)	0.004
Quartile 3 (2.7-5.5g)	0.25	(0.13-0.46)	<0.001
Quartile 4 (≥5.6g)	0.11	(0.06-0.21)	<0.001
OCS dose during 3 months prior to anti-IL-5/5Ra therapy			<0.001
Quartile 1 (≤0.03g)	1		
Quartile 2 (0.04-0.45g)	0.55	(0.30-0.98)	0.044
Quartile 3 (0.45-0.9g)	0.40	(0.22-0.72)	0.002
Quartile 4 (≥0.91g)	0.21	(0.11-0.39)	<0.001
Start year of anti-IL-5/5RA therapy			<0.001
2015-2016	1		
2017	1.8	(1.1-3.0)	0.032
2018	2.9	(1.8-4.9)	<0.001
First OCS exposure before anti-IL-5/5Ra therapy			<0.001
≤12 months	1		
12-21 months	0.3	(0.15-0.59)	<0.001
>21 months	0.29	(0.16-0.54)	<0.001
Atopic dermatitis			
Yes	1.1	(0.55-2.1)	0.857
Allergic rhinoconjunctivitis			
Yes	1.4	(0.82-2.4)	0.221
Chronic rhinosinusitis			
Yes	1.5	(0.91-2.5)	0.116
Aspirin intolerance			
Yes	1.5	0.77-3.0)	0.228
Depression			
Yes	1.5	(0.74-2.9)	0.268
Gastroesofageal reflux disease			
Yes	1.2	(0.68-2.1)	0.545
Bronchiectasis			
Yes	0.64	(0.37-1.1)	0.105
Obstructive sleep apnea			
Yes	0.64	(0.33-1.2)	0.186

Abbreviations: FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, IL: Interleukin, OCS: Oral corticosteroids, OR: Odds Ratio.



Chapter 5

Blueprint for Harmonizing Non-Standardized Disease Registries to Allow Federated Data Analysis – prepare for the future

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ABSTRACT

Real-world evidence from multinational disease registries is becoming increasingly important not only for confirming the results of randomized controlled trials, but also for identifying phenotypes, monitoring disease progression, predicting response to new drugs, and early detection of rare side effects. With new open access technologies, it has become feasible to harmonize patient data from different disease registries and use it for data analysis without compromising privacy rules. In this article, we provide a blueprint for how a clinical research collaboration can successfully use real-world data from existing disease registries to perform federated analyses. We describe how the European Severe Asthma Clinical Research Collaboration SHARP fulfilled the harmonization process from non-standardized clinical registry data to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) and built a strong network of collaborators from multiple disciplines and countries. The blueprint covers organizational, financial, conceptual, technical, analytical and research aspects and discusses both the challenges and the lessons learned. All in all, setting up a federated data network is a complex process that requires thorough preparation, but above all, it is a worthwhile investment for all clinical research collaborations, especially in view of the emerging applications of artificial intelligence and federated learning.

INTRODUCTION

Targeted biologic therapies have significantly improved the lives of many patients with chronic inflammatory diseases such as rheumatoid arthritis, ulcerative colitis and asthma.[1-3] Unfortunately, biological therapies are expensive, while it is often unclear which patients benefit most from a particular biological agent.[4-6] National disease registries have therefore been set up in many countries at the initiative of governments, insurers or medical associations to monitor the effectiveness, costs and side effects of biologics.[7]

In the case of severe asthma, individual national registries have yielded interesting publications, although many important research questions including rare adverse effects or comparative effectiveness of different biologics could not be answered due to a lack of sufficient statistical power and reproducibility.[8-12] In addition, real-world evidence from multinational disease registries became increasingly important not only for confirming the results of randomized controlled trials, but also for identifying phenotypes, monitoring disease progression, and targeting the right biologic to the right patient.[13]

Meanwhile, the European Respiratory Society (ERS) had encouraged and financially supported the establishment of a clinical research collaboration (CRC) called SHARP (Severe Heterogeneous Asthma Research, Patient-centered).[14] The ambition of SHARP was to connect all existing severe asthma registries in Europe. To that end, patient data from different registries had to be harmonized to allow data-analyses in such a way that would not compromise the privacy of patients. Because some registries were reluctant to transfer patient data outside the institution where it was collected, SHARP opted for a federated analysis approach, which uses patient-level data from different sources without actually pooling the data together in a central database.

Several harmonization and federation approaches, platforms and structures were considered.[15-20]. SHARP decided to use the open source Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), developed by the Observational Health Data Sciences and Informatics Program (OHDSI), which is currently one of the top-rated models for sharing medical data.[21] This model best meets criteria such as content coverage, integrity, flexibility, ease of retrieval, compatibility of standards and ease/scope of implementations, privacy and connectivity.[22,23] Importantly, the OHDSI/OMOP CDM is the standard used by European Health Data Evidence Network (EHDEN), which is a key initiative that

sets the pace for federated analytics in Europe and the US[24]. Thus, OMOP offered great potential for connection to this fast-growing network.

In this article, we describe the harmonization process that SHARP has gone through and provide a blueprint for how to successfully use real-world data from existing disease registries to perform federated analysis. The blueprint covers organizational, financial, conceptual, technical, analytical and research aspects and discusses both the challenges and the lessons learned. The blueprint can be used as a guide for other clinical research networks with a similar ambition to link registries containing patient data.

Harmonization of severe asthma registries

SHARP's initiative to link data from disease registries from different countries was not only ambitious, but also innovative and unique, as no previous examples of this had been published before. Initially, the whole project seemed unfeasible due to the incompatibility of the local data models. Each country had its own electronic case reports forms (eCRF) and database structure, in its own language. In addition, legal and regulatory requirements and strict data protection and privacy regulations (e.g., the General Data Protection Regulation (GDPR)) restricted the transfer of patient-level data outside a healthcare provider.[25] Transfer of data outside the country of origin was excluded.

With the ODHSI/OMOP CDM it seemed feasible to meet these challenges.[21] Following the initiative of the European Health Data Evidence Network (EHDEN), research studies would be conducted in a federated manner so that personal data would remain on the local sites, thus retaining full control over what happened to their data and what studies they would participate in.[24] In particular, the harmonization process would remove patient identifiers and, furthermore, only aggregated summary statistics would be exported for meta-analysis. Since aggregated data are privacy-proof by nature, federated analyses comply with the GDPR and ethical research guidelines.

Without previous examples on how to harmonize non-standardized disease registries and build a federated analysis platform (FAP) SHARP wasn't quite sure what to expect. On paper, the procedure seemed simple (Fig. 1): match the field names from the local database with concepts in the CDM; create an Extract, Transform, Load (ETL) procedure to automate the mapping of the local database to a unified format; make the translated data available for local analysis; perform an identical analysis on each registry; combine the aggregated results. However,

the reality was that we had to overcome challenges at the organisational, financial, conceptual, technical, analytical and research levels.

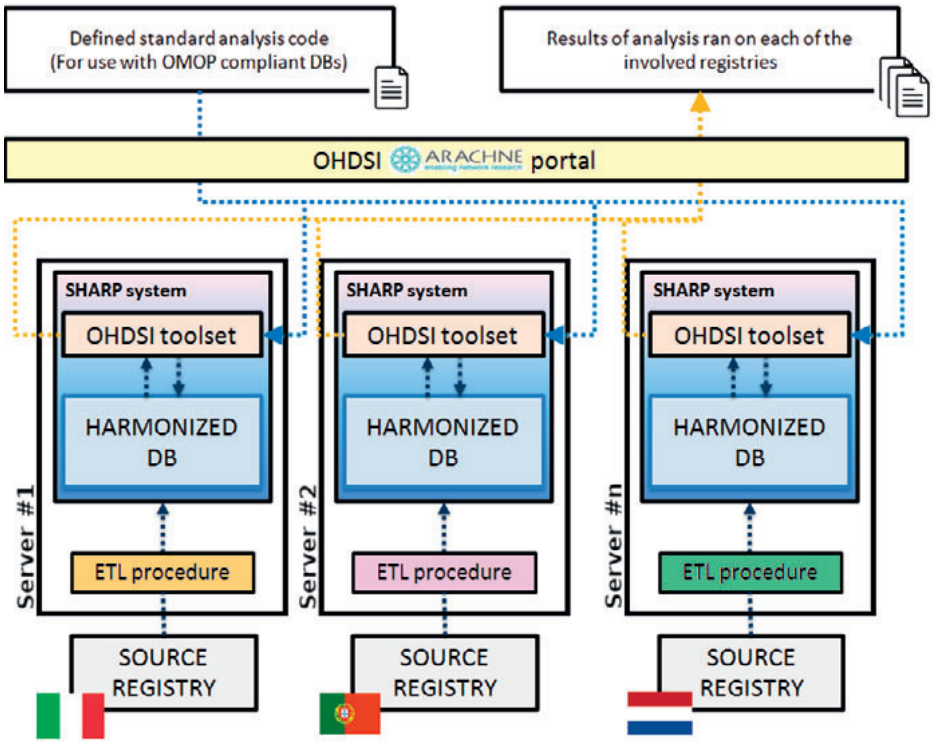

Figure 1. Architecture of the Federated Analysis Platform. Field names of the different national registries are mapped to concepts in the common data model. An ETL procedure is created to automate the mapping from the local database into a unified format; the harmonized data are made available for local analysis using the OHDSI toolset or R-code; an identical analysis is run on each registry; the results are combined using federated analysis tools. DB: database; ETL: Extract, Transform, Load; OHDSI: Observational Health Data Sciences and Informatics; OMOP: Observational Medical Outcomes Partnership; SHARP: Severe Heterogeneous Asthma Registry – Patient Centered.

Key learnings

In the course of the harmonization process, SHARP learned a number of important lessons, which it would like to share here with other clinical research collaborations that also have the ambition to implement such harmonization. These lessons are listed below by category.

Basic operational pre-requisites

In order for a harmonization process between existing disease registries to be successful, a number of general preconditions must be met. These concern professional project management, availability of sufficient financial resources and signed collaboration agreements between all parties. In addition, it must be ensured that the local ethics committees, the institutions and the patients have given written informed consent for the use of their medical data for scientific research.

As the first to gain experience with this complex harmonization process, SHARP was not well prepared for these preconditions. Until then, it had only collected summary data from the various European regsitries with little financial support. [26] The administrative burden quickly became a challenge for the limited support of the ERS and a dedicated, full-time project manager had to be appointed. In addition, legal services in order to establish service- and research agreements, a professional statistician and the EHDEN-trained SME's (Small and Mid-sized Enterprises) responsible for the mapping of variables in the local databases to the OMOP CDM and for the building of a FAP, were all necessary and all had to be paid. All in all, a budget of around € 200,000 per annum was required to cover these expenses.

Understanding the OHDSI/OMOP CDM

An absolute requirement for succesfully building a FAP is that every stakeholder understands the harmonization concept well and has no doubts or hesitation in participating in its implementation.

For SHARP the use of OHDSI/OMOP CDM for the harmonization of patient-level data was new and conceptually different from the traditional use of such data for scientific research. [27] Time and again, SHARP encountered lack of confidence in the OHDSI/OMOP concept. This was mainly due to insufficient familiarity with the concept and lack of knowledge and understanding. Clinicians were concerned that patients' privacy was not sufficiently guaranteed. Local legal officers were unsure whether the data handling was secure enough, registry owners were unsure about data ownership, researchers were concerned that their data could be misused by competitors, and IT administrators were reluctant to give third parties access to their servers, due to regulatory concerns or internal IT procedures. Only intensive and repeated education and communication allowed the various parties and partners to ultimately be convinced and enthusiastically take part in the project.

Mapping registry data to the OMOP CDM

A key part of the harmonization process is the mapping of source data to the OMOP CDM. Due to diversity of format and language of the SHARP registries, this had to be manually conducted for each registry, one at a time. The process required fluent and efficient collaboration between the project manager, clinical expert, source data expert, medical terminologist/mapping expert, developer/tester, and statistician.

Not surprisingly, the mapping process faced several challenges, including incomplete registering at source, for example the lack of start and stop dates of medications, and dates when various procedures had taken place. Ideally, the mapping process should be performed on the basis of a registry 'data dictionary' - i.e. a file containing variable names, data types, units of measure, etcetera, because this enables the use of existing mapping tools. In SHARP, the registries could not provide such a data dictionary. The mapping process therefore required a more "iterative" approach than expected, as there were many "mismatches" between the data types and the actual content of the source. All these issues could only be resolved by joining forces. Unfortunately for SHARP, in-person communication was severely hampered by the COVID-19 pandemic and the lock-down measures.

IT requirements and data access

The mapping of source data to the OHDSI/OMOP CDM is automated in an ETL (Extract, Transform, Load) procedure, reading the source data and writing the harmonized data into an OMOP CDM compatible database. Smooth operation requires a server located in the registry's data center (or in a cloud environment, if local IT regulations allow) for taking snapshots of de-identified source data. The server can also host the analytical tools (R environment, OHDSI tools), alternatively these tools can be hosted in a dedicated environment. Of course, the local servers should be accessible by the SME, but for SHARP this proved to be difficult in some cases due to local IT regulations. Nevertheless, it is highly recommended to establish access for the SME, since otherwise local IT teams have to be trained to fulfil the job.

Data quality assessments

In order to obtain the best quality of harmonized data and minimal loss of original data, it is important that source data comply with the rules of the data dictionary, which was not always the case. For a successful mapping between registry data and OMOP CDM, it is therefore important to test and validate the data quality. To this end, SHARP deployed a professional statistician who could form a bridge between the clinicians and the mapping and source data expert. This statistician wrote R scripts for descriptive statistical analysis that could be performed automatically by

all local registers. Due to the diversity of the registry structures and the different levels of completeness of each variable considered, the R script at each stage had to include checks on the numerical range and to account for high levels of (or complete) missing data. The local registries were then presented with their own data overviews in well-arranged tables and graphic displays. Ideally such checks should eventually be performed on all variables of each registry before finalising the mapping.

At SHARP, quality checks revealed unexpected missing data codes, impossible values and some mismatches due to the use of free text fields by the clinicians who had entered data. Where necessary, changes were made to the mapping schema and in some cases to the source data in the local registry database. Again, these solutions required time, close collaboration between clinicians, source data experts, mapping experts and data analysts.

Data analytical aspects

Using a FAP and analyzing real-world data from different disease registries in different countries requires strong analytical skills. In fact, the person in question must unite epidemiological, biostatistical and observational data science expertise, be a confident programmer, and be willing to learn the ins and outs of the OHDSI/OMOP CDM. Also, the statistician should be able to perform an appropriate meta-analysis of summary statistics to draw conclusions from all participating registers. Of course, and luckily, more than one person may fulfil different aspects of this role in the studies.

While processing data from the SHARP registries, it became clear that a statistician needs to be engaged at the outset of the project and be involved in the writing of all protocols and analysis plans. This helps to ensure that the necessary data is available and mapped across all relevant registries, and that any local categorization of data does not preclude the planned analysis.

Recommendations and blueprint

Table 1 shows the blueprint with recommendations for an optimal harmonization process between disease registry data and OMOP CDM for multinational federated analyses.

Table 1. Blueprint for harmonizing disease registries using OMOP CDM.

Topic	Recommendation
Basic conditions	- Selection of a legal body for clinical research collaboration (CRC) - Securing of sufficient financial resources for ≥3 years - Appointment of a full-time dedicated project manager - Establishment of a contract with an SME specializing in OHDSI, OMOP CDM and mapping - Establishment of contract with a hands-on statistician with programming skills - Written confirmation from each registry that patients have given written consent to use their medical data for (international) clinical research - Identification for each local registry of named individuals in the following roles: - Registry owner - Legal officer - Clinical expert - Source data expert - IT contact/administrator - Translator of medical terminology - Platform/System user - Conclusion of collaboration agreements between CRC and registries
Conceptual aspects	- Production of a document and a Power Point presentation explaining the OMOP CDM and the federated approach to all stakeholders - Organization of a plenary kickoff meeting with all stakeholders - Organization of regular team meetings for each registry to monitor progress
Technical aspects	- Provision/hire of a dedicated Linux server for each registry (local data center or cloud environment) for the installation and setup of the FAP, with access to a local copy of the source database; - Provision to all required parties of access to the Linux registry servers - Testing of the functioning of the FAP on local Linux servers by SME
Mapping aspects	- Checks source data quality - Provision of registry data dictionary to SME by source data experts - Provision of a representative, but anonymized registry data sample by local team to smoothen ETL process and avoid “black box mapping” - Assistance by clinical experts in optimizing the mapping - Provision by SME to statistician(s) of a codebook of the variables mapped

Table 1. Continued.

Topic	Recommendation
Analytical aspects and Quality control	- Learning by statistician(s) on the principles of OHDSI and OMOP comon data model - Provision by SME of access to FAP for statistician(s) - Creation by statistician of scripts in R (or OHDSI tools for the production of descriptive summary statistics - Execution by local analyst in each country of the pre-written R-script via the FAP - Checks by clinical on the validity of the output and provision of feedback to statistician and SME - Revision by source data expert and SME of any mapping issues. - Creation of a second round of data summaries and a repeat of the quality control process - Production of final OMOP CDM tables
Research studies	- Creation of research protocol and approval by CRC, local clinical experts and registry owners - Identification of dedicated local teams for each registry, comprising clinical experts, source data experts and data analysts. - Creation of a formal analysis plan by a statistician, for review and approval by representatives of all participating registries - Creation by statistician of analysis scripts in R (or OHDSI tools) - Execution by local data analysts of pre-written scripts in R (or ODHSI tools) using the FAP. - Fostering of collaboration between best practices for statisticians and data analysts via workshops to discuss issues like imputation rules, filters and exclusions - Production of final statistical tables and graphics for each registry singly, according to the analysis plan - Meta analysis by statistician of summary statistics from all registries - Writing and submission of manuscript

CDM: Common Data Model; CRC: Clinical research Collaboration; ETL: Extract, Transform, Load; FAP: Federated Analysis Platform; IT: Information Technology; OHDSI: Observational Heath Data Sciences and Informatics; OMOP: Observational Medical Outcomes Partnership; SME: Small and Medium-sized Enterprise.

A schematic summary of required steps for harmonizing disease registries using OHDSI/OMOP CDM is given in Figure 2. An estimate of the time required per item is given in Table E1 and Figure E1. Registries that are currently connected or in the process of being connected are listed in table E2.

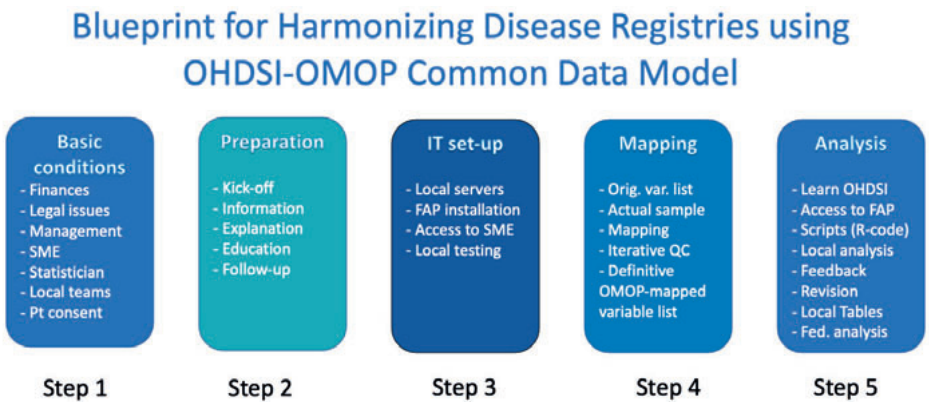

Figure 2. Schematic summary of harmonization steps. Schematic summary of steps to be taken for a successful harmonization process of local non-standardized disease registries to the OHDSI/OMOP Common Data Model for federated analyses. FAP: Federated Analysis Platform; Fed: Federated; IT: Information Technology; OHDSI: Observational Health Data Sciences and Informatics; OMOP: Observational Medical Outcomes Partnership; Orig: Original; Pt: Patient; QC: quality Check; SME: Small and Medium-sized Enterprise; Var: variable

DISCUSSION

In this article, we described our experience in harmonizing patient data from different European severe asthma registries using the OHDSI/OMOP CDM. Based on the lessons learned, we put together a blueprint that can be used by researchers in other disease areas where there is a desire to establish federated data networks of real-world patient data already collected in non-standardized registries. The harmonization process was not without challenges, but it was above all a unique experience to connect colleagues and partners from different countries, specialties and disciplines in one large federated project.

To date, most studies on OHDSI/OMOP CDM were related to architectural concepts and tool development.[27] However, over the last couple of years, an increasing number of publications have appeared using the OMOP CDM in prospective network studies with observational patient data, in particular related to the COVID-19 pandemic.[28-32]. Other studies have used large administrative claims databases [33,34] or electronic medical records databases.[35,36] Our study is the first that used the OMOP CDM to harmonize non-standardized national disease registries.

When SHARP CRC was founded in 2017, its vision was to incrementally change the research culture across Europe, emphasizing ambitions that serve the collective

needs of the asthma research community and bring people with asthma to the center of the research environment into a reality context.[14] SHARP's goals included better understanding the mechanisms of severe asthma, improving treatment for severe asthma, and exploring ways to prevent severe asthma. It wanted to achieve this by establishing a platform that would allow the integration of local national asthma registries into a pan-European multicenter registry of patients with severe asthma.[21] At the same time, the scientific community expressed the increasing need for more large-scale real-world research. Not only for confirming the results of randomized controlled trials, but also for identifying phenotypes, monitoring disease progression, predicting response to new drugs and detecting rare side effects.[38,39] However, due to concerns regarding data privacy, data security, data access rights and data ownership, some SHARP registries were reluctant to transfer patient-level data to one central database, as was the case with other international registries such as the International Severe Asthma Registry ISAR.[40]. However, in order not to lose the precious data from these existing registries, it was then decided to establish a federated data platform and use the OHDSI/OMOP CDM to harmonize the databases.[21]

At that time, the use of OMOP CDM was relatively new and had never been applied to existing disease registries. Since there was no example of how to approach the harmonization process, it was not surprising that SHARP encountered multiple challenges and obstacles, from which it ultimately learned a lot.

In retrospect, the unfamiliarity and misunderstanding of the OMOP CDM concept among doctors, researchers, legal entities and IT administrators was perhaps the main reason why the process was sometimes unnecessarily delayed. There were concerns that data privacy would not be guaranteed, data would fall into the wrong hands and the security of data centers would be compromised. Therefore, we cannot emphasize enough the need to repeatedly explain the concept and process of harmonization to all stakeholders, through meetings, presentations and personal discussions.

Furthermore, it appeared that collaboration between clinicians, IT technicians, registration holders and legal entities was essential, and that they all should be able to devote sufficient time and attention to the project. Not only for the initial harmonization process, but also prior to any future research project, such multidisciplinary dedicated teams should be set up for each registry. Team members should be able to consult each other easily and ad hoc, preferably by mobile phone.

Investing in building the FAP and achieving the harmonization of severe asthma registries has brought many benefits to SHARP CRC. Firstly, thanks to the joint effort and overcoming adversity, it has created a strong and solid partnership between many stakeholders including patients, clinicians, researchers, pharmaceutical industries, IT technicians, data analyst and consultants. Secondly, it now features a state-of-the-art platform that allows for innovative and large-scale real-word studies with relatively little effort. Finally, and perhaps most importantly, because of its privacy-protected structure, scalability and generalization, the SHARP FAP is now perfectly equipped for the future in which artificial intelligence and federated learning will play an increasingly important role in generating evidence with real-world data.[41-43]

CONCLUSION

We have provided a blueprint for what it takes as a nonprofit clinical research collaboration to successfully use real-world data from existing disease registries for executing federated analyses. The open access OHDSI/OMOP CDM has enabled patient data from different disease registries to be harmonized and used for data analysis without compromising privacy rules. We have learned that building a FAP to enable large-scale analysis of patient-level data from non-standardized registries is a complex process and can only be successful if all parties fully understand and support the concept. At the same time, it ensures strong collaboration and builds an enriching network that enhances the knowledge and interrelationships of all partners with the common goal of using real-word data efficiently. We believe that, especially given the increasing adoption of artificial intelligence and federated learning, the harmonization of disease registry data to a common data model is a worthwhile investment, which we can certainly recommend to other clinical research collaborations. Ultimately, the rewards of such efforts will manifest in terms of improved disease understanding and better patient care.

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SUPPLEMENTARY MATERIALS

Table E1. Estimation of the time required for building a FAP.

Topic	Tasks	Estimated average time needed
Basic conditions	Setting-up a collaboration network/consortium - Writing of a protocol and governance document - Selection of a legal body (foundation/society) for a clinical research collaboration - Securing of sufficient financial resources for ≥3 years - Appointment of a full-time dedicated project manager	10 months
	- Establishment of a contract with an SME specializing in OHDSI, OMOP CDM and mapping - Establishment of contract with a hands-on statistician with programming skills - Written confirmation from each registry that patients have given written consent to use their medical data for (international) clinical research - Identification for each local registry of named individuals in the following roles: - Registry owner - Legal officer - Clinical expert - Source data expert - IT contact/administrator - Translator of medical terminology - Platform/System user - Conclusion of collaboration agreements between CRC and registries	8 months
Conceptual aspects	- Production of documents and a Power Point presentation explaining the OMOP CDM and the federated approach to all stakeholders - Organization of a plenary kick-off meeting with all stakeholders	3 months
	- Organization of regular team meetings for each registry to monitor progress	Per registry 2h/week

Table E1. Continued.

Topic	Tasks	Estimated average time needed
Technical aspects	- Provision/hire of a dedicated Linux server for each registry (local data centre or cloud environment) for the installation and setup of the FAP, with access to a local copy of the source database; - Provision to all required parties of access to the Linux registry servers - Testing of the functioning of the FAP on local Linux servers by SME	Per registry 2 months
Mapping aspects	- Checks source data quality - Provision of registry data dictionary to SME by source data experts - Provision of a representative, but anonymized registry data sample by local team to smoothen ETL process and avoid “black box mapping” - Assistance by clinical experts in optimizing the mapping - Provision by SME to statistician(s) of a codebook of the variables mapped	Per registry 3 months
Analytical aspects and Quality control	- Learning by statistician(s) on the principles of OHDSI and OMOP common data model - Provision by SME of access to FAP for statistician(s) - Creation by statistician of scripts in R (or OHDSI tools for the production of descriptive summary statistics	1 month
	- Execution by local analyst in each country of the pre-written R-script via the FAP - Checks by clinical on the validity of the output and provision of feedback to statistician and SME Revision by source data expert and SME of any mapping issues. - Creation of a second round of data summaries and a repeat of the quality control process - Production of final OMOP CDM tables	Per registry 3 months
Research studies	- Creation of research protocol and approval by CRC, local clinical experts and registry owners - Identification of dedicated local teams for each registry, comprising clinical experts, source data experts and data analysts. - Creation of a formal analysis plan by a statistician, for review and approval by representatives of all participating registries - Creation by statistician of analysis scripts in R (or OHDSI tools)	Depending the magnitude and complexity of the study ≥6 months

Table E2. Countries engaged in SHARP CRC and their registry's status for the SHARP FAP.

SHARP Countries	Registry Name	Status: Connection to SHARP FAP	Comments
Austria	ASA-Net: Austria Severe Asthma Net	Not Connected	Under communication to integrate SHARP Central Registry
Belgium	BSAR: Belgium Severe Asthma Registry	Connected	
Croatia	SHARP Central	Connected	
Czech Republic	GAN: German Asthma Network	Connected	
Denmark	DSAR: Danish Severe Asthma Registry	Connection ongoing	
Estonia	SHARP Central	Connected	
Finland		Not Connected	Under communication to integrate the FAP
France	RAMSES: The French registry of severe asthma patients	Connected	
Germany	GAN	Connected	
Greece	HTS-SAR: Hellenic Thoracic Society -Severe Asthma Registry	Connected	
Hungary	SHARP Central	Connected	
Iceland		Not Connected	Under communication to integrate the FAP
Ireland	SHARP Central	Connection ongoing	
Italy	SANI: Severe Asthma Network Italy	Connected	
Latvia	SHARP Central	Connected	
Lithuania	SHARP Central	Connected	

Table E2. Continued.

SHARP Countries	Registry Name	Status: Connection to SHARP FAP	Comments
Netherlands	RAPSODI/SHARP Central	Connected	
Poland	SHARP Central	Connected	
Portugal	RAG: Registo de Asma Grave Portugal	Connected	
Romania	SHARP Central	Connected	
Russia		Not Connected	Russian Pulmonary society declined the invite to the SHARP FAP
Serbia	SHARP Central	Connected	
Slovenia	SHARP Central	Connected	
Spain	GEMA: Spanish Asthma Guidelines	Connected	
Sweden	SHARP Central	Connected	
Switzerland	GAN	Connected	
Turkey	SHARP Central	Connected	
United Kingdom	UKSAR: UK Severe Asthma Registry	Connection ongoing	

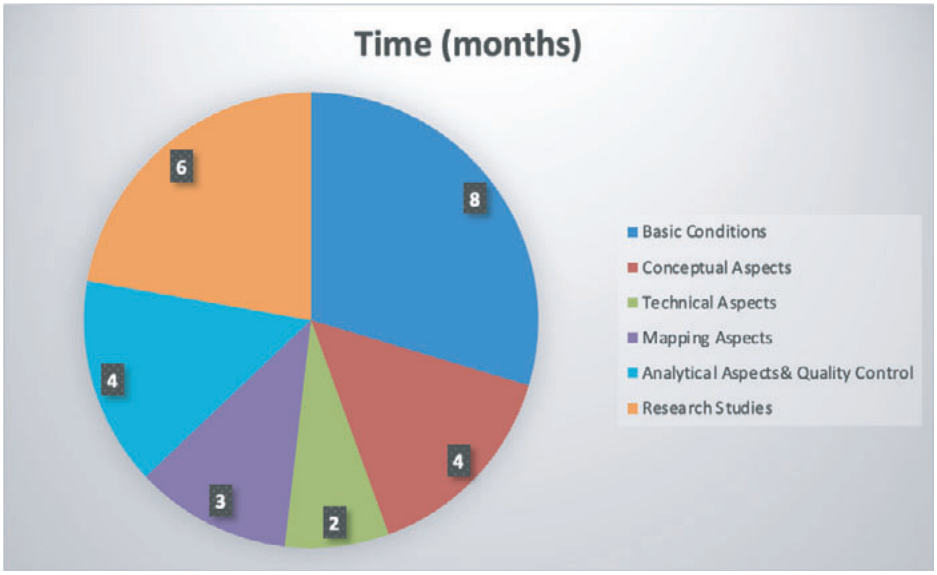
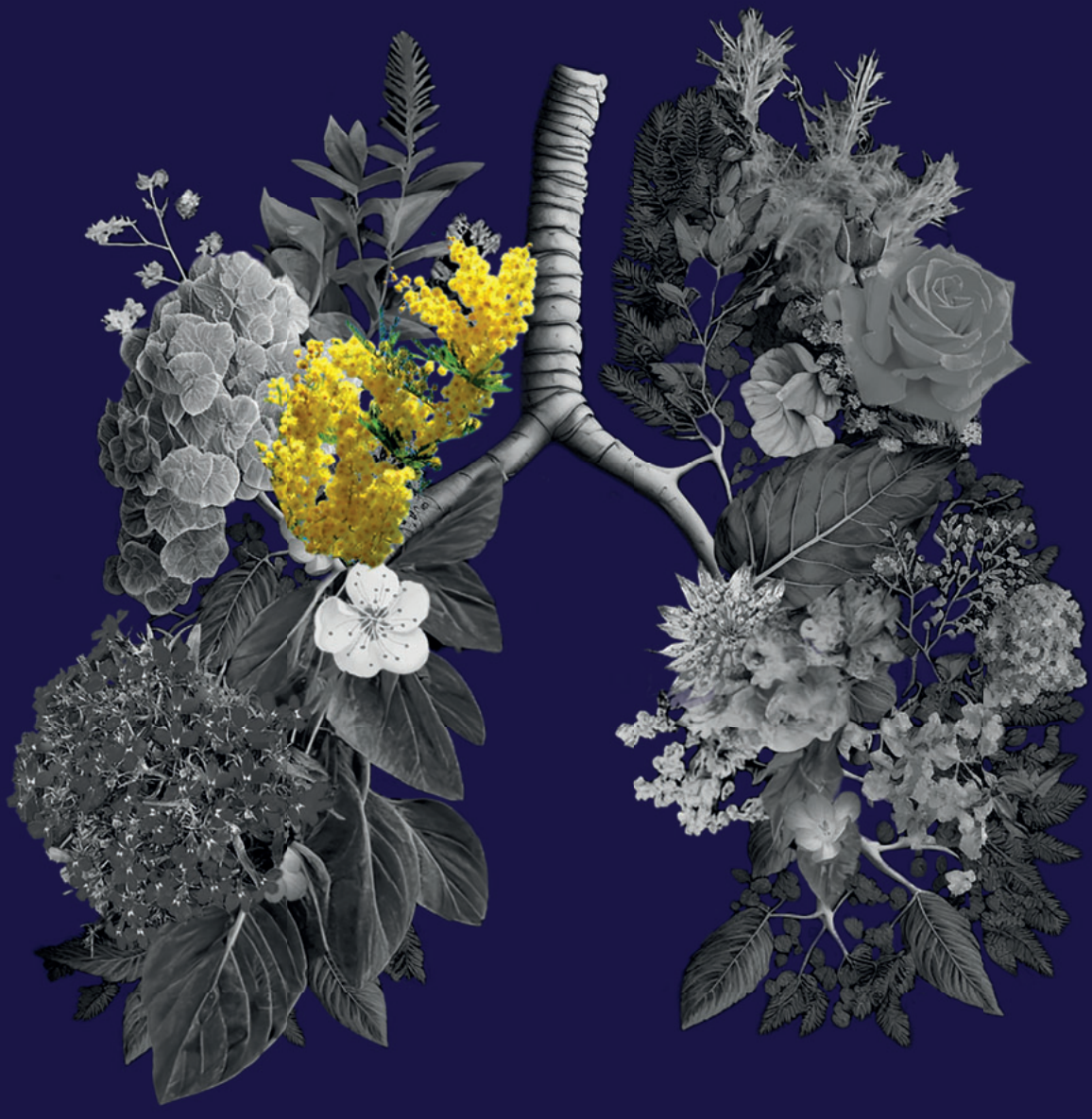


Figure E1. Pie Chart and time required for building a FAP plus proof of principle study.



Chapter 6

Evaluation of Real-World Mepolizumab Use in Severe Asthma across Europe - the SHARP experience with privacy-preserving federated analysis

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ABSTRACT

Background

An objective of the Severe Heterogeneous Asthma Registry, Patient-centered (SHARP) is to produce real-world evidence on a pan-European scale by linking non-standardized, patient-level registry-data. Mepolizumab has shown clinical efficacy in RCTs and prospective real-world studies and could therefore serve as a proof of principle for this novel approach.

Aim

To harmonize data from 10 national severe asthma registries and characterize patients receiving mepolizumab, assess its effectiveness on annual exacerbations and maintenance oral glucocorticoid (OCS) use, and evaluate treatment patterns.

Methods

Registry data (5,871 patients) were extracted for harmonization. Where harmonization was possible, patients who initiated mepolizumab between 1-1-2016 and 31-12-2021 were examined. Changes of a 12 (range 11-18) months period in frequent (≥2) exacerbations, maintenance OCS use and dose were analyzed in a privacy-preserving manner using meta-analysis of generalized estimating equation parameters. Periods before and during the COVID-19 pandemic were analyzed separately.

Results

In 912 patients who fulfilled selection criteria mepolizumab significantly reduced frequent exacerbations (OR;95%CI: 0.18;0.13-0.25), maintenance OCS use (OR;95%CI: 0.75;0.61-0.92) and dose (mean; 95%CI: -3.93 mg/day; -5.24--2.62) in the Pre-Pandemic group, with similar trends in the Pandemic group. Marked heterogeneity was observed between registries in patient characteristics and mepolizumab treatment patterns.

Conclusions

By harmonizing patient-level registry data and applying federated analysis, SHARP demonstrated the real-wold effectiveness of mepolizumab on asthma exacerbations and maintenance OCS use in patients with severe asthma across Europe, consistent with previous evidence. This paves the way for future pan-European real-world severe asthma studies using patient-level data in a privacy-proof manner.

INTRODUCTION

Meta-analyses of randomized controlled trials (RCTs) have shown that biological therapies targeting interleukin (IL)-5 are effective in patients with severe eosinophilic asthma and lead to significant improvements in exacerbation rates, oral corticosteroid (OCS) use, asthma control and health related quality of life[1-3]. However, these RCTs are performed in highly selected populations under standardized and fully controlled conditions typically different from those in clinical practice[4,5]. Therefore, real-world evidence is an indispensable complement to RCTs as it will help to elucidate which patients are prescribed these therapies and how effective they are in terms of relevant clinical endpoints[6].

Many European countries have established registries of patients with severe asthma in order to collect real-world data on the impact of novel biological treatments[7]. Unfortunately, each single country usually has a limited number of included patients, restricting the ability to deliver generalizable evidence and answer important research questions. Therefore, combining patient-data from multiple countries and institutes is required in order to generate more robust and meaningful outcomes by increasing sample size and statistical power.

The European Respiratory Society (ERS) clinical research collaboration SHARP (Severe Heterogeneous Asthma Registry, Patient-centered) was set up to harmonize severe asthma management across Europe and unravel heterogeneity in a patient-centered way[8]. An objective of SHARP is to produce real-world evidence on a pan-European scale by linking together all available data from the national severe asthma registries that are part of the SHARP network. However, linking data from pre-existing registries is challenging, due to unavoidable discrepancies between the data collection models and limitations on the transfer of privacy-sensitive data[9]. For that reason, SHARP leveraged a federated analytics platform that enabled privacy-preserving analysis of distributed datasets and could deliver accurate results without revealing sensitive data[10-12].

The first research question that SHARP aimed to answer using this federated analytics platform, and which would also serve as proof of principle for this novel approach, was to assess the real-world effectiveness of mepolizumab in patients with severe asthma in Europe. Mepolizumab was the first anti-interleukin-5 biologic for severe eosinophilic asthma available in most European countries[13]. Its clinical efficacy has been demonstrated in multiple randomized, double-blind clinical trials showing roughly a halving of the rate of severe asthma exacerbations, a significant

reduction in maintenance oral glucocorticoid use and improved health-related quality of life[14-17]. Other prospective and closely monitored studies also showed that unselected patients with severe eosinophilic asthma who were prescribed mepolizumab in a real-life setting showed similar improved outcomes[18,19].

The present study was designed to evaluate the real-world use of mepolizumab in patients with severe asthma who had been included and followed up in national disease registries of several European countries since the introduction of mepolizumab. The aim of the study was to characterize patients receiving mepolizumab, evaluate treatment patterns, and assess the effectiveness of mepolizumab on the annual rate of exacerbations and maintenance oral glucocorticoid use, using a federated analysis approach.

METHODS

Study population and design

This was a real-world observational study involving the extraction and analysis of patient-level data from non-standardized severe asthma registries from 10 countries in Europe. Most European registries included patients who fulfilled the severe asthma criteria according to the ERS/American Thoracic Society (ATS) guidelines [20], or to national asthma guidelines, and in some cases other patients who attended specialist asthma centres were included as well based on clinical judgement of the treating specialist. The final results were obtained from adult patiens with severe asthma who initiated mepolizumab between 1 January 2016 and 31 December 2021 and had a follow-up visit available at 1 year (11-18 months) after mepolizumab initiation, or at the time of stopping mepolizumab, if sooner. Patients were excluded if they had received another biological treatment for severe asthma in the 12 months prior to inclusion in order to ensure that the change in clinical outcomes was as much as possible due to mepolizumab treatment.

We distinguished two separate study periods as it was likely that the COVID-19 pandemic would have influenced the treatment of patients with mepolizumab in terms of initiation, modification and discontinuation of concomitant treatments, as well as outcomes such as the number of asthma exacerbations[21]. The first period was pre-pandemic (PP) and was defined by the initiation and follow-up of mepolizumab treatment between 1 January 2016 and 31 March 2020. The second period spanned the pandemic (Pan) and was defined by initiation and/or follow-up of mepolizumab treatment between 1 April 2020 and 31 December 2021.

Patients' informed consent for using their data for international research purposes was collected at registry enrolment; the respective national medical ethics committees approved the study protocol.

Data Source

Ten individual SHARP registries agreed to participate in the study and to have their data used for federated analyses. The database field names of each national registry were harmonized to concepts via the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) developed by the Observational Health Data Sciences and Informatics (OHDSI) community [11,22]. A Federated Analysis IT-Platform (FAP) was then developed and implemented by SHARP in order to generate summary statistics from the harmonized registries, ensuring that individual patient data would remain at the local sites.

The process of, and experiences with, the registry mapping, development and implementation of the FAP has been described separately[23].

Study outcomes

Two time points were considered: Initiation of mepolizumab (baseline) and 11-18 months after baseline (follow-up). Clinical comparisons were drawn between the baseline and follow-up.

Primary outcomes

Co-primary study outcomes included: (1) change in frequent (≥2/year) severe exacerbations and (2) change in maintenance use and daily dose of oral corticosteroids after 1 year (11-18 months) of mepolizumab treatment.

Secondary outcomes

Secondary outcomes included the description of 1) characteristics of patients prescribed mepolizumab in the 10 registries; 2) mepolizumab treatment patterns (i.e. rates of discontinuation of mepolizumab and/or switching to another biologic).

Study variables and definitions

Study variables included: demographics, pulmonary function (Forced Expiratory Volume in one second (FEV_1), comorbidities (nasal polyposis), inflammatory markers (blood eosinophils, fraction of exhaled nitric oxide (FeNO), total Immunoglobulin E (IgE)), exacerbation rate, OCS use, OCS maintenance dose, and pattern of mepolizumab treatment (discontinuation or switch to another biologic).

Severe asthma exacerbations were defined by at least one of the following criteria: 1) patient reported use of OCS courses (if not on maintenance OCS) 2) patient reported doubling of maintenance dose of OCS for at least 3 days; 3) Patient reported unscheduled emergency visits or hospitalization for asthma. Frequent exacerbations were defined as ≥2 exacerbations per year. This categorical variable was chosen to maximize the availability of this outcome variable due to different methods of recording annual exacerbation rate across registries.

Maintenance oral corticosteroid dose was expressed as the prednisolone-equivalent daily maintenance dose of oral corticosteroids (mg/day).

Statistical analysis

Continuous variables were expressed as means (SD) or median (IQR) as appropriate, and categorical variables as n (%). Generalized estimating equations (GEE) were used to derive a parameter estimate for the difference between time windows (baseline and follow-up). The outcomes of interest were regressed upon time-window (pre/post), and a sandwich estimator was used to correct the standard errors for within-person correlation, where present. It is noted that there was a mixture of paired and unpaired observations. An inverse variance-weighted, fixed-effects meta-analysis was used combine results and estimate effect sizes across participating registries, and results were presented in a forest plot. The PP and Pan groups were analyzed separately. To describe treatment patterns of mepolizumab, a tabular summary was generated, by registry. The discontinuation date was set at 28 days after the last known prescription. Discontinuation was also considered to have occurred if there was a break of at least 90 days between prescriptions; the 90 days were measured from the end of the last known prescription plus 28 days. All statistical analyses were performed using R Statistical Software version 4.1.2[24].

RESULTS

Patients

Figure 1 shows the flow chart of inclusion in the study. Of 5871 patients with severe asthma included in the 10 national registries, 2109 initiated mepolizumab treatment. A total of 912 patients met the additional inclusion criteria of consent for an international study; initiation of treatment between 1 January 2016 and 31 December 2021 and no biologic treatment for severe asthma for one year prior. Six hundred and seventy-one patients initiated mepolizumab and had follow-up data before the COVID-19 pandemic (PP) and 241 patients either initiated mepolizumab or were followed-up during the pandemic (Pan) (Figure 1).

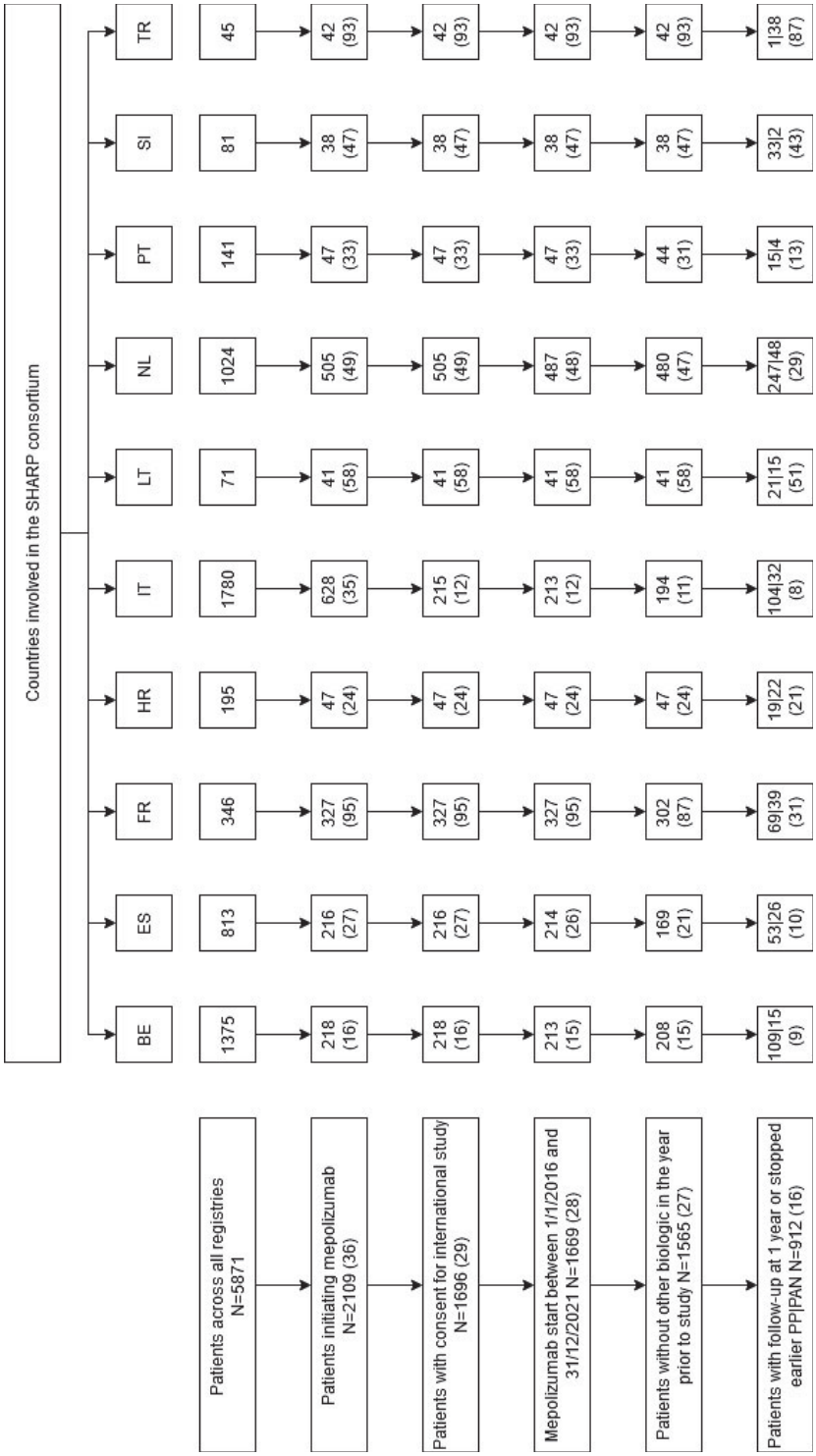

Figure 1: Flow chart of selected patients (N (%)). Abbreviations: BE: Belgium, ES: Spain, FR: France, HR: Croatia, IT: Italy, LT: Lithuania, NL: Netherlands, PAN: Pandemic group, PP: Pre-Pandemic group, PT: Portugal, SI: Slovenia, TR: Turkey.

Table 1: Baseline characteristics per country, Pre-Pandemic

	BE (N=109)	ES (N=53)	FR (N=69)	HR (N=19)
Age at index (years)*	55.39 (15.92)	58.3 (13.63)	52.55 (13.25)	54.32 (13.84)
Female‡	62 (56.9)	40 (75.5)	44 (63.8)	15 (78.9)
BMI (kg/m2)*	27.04 (5.37)	28.6 (5.36)	26.08 (4.25)	25.92 (5.2)
Age of onset (years)*	-	-	34.65 (18.97)	36.32 (17.88)
Adult onset‡	-	-	53 (81.5)	16 (84.2)
Current smoker‡	3 (2.8)	1 (2)	4 (6)	1 (5.3)
Previous smoker‡	37 (33.9)	18 (36)	27 (40.3)	5 (26.3)
Pack years†	15.5 (8,30)	8 (3,30)	11.25 (5,18)	22.5 (12,37)
Blood eosinophil count (*10^9 cells/L) †	0.59 (0.36,1)	0.52 (0.4,0.8)	0.31 (0.12,0.51)	0.5 (0.15,1.01)
Total IgE (kU/L) †	111 (60,207)	71 (65,262)	93.7 (43,224)	271 (8.3,287)
Frequent exacerbations (≥2/year) ‡	54 (79.4)	-	-	11 (68.8)
OCS maintenance‡	22 (35.5)	8 (80)	12 (29.3)	-
Daily OCS dose (mg/day)*	7.98 (3.05)	9.12 (8.69)	16.36 (8.97)	-
FEV_1 pre-BD (%pred)*	58.29 (18.86)	57.69 (18.55)	49.43 (17.94)	59.88 (23.19)
FEV_1 post-BD (%pred)*	-	60.82 (18.98)	57 (12.55)	48.62 (19.33)
FeNO (ppb)†	46 (23,68)	21 (19.2,27.3)	30 (10.82,80)	29.5 (23.5,66)
Nasal polyps‡	56 (51.4)	27 (50.9)	22 (31.9)	9 (47.4)

*: Mean (SD), †: Median (IQR), ‡: n (%)
Abbreviations: BE: Belgium, BMI: Body Mass Index, ES: Spain, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, FR: France, HR: Croatia, IQR: interquartile range, IT: Italy, LT: Lithuania, NL: Netherlands, OCS: Oral corticosteroids (prednisone equivalents), PT: Portugal, SD: Standard Deviation, SI: Slovenia, TR: Turkey.

IT (N=104)	LT (N=21)	NL (N=247)	PT (N=15)	SI (N=33)	TR (N=1)
56.15 (11.34)	55.86 (12.66)	54.84 (14.78)	56.33 (15.23)	57.85 (11.38)	-
67 (64.4)	13 (61.9)	128 (51.8)	10 (66.7)	23 (69.7)	-
24.98 (4.45)	27.86 (5.21)	28.14 (5.59)	27.85 (4.3)	25.62 (4.66)	-
37.43 (16.48)	36.05 (21.3)	37.96 (20.08)	33.33 (21.89)	40.53 (16.99)	-
92 (88.5)	17 (81)	180 (77.6)	9 (60)	28 (87.5)	-
3 (2.9)	0 (0)	1 (0.4)	0 (0)	0 (0)	-
23 (22.1)	4 (19)	107 (43.3)	2 (13.3)	10 (30.3)	-
10.5 (5.4,22.5)	12 (3.25,22.5)	10 (5,20)	12.5 (5,20)	15 (7.5,20)	-
0.59 (0.3,0.8)	0.41 (0.35,0.56)	0.39 (0.2,0.63)	-	0.37 (0.22,0.61)	-
99.8 (48.2,181)	36.6 (19,103)	110 (50,246)	17 (15,51)	150 (47,247)	-
45 (53.6)	19 (95)	114 (65.9)	-	23 (74.2)	-
47 (52.2)	5 (26.3)	73 (60.3)	3 (60)	12 (42.9)	-
19.12 (14.41)	19 (7.42)	14.37 (14.31)	-	10.25 (7.53)	-
76.51 (21.54)	69.7 (34.79)	75.16 (21.85)	74.81 (31.73)	66.74 (21.77)	-
83.14 (17.89)	62.33 (22.01)	80.84 (21.28)	66.9 (15.72)	77.88 (10.51)	-
44 (30,73)	40 (27,72)	36 (23,64)	-	89.5 (60,101)	-
62 (59.6)	6 (28.6)	115 (46.6)	4 (26.7)	17 (51.5)	-

Table 2: Baseline characteristics per country, during the COVID-19 Pandemic

	BE (N=15)	ES (N=26)	FR (N=39)	HR (N=22)
Age at index (years)*	58.87 (13.26)	58.19 (11.28)	51.82 (16.66)	56.32 (13.76)
Female‡	8 (53.3)	17 (65.4)	23 (59)	19 (86.4)
BMI (kg/m2)*	27.53 (4.02)	28.77 (4.16)	26.36 (3.97)	27.46 (7)
Age of onset (years)*	-	-	39.44 (18.59)	39.55 (16.96)
Adult onset‡	-	-	32 (82.1)	21 (95.5)
Current smoker‡	2 (13.3)	1 (4.2)	1 (2.6)	1 (4.5)
Previous smoker‡	6 (40)	6 (25)	12 (31.6)	6 (27.3)
Pack years†	15 (10,30)	10.5 (3.8,20.3)	19.5 (10,37.5)	25 (15,40)
Blood eosinophil count (*10^9 cells/L) †	1 (0.61,1.25)	0.5 (0.33,0.65)	0.31 (0.1,0.52)	0.7 (0.28,0.88)
Total IgE (kU/L) †	216 (78,317)	83.5 (47,133.5)	157 (101,233)	111 (63.9,264)
Frequent exacerbations (≥2/year) ‡	5 (62.5)	-	5 (83.3)	12 (66.7)
OCS maintenance‡	1 (16.7)	4 (44.4)	6 (20.7)	2 (50)
Daily OCS dose (mg/day)*	5 (-)	12.43 (15.05)	17.76 (18.54)	12.5 (4.95)
FEV_1 pre-BD (%pred)*	62.83 (23.88)	82.72 (20.43)	70.33 (22.24)	64.52 (21.19)
FEV_1 post-BD (%pred)*	-	84.81 (23.51)	83.24 (15.81)	66.84 (18.38)
FeNO (ppb)†	44.5 (21.5,91.5)	67.85 (62,91)	85 (20.7,89)	30.5 (14.5,50)
Nasal polyps‡	10 (66.7)	9 (34.6)	17 (43.6)	8 (36.4)

*: Mean (SD), †: Median (IQR), ‡: n (%)
Abbreviations: BE: Belgium, BMI: Body Mass Index, ES: Spain, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, FR: France, HR: Croatia, IQR: interquartile range, IT: Italy, LT: Lithuania, NL: Netherlands, OCS: Oral corticosteroids (prednisone equivalents), PT: Portugal, SD: Standard Deviation, SI: Slovenia, TR: Turkey.

IT (N=32)	LT (N=15)	NL (N=48)	PT (N=4)	SI (N=2)	TR (N=38)
56.94 (10.3)	61.13 (12.52)	60.27 (12.17)	-	-	48.34 (10.89)
24 (75)	8 (53.3)	27 (56.2)	-	-	19 (50)
25.67 (4.24)	29.74 (4.17)	28.83 (5.74)	-	-	26.87 (3.89)
37.47 (14.81)	43.67 (19.45)	38.32 (23.9)	-	-	36.16 (12.4)
28 (87.5)	13 (86.7)	35 (74.5)	-	-	36 (94.7)
0 (0)	1 (6.7)	0 (0)	-	-	1 (2.6)
10 (31.2)	5 (33.3)	27 (56.2)	-	-	10 (26.3)
8.75 (2.5,15)	16.5 (5,30)	11 (5,15)	-	-	5.5 (4,7)
0.6 (0.39,0.76)	0.64 (0.4,0.76)	0.31 (0.2,0.52)	-	-	0.7 (0.4,1.2)
131.1 (51.9,208)	160 (42.8,220)	118 (57,221)	-	-	168 (94.7,292)
15 (65.2)	13 (92.9)	25 (61)	-	-	30 (81.1)
14 (45.2)	1 (10)	12 (50)	-	-	18 (50)
25.68 (14.52)	40 (-)	11.82 (8.59)	-	-	16.56 (10.69)
74.89 (20.25)	54.25 (12.72)	79.51 (23.74)	-	-	72.12 (22.77)
91.33 (27.86)	63 (20.4)	90.95 (23.96)	-	-	68.17 (19.23)
23 (21,80)	41.5 (30,61)	34.5 (14,48)	-	-	22 (16,25)
16 (50)	5 (33.3)	14 (29.2)	-	-	24 (63.2)

Tables 1 (PP) and 2 (Pan) summarize the characteristics of the study patients from each national registry at initiation of mepolizumab treatment for the two time-periods. The majority of patients had ≥2 exacerbations per year and the use of maintenance OCS ranged from 26.3% to 80% in the PP group and 10% to 50% in the Pan group. Although no patient had received biological treatment for severe asthma in the one year prior to inclusion in this analysis, six patients in the PP group, and one in the Pan group had earlier received another biologic for severe asthma.

Exacerbation rate

Annual exacerbation rate data were available from 369 patients in the PP group and from 194 patients in the Pan group (Figure 2). The odds of having experienced ≥2 exacerbations per year after mepolizumab initiation was significantly reduced for both the PP group (OR;95%CI: 0.18;0.13-0.25, p<0.001) and the Pan group (OR;95%CI: 0.08;0.05-0.13, p<0.001).

Maintenance oral corticosteroids use

Figure 3 shows the odds of receiving maintenance OCS therapy at follow-up. Data on maintenance OCS use were available for 449 patients in the PP group and 138 patients in the Pan group. For the PP group, the odds of patients receiving maintenance OCS at follow-up was significantly reduced from baseline (OR;95%CI: 0.75;0.61-0.92, p=0.005), whereas for the Pan group the effect was not statistically significant (OR;95%CI: 0.91;0.67-1.23, p=0.527). The reduction in maintenance OCS dose is shown in Figure 4. Data on daily OCS maintenance dose were available for 161 patients in the PP group. The maintenance OCS dose was significantly different from baseline (mean; 95%CI: -3.93 mg/day; -5.24- -2.62, p<0.001). For the Pan group, the dose of maintenance OCS at follow-up was not significantly different from baseline (mean; 95%CI: -0.88 mg/day; -1.91-0.15, p=0.096). However, the available data were extremely limited, with only two countries contributing (Italy (n=15); Turkey (n=19)).

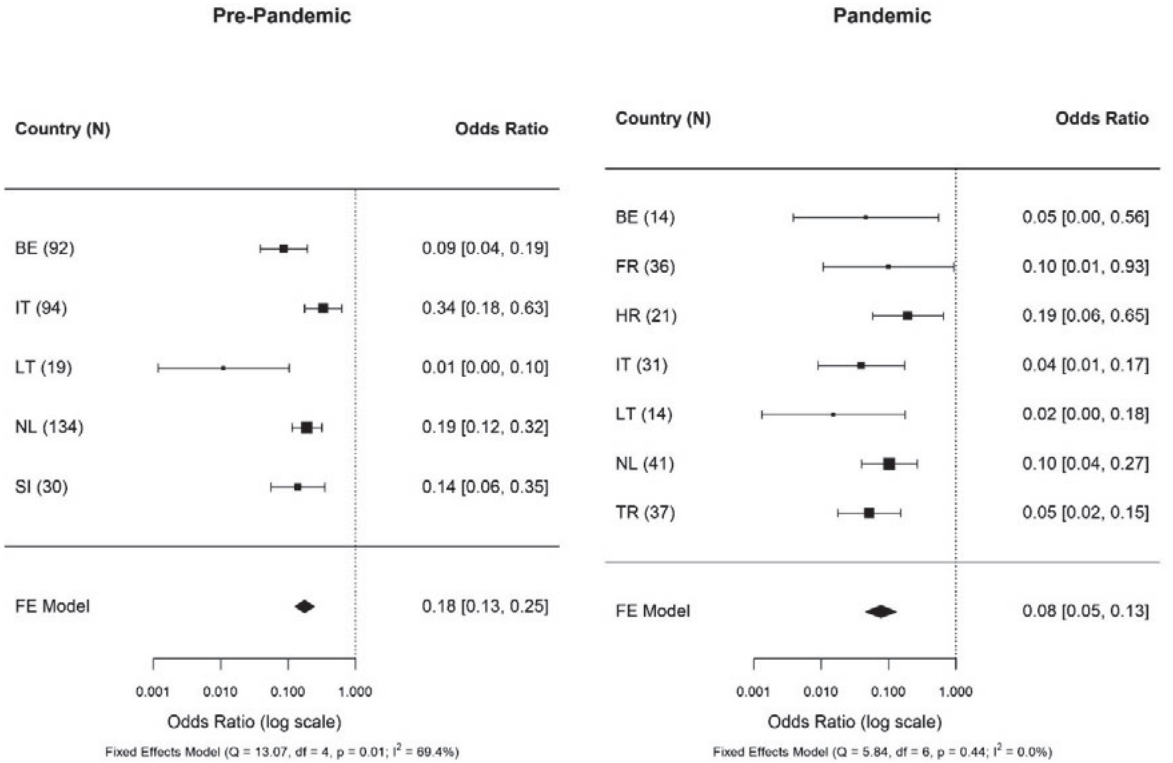

Figure 2: Forest plot of the odds of having experienced ≥2 exacerbations per year after mepolizumab initiation. This figure shows the odds of having experienced ≥2 exacerbations per year after mepolizumab initiation compared to the year before initiating mepolizumab for the individual countries and the countries combined. The odds were statistically significantly reduced for both the Pre-Pandemic group (N=369) as for the Pandemic group (N=194).

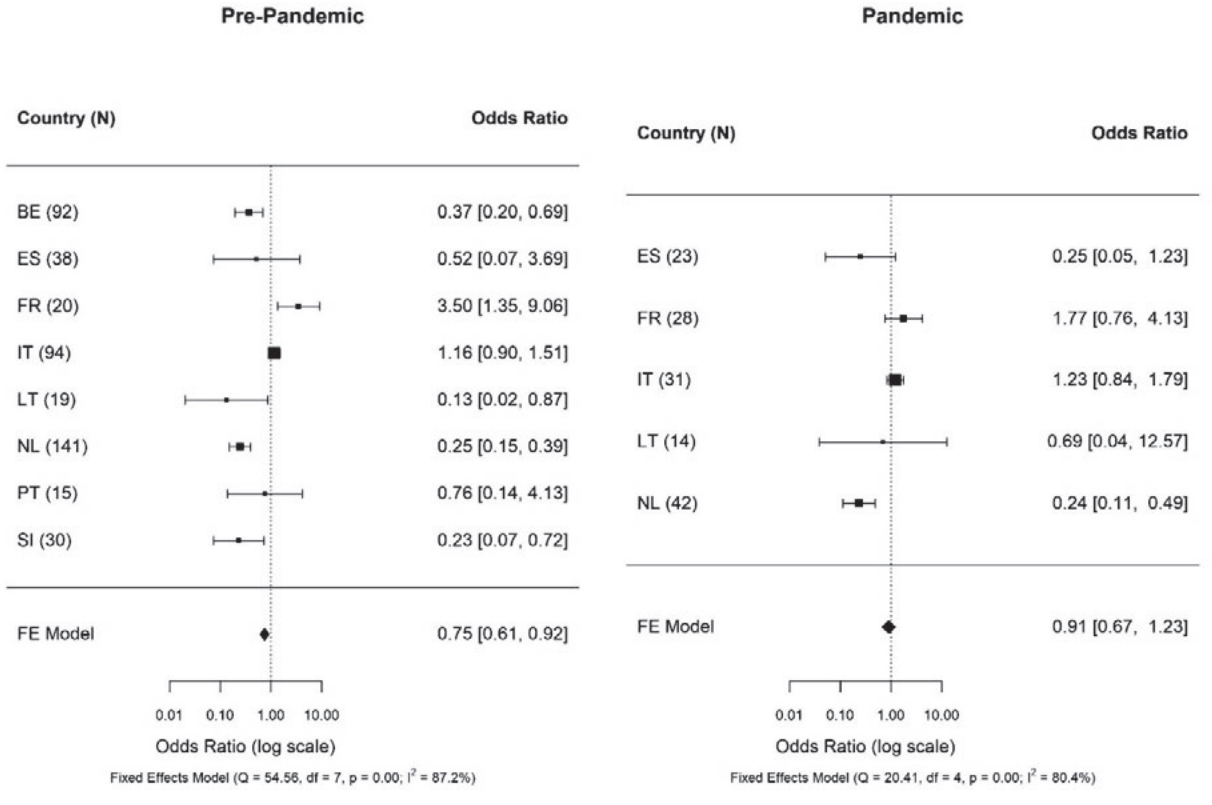

Figure 3: Forest plot of the odds of receiving maintenance oral corticosteroid treatment after mepolizumab initiation. This figure shows the odds of receiving maintenance oral corticosteroid treatment after mepolizumab initiation for the individual countries and the countries combined. The odds were statistically significantly reduced from baseline for the Pre-Pandemic group (N=449), but not for the Pandemic group (N=138).

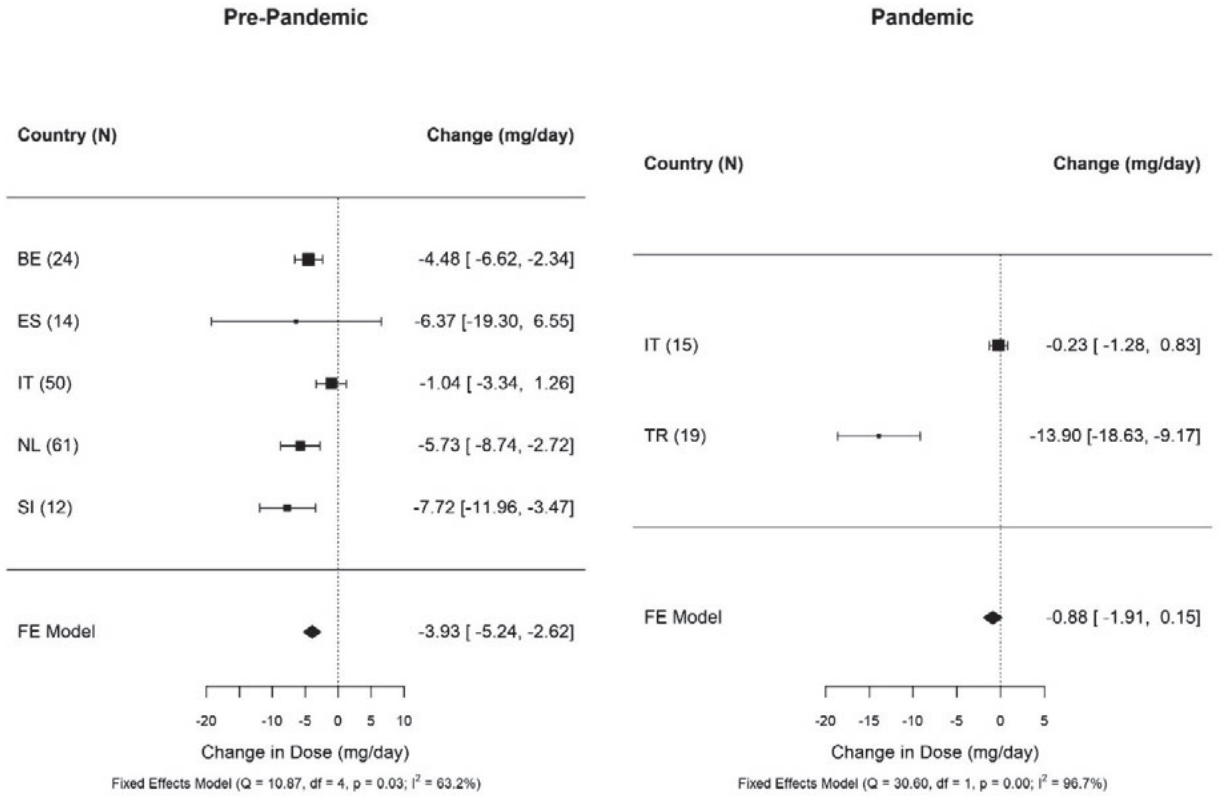

Figure 4: Forest plot of the reduction in mean maintenance oral corticosteroid dose after mepolizumab initiation. This figure shows the reduction in mean maintenance oral corticosteroid dose after mepolizumab initiation for the individual countries and the countries combined. The dose was statistically significantly reduced from baseline for the Pre-Pandemic group (N=161), but not for the Pandemic group (N=34).

Characteristics of patients prescribed with mepolizumab

The baseline characteristics of patients in the analysis set are shown graphically by country in Figure E1 in the supplementary materials. These figures show marked heterogeneity in characteristics, both within individual registries between the periods before and during the pandemic, and between registries. For example, the proportion of previous smokers ranges from 13.3% to 43.3% in the PP group and 25% to 56.2% in the Pan group. Similarly, BMI, age and total IgE show marked differences between periods and between registries.

Treatment patterns

A total of 475 (71%) patients in the PP group continued mepolizumab treatment at follow-up, while 291 (91%) patients in the Pan group continued mepolizumab treatment (Tables 3 and 4). There were marked differences between countries in the number of patients that stopped biological treatment or switched to another biologic. One third of patients in France stopped biological therapy in the pre-pandemic period and patients in the French and Dutch registries most frequently switched to another anti-IL-5 targeting biologic (23% and 26% respectively, in the pre-pandemic period).

Table 3: Treatment patterns in Pre-Pandemic period

	All N=671	BE (N=109)	ES (N=53)	FR (N=69)	HR (N=19)	IT (N=104)	LT (N=21)	NL (N=247)	PT (N=15)	SI (N=33)	TR (N=1)
Patients who continued using mepolizumab at follow-up (N,%)	475 (71)	92 (84)	40 (76)	27 (39)	15 (79)	96 (92)	19 (90)	141 (57)	15 (100)	30 (91)	-
Patients who stopped all biological therapy during follow-up (N,%)	94 (14)	14 (13)	8 (15)	23 (33)	4 (21)	6 (6)	1 (5)	35 (14)	0 (0)	3 (9)	-
Patients who switched to another biological during follow-up (N,%)	101 (15)	3 (3)	5 (1)	19 (28)	0 (0)	2 (2)	1 (5)	71 (29)	0 (0)	0 (0)	-
Omalizumab (N)	6	0	0	2	-	1	0	3	-	-	-
Reslizumab (N)	37	0	2	0	-	0	0	35	-	-	-
Benralizumab (N)	52	3	3	16	-	1	1	28	-	-	-
Dupilumab (N)	6	0	0	1	-	0	0	5	-	-	-
Months of mepolizumab therapy in patients who stopped or switched during follow-up (Median, IQR))	*	6 (5.2, 9.6)	4.9 (3.4,9.2)	6 (5,9.9)	4.8 (3.9,5)	7.2 (3.2,8.2)	5.6 (4.2,7)	5.5 (3.6,8.4)	-	11.1 (7.4,11.5)	-

* Not calculable from medians extracted
Abbreviations: BE: Belgium, ES: Spain, FR: France, HR: Croatia, IQR: interquartile range, IT: Italy, LT: Lithuania, NL: Netherlands, PT: Portugal, SI: Slovenia, TR: Turkey.

Table 4: Treatment patterns in the Pandemic period

	All (N=241)	BE (N=15)	ES (N=26)	FR (N=39)	HR (N=22)	IT (N=32)	LT (N=15)	NL (N=48)	PT (N=4)	SI (N=2)	TR (N=38)
Patients who continued using mepolizumab at follow-up (N,%)	219 (91)	14 (93)	23 (88)	36 (92)	21 (95)	31 (97)	14 (93)	42 (88)	-	-	38 (100)
Patients who stopped all biological therapy during follow-up (N,%)	13 (5)	1 (7)	3 (12)	0 (0)	1 (5)	1 (3)	1 (7)	6 (12)	-	-	0 (0)
Patients who switched to another biological during follow-up (N,%)	3 (1)	0 (0)	0 (0)	3 (8)	0 (0)	0 (0)	0 (0)	0 (0)	-	-	0 (0)
Omalizumab (N)	0	-	-	0	-	-	-	-	-	-	-
Reslizumab (N)	0	-	-	0	-	-	-	-	-	-	-
Benralizumab (N)	1	-	-	1	-	-	-	-	-	-	-
Dupilumab (N)	2	-	-	2	-	-	-	-	-	-	-
Months of mepolizumab therapy in patients who stopped or switched during follow-up (Median, IQR))	*	5.5 (5.5,5.5)	3.8 (2,4.8)	8.8 (8,9.4)	11.7 (11.7,11.7)	2.7 (2.7,2.7)	2.8 (2.8,2.8)	5.3 (2,6)	-	-	-

* Not calculable from medians extracted

Abbreviations: BE: Belgium, ES: Spain, FR: France, HR: Croatia, IQR: interquartile range, IT: Italy, LT: Lithuania, NL: Netherlands, PT: Portugal, SI: Slovenia, TR: Turkey.

DISCUSSION

In this study, SHARP succeeded in linking existing patient-level data from 10 different national registries for severe asthma to evaluate the use of mepolizumab therapy across Europe. With the use of a federated analysis approach, the study shows that treatment with mepolizumab significantly reduces severe exacerbations, as well as maintenance OCS use in patients with severe asthma. In addition, the results show substantial heterogeneity among patients initiating mepolizumab, and different patterns of mepolizumab treatments across European countries. The registry data used for this study were pre-existing and turned out to be far from complete for current purposes. This fact, in combination with strict requirement for defined entry and outcome data to be available to enable the federated analysis to be undertaken, resulted in a high analysis dropout rate. Thus, the results of this study, while in line with those of RCTs, should be interpreted with these limitations in mind.

The present real-world study supports and complements the results from RCTs and previous real-world studies on the effectiveness of mepolizumab therapy[5,14-17,25-28]. While RCTs involved large numbers of patients from around the world, most real-world studies were conducted with data from a single institution or national registry. In addition, these studies often included small numbers of patients[29]. We are aware of only one real-world study that used data from patients with severe asthma from different countries[18]. In contrast to our study, patients in this study were prospectively followed over time, capturing data from clinical practice and recorded in a standardized way. Our study, which made use of data already collected by clinicians in 10 different European countries, not only confirms the beneficial effects of mepolizumab from the previously published studies, but perhaps even more convincingly reflects the effectiveness of this biological agent in daily clinical practice.

In our study, we used a relatively new approach to link privacy-sensitive data from clinical disease registries. That process was not without its challenges. The complexity and labour-intensive nature of harmonising privacy-sensitive data from different sources has recently been extensively described by Biedermann and colleagues. In their study, three registries of pulmonary hypertension patients were linked and the data analysed in a federated manner[22]. The harmonization process in our study was even more complex, as all registries had a different data model. This makes our study the first to have harmonized and used non-standardized real-world disease registries to obtain real-world evidence. The harmonization process has been completed and the present proof-of-principle study has demonstrated

that this federated approach can produce valid results. The platform can now be further used to obtain real-world evidence to help guide better treatment and care to the many thousands of patients with severe asthma in Europe.

In addition to the exceptional method by which we have linked registries in a privacy-protective way, our research is unique in several respects. Successfully analysing patient-data that have been collected in clinical practice and entered into local registries by clinicians from 10 different countries without the involvement or monitoring of contract research organizations including pharmaceutical companies is unprecedented to date. This is probably the best method to get as close as possible to daily clinical practice and to compare treatment practices across countries. Another strength of our study is that our large-scale approach has allowed us to analyse pre- and during pandemic data separately, so that we could avoid bias due to the alterations in circulating pathogens and changed circumstances of care for patients with severe asthma.

Nevertheless, this study has its limitations. First, there are the limitations inherent to conducting real-world studies, for example lack of a control group. Second, many patients' data could not be included in the analysis because data were missing or incomplete, or because the moment of data collection was not recorded. In addition, some patients had not given informed consent to use their data for research outside the institution in which they were treated. Third, treatment outcomes could only be evaluated for patients still on mepolizumab after 1 year of follow-up, which may have led to a selection bias, potentially overestimating our results. Furthermore, a potential limitation of the analysis is that patients considered at baseline overlapped with, but were not exactly the same as those considered at follow-up. Where paired data were available, the correlation was appropriately accounted for in the analysis. Due to reasons of statistical power, the GEE analyses were not adjusted for possible confounders. Future larger studies might be able to repeat the analyses and include covariates. Finally, there was the effect of the COVID-19 pandemic. This led to many hurdles in data collection and forced us to split the analysis into two periods. Although this reduced the statistical power of the study, we still were able to demonstrate the beneficial effect of mepolizumab in reducing exacerbations in both the pre-pandemic and pandemic time periods.

Our study shows that mepolizumab treatment leads to a reduction in the number of exacerbations and in the use of maintenance oral corticosteroids. While this outcome was expected, it was reassuring to observe this finding in a setting alternative to randomized controlled trials or prospective observational studies,

as patients included in an RCT are strictly selected, and may differ significantly from real-world populations. Our results imply that physicians should not be concerned that the effect of mepolizumab in their patients with severe eosinophilic asthma will be below expectations, even if they are less rigorously selected in terms of factors that were exclusion criteria in the RCTs. Of note was the consistent reduction in exacerbations across the countries despite the heterogeneity in the patient populations, with respect to baseline demographics.

The characteristics of real-world patients not only differ from those in the RCTs, but our study also found that patients prescribed mepolizumab differed considerably between the different European countries. This heterogeneity may be due to differences in biologics reimbursement practices, to recommendations in national guidelines, or to preferences and choices of individual physicians. The differences in patient characteristics treated with mepolizumab before and during the pandemic may have influenced the extent to which some patients could or could not cope with remote care[21]. The heterogeneity of our population also illustrates that the definition of "severe asthma" does not appear to be used unambiguously. A revision of the international ERS/ATS definition of severe asthma may therefore be required. Interestingly, we also observed differences in oral corticosteroid tapering strategies, and this important medical practice also requires greater attention and harmonisation. Fortunately, an important first step in the right direction was recently taken with the PONENTE study[30,31].

A remarkable finding of our study is the difference between countries in the proportion of patients who continue or discontinue mepolizumab, or switch to another biological treatment. These switchers are likely to be patients who have partially responded to mepolizumab treatment, though have not yet shown full normalization of all outcome parameters[32]. The fact that such a switch has not been observed in all countries likely reflects different availability of alternative biologics and contrasting practices and levels of acceptance of what is a beneficial outcome. These findings define an area in which greater insight is needed. Until now the best treatment with biologics can only be found based on physician knowledge and experience. It would be less burdensome for all parties if switching of biologics were not necessary and we had good predictors of response. By continuing to use the federated analysis approach and by further optimizing national databases and enriching them with biological samples, finding reliable predictors will very likely become possible in the future. More so, if we apply artificial intelligence, machine learning and federated learning to clinical outcome data. The SHARP federated analysis platform is optimally suited for this.

In this study, SHARP demonstrated the real-world effectiveness of mepolizumab in patients with severe asthma from 10 different European countries. Mepolizumab reduced asthma exacerbations and OCS use consistent with evidence generated by RCTs. We observed heterogeneity in characteristics of patients receiving mepolizumab and in treatment patterns across countries, signalling the need for further alignment of asthma management across European countries. Our study can be seen as a successful proof of principle as to whether a federated analysis approach can be used to link privacy-sensitive data from different sources. It can thus serve as an example for other clinical research collaborations with a similar ambition. While there is still some room for improvement regarding completeness and quality of data, the SHARP federated analysis platform has great potential for future pan-European real-world severe asthma studies using patient-level data in a privacy-protected way.

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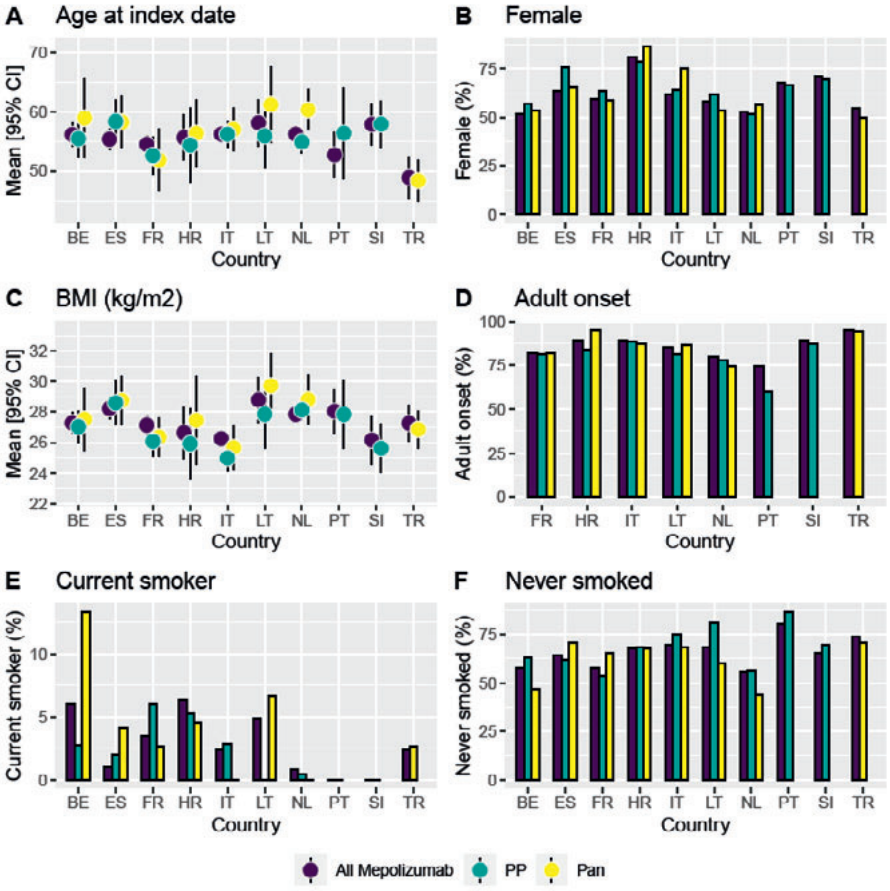
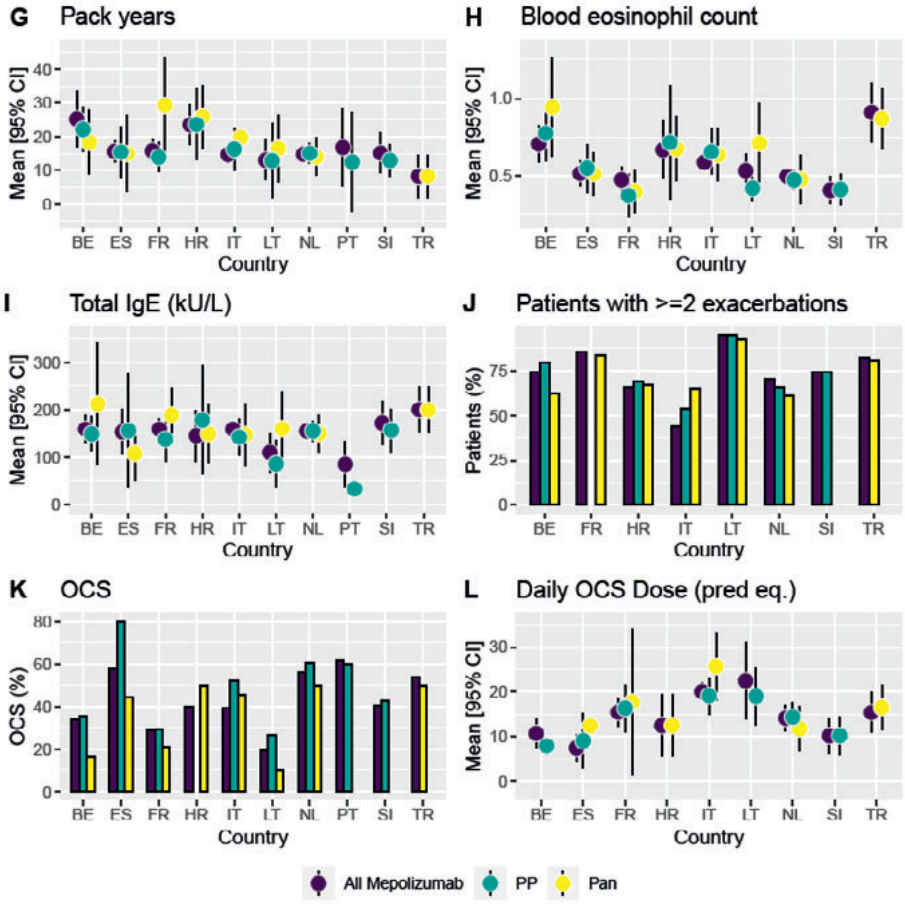
SUPPLEMENTAL MATERIALS

Supplemental Figure E1: Baseline characteristics shown graphically by country. This figure (Panels A-P) shows the baseline characteristics of patients in the analysis set graphically by country for all patients initiating mepolizumab, the Pre-Pandemic group and the Pandemic group. These figures show marked heterogeneity in characteristics, both within individual registries between the periods before and during the pandemic, and between registries.




G
Pack years
Mean [95% CI]
Country
H
Blood eosinophil count
I
Total IgE (kU/L)
J
Patients with >=2 exacerbations
Patients (%)
K
OCS
OCS (%)
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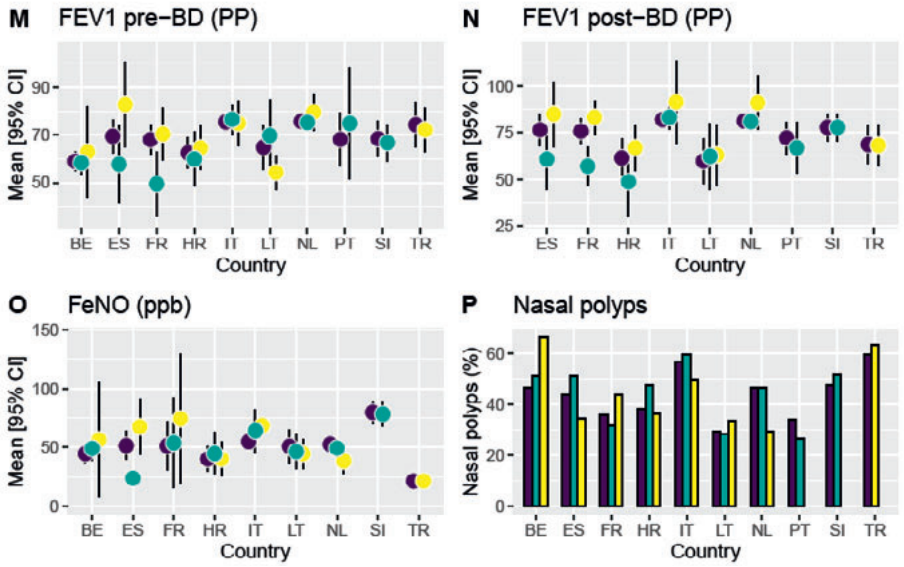
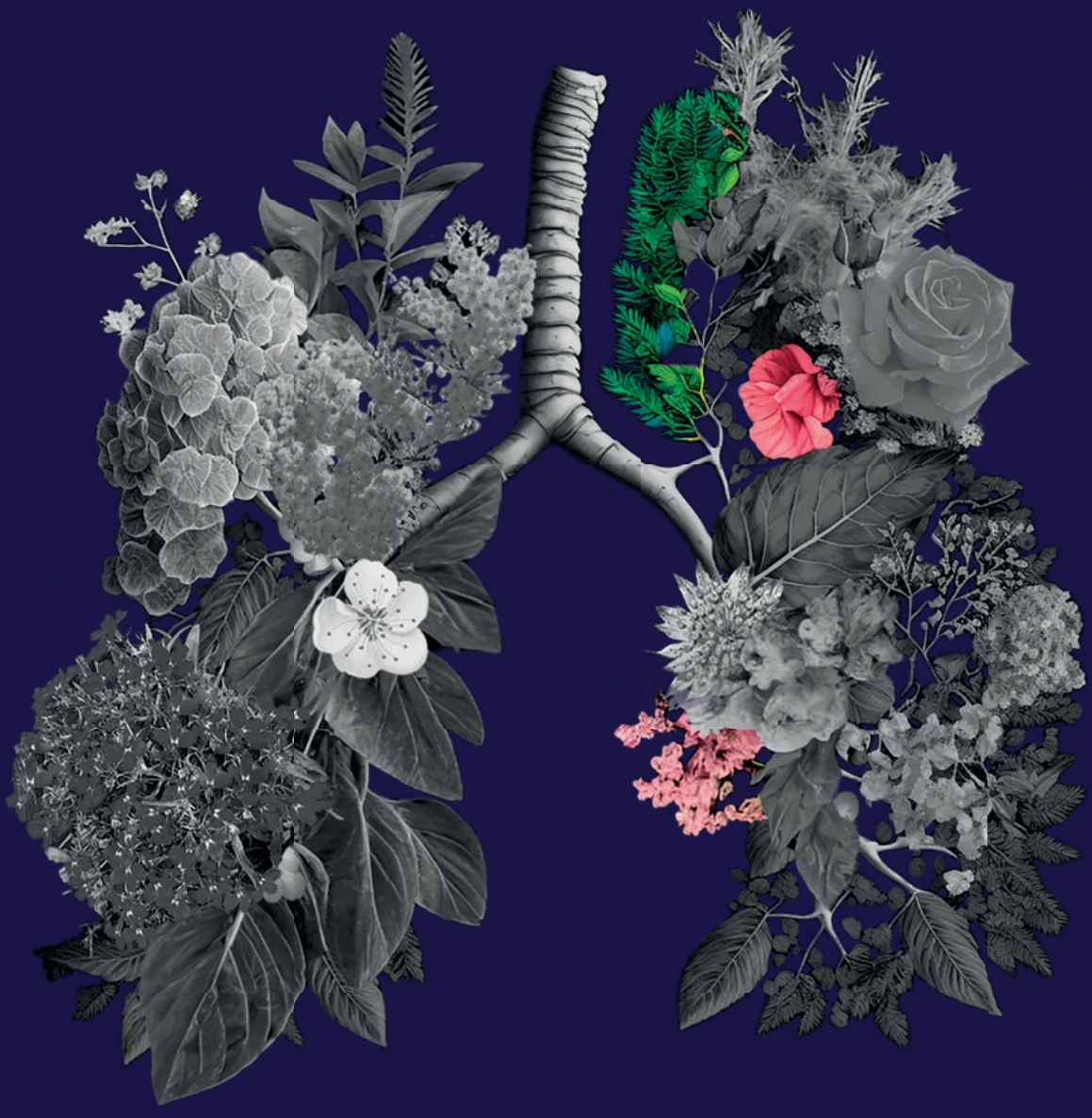
Daily OCS Dose (pred eq.)
BE ES FR HR IT LT NL PT SI TR
All Mepolizumab
PP
Pan

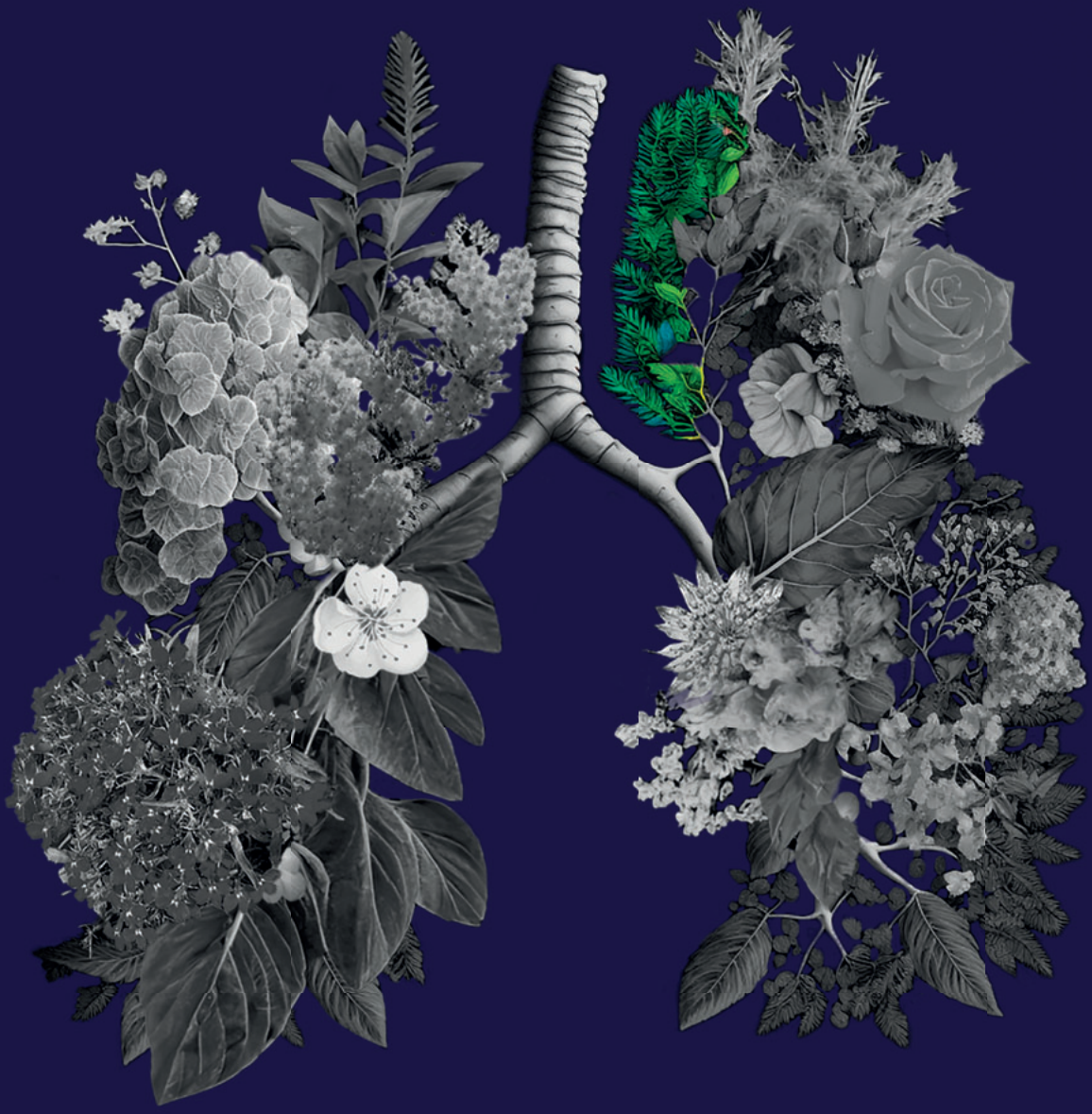


Abbreviations: BE: Belgium, BMI: Body Mass Index, CI: Confidence Interval, ES: Spain, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, FR: France, HR: Croatia, IT: Italy, LT: Lithuania, NL: Netherlands, OCS: Oral corticosteroids (prednisone equivalents), PT: Portugal, SI: Slovenia, TR: Turkey.



Part II

Prediction of response



Chapter 7

Prediction of response to biological treatment with monoclonal antibodies in severe asthma

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ABSTRACT

In recent years, major developments have occurred in severe asthma management. Different asthma phenotypes and subgroups have been identified and new treatment options have become available. A total of five monoclonal antibodies is currently approved in severe asthma treatment: omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab. These drugs have been shown to reduce exacerbations and to have an oral corticosteroid-sparing effect in many patients with severe asthma. However, biological treatment is not successful in all patients and should be discontinued in non-responsive patients. Treating the right patient with the right biologic, and therefore biologic response prediction, has become a major point of interest in severe asthma management. A variety of response outcomes is utilized in the different clinical trials, as well as a huge range of potential predicting factors. Also, regarding the timing of the response evaluation, there are considerable differences between studies. This review summarizes the results from studies on predicting responses and responders to biological treatment in severe asthma, taking into account clinical, functional and inflammatory parameters assessed prior to the start of treatment as well as following a few months of therapy. In addition, future perspectives are discussed, highlighting the need for more research to improve patient identification and treatment responses in the field of biological treatment in severe asthma.

1. INTRODUCTION

Patients with severe asthma require high-dose inhalation therapy to control their disease. These patients experience frequent exacerbations, and they often depend on the chronic use of oral corticosteroids (OCS) with associated serious adverse effects.[1] In recent years, major developments occurred in severe asthma management. Different asthma phenotypes and subgroups were identified[2] and new treatment options have become available in the form of monoclonal antibodies (MABs).[3] Although these novel biological agents have shown promising results in many patients with asthma, it is evident that not all patients respond equally well. This difference in treatment response may be multifactorial and related to the heterogeneity of the severe asthma population or the different underlying molecular pathways, but also drug and treatment strategy related factors may play a role. Optimal use of biologics, both in terms of costs and prevention of unnecessary patient exposure, is of the utmost importance. A Dutch cost estimation indicates the drug costs per patient per year in the Netherlands at €15.000,-.[4] Unfortunately, it is not yet clear which patients will respond to which biologic. Therefore, biologic response prediction has become a major point of interest in severe asthma management.

The present article shortly describes asthma phenotypes and inflammatory mechanisms and pathobiologic features leading to severe asthma. Furthermore, the pharmacological mechanism of action and clinical outcomes of the currently available biologics for severe asthma are summarized. Then we thoroughly review predictors of response to the currently registered biologics and, finally, discuss recent developments and future perspectives in response prediction.

2. ASTHMA SUBTYPES AND PATHOBIOLOGY

Asthma is a heterogeneous, inflammatory airway disease in which different phenotypes have been identified based on clinical, functional or inflammatory parameters.[2] Late-onset eosinophilic asthma is currently one of the most well-defined asthma phenotypes with a clearly different clinical profile from that seen in classic childhood-onset allergic asthma.[5] Patients with late-onset eosinophilic asthma show eosinophilic inflammation in blood as well as sputum and frequently report absence of atopy, chronic rhinosinusitis with nasal polyposis as comorbidity and a good response to systemic corticosteroids.[6] Both phenotypes are associated with so-called type 2 inflammation.[7-9] In addition to these two type 2 phenotypes, there is a heterogeneous group of patients without evidence of type 2 inflammation.

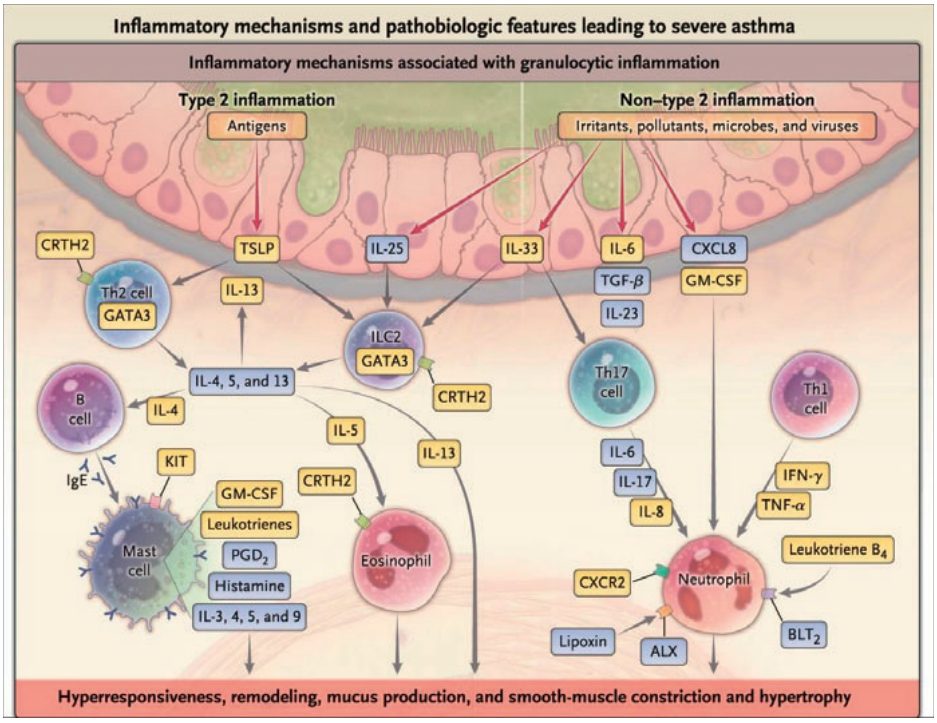

Figure. 1. Inflammatory mechanisms leading to severe asthma. Abbreviations: TSLP = thymic stromal lymphopoietin, IL = interleukin, Th2 = T-helper 2, ILC2 = innate lymphoid cell 2, IgE = immunoglobulin E. Triggering factors (antigens, pollutants) activate the airway inflammation cascade via epithelial-produced factors (TSLP, IL-25 and IL-33). Th2 and ILC2 activation leads to IL-4, IL-5 and IL-13 production. B-cell activation by IL-4 leads to IgE release in allergic asthma, while IL-5 leads to eosinophil recruitment, migration and activation. In collaboration with these factors, IL-13 leads to airway hyperresponsiveness, remodeling, mucus production and smooth-muscle contraction and hypertrophy. Adapted from The New England Journal of Medicine, Elliot Israel, Helen K. Reddel, Severe and Difficult-to-Treat Asthma in Adults, 377, 965 Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Type 2 inflammation (Figure 1[7]) is mainly characterized by the presence of type 2 cytokines (Interleukin (IL)-4, IL-5 and IL-13) and eosinophilia.[7,9,10] In allergic asthma, antigens are presented to naive T-cells by dendritic cells, converting them to T-helper (Th)2-cells.[11,12] In addition, epithelial cells produce thymic stromal lymphopoietin (TSLP) when triggered by antigens, promoting the Th2-cell conversion and innate lymphoid cells-2 (ILC2s) activation.[13,14] The cytokine production by Th2-cells (IL-4, IL-5 and IL-13[9,10]) and ILC2 cells (IL-5 and IL-13[15]) is regulated by transcription factor GATA-3.[16-18]

IL-4 and IL-13 were amongst the first cytokines that were identified as important drivers of type 2 inflammation. IL-4 stimulates B-cell isotope switching, leading to immunoglobulin E (IgE) production.[19,20] Binding of IgE on the high-affinity IgE receptor (FcεRI) on mast cells and basophils leads to the production of multiple mediators and cytokines that cause airway smooth muscle contraction, remodeling, eosinophilic infiltration and amplification of the inflammatory cascade.[7,21-23] IL-13 stimulates airway epithelium to promote enhanced mucus production and goblet cell hyperplasia and also acts on smooth muscle cells inducing hyperresponsiveness and remodeling.[24,25] There is a close link between IL-4 and IL-13 activity because both activate the alpha subunit of the IL-4 receptor (IL-4Rα).[26,27]

IL-5 is an essential cytokine in promotion, migration, maturation and survival of eosinophils.[23,28] Eosinophils are able to degranulate, releasing cytotoxins with antimicrobial effects as well as potency to damage host tissue. But especially their immune-modulatory capacity, involving the innate as well as the adaptive immune system, seems to play an important role, promoting a type 2 inflammatory environment in the lungs.[24]

In non-allergic asthma ILCs play a major role. Non-allergic triggers, such as pollutants, irritants or microbes, stimulate the airway epithelial cells to produce TSLP, IL-33 and IL-25. ILCs are activated by these cytokines to ILC2s which produce IL-5 and IL-13, leading to the before mentioned effects on the airways.[9]

2.1 Biologics: mechanism of action

Five biologics are currently registered in the EU for the treatment of severe asthma, all targeting type 2 inflammation. There are currently no effective and safe biologics available for non-type 2 asthma. Structural information and fasta-sequences are displayed in table 1. Unfortunately, no crystallographic information is available in the public domain. In 2003 omalizumab was registered for the treatment of moderate-to-severe allergic asthma. Omalizumab binds IgE, preventing its function in binding and activating the FcεRI.[34] In 2015 mepolizumab was registered for the treatment of severe eosinophilic asthma. Mepolizumab binds free serum IL-5, preventing it from binding and activating the alpha chain of the IL-5 receptor complex on eosinophils.[35] Reslizumab was registered in 2016 and has the same mechanism of action as mepolizumab.[36] In 2018, the third IL-5 targeting biologic, benralizumab, was registered, which binds the alpha chain of the IL-5 receptor on eosinophils, preventing IL-5 binding and subsequently eosinophil activation. Furthermore, the constant heavy chain 2 part of the Fc-region of benralizumab lacks fucose sugar residue, greatly enhancing it's affinity to the FcyRIIIa receptors on natural killer (NK)-

cells and macrophages, leading to antibody-dependent cell-mediated cytotoxicity, depleting the number of eosinophils.[37,38] Finally, dupilumab is the fifth biologic, registered in 2019 for severe eosinophilic asthma. Dupilumab binds the alpha subunit of the IL-4 receptor, preventing the function of both IL-4 and IL-13.[39]

Table 1: Overview of biologic structural information.

Biologic	Type	Fasta-sequence
Omalizumab[29]	Humanized immunoglobulin-G1κ	**Heavy chain** VQLVESGGGLVQPGGSLRLSCAVSGYSITSGYSWNWI RQAPGKGLEWVASITYDGSTNYADSVKGRFTISRDDS KNTFYLQMNSLRAEDTAVYYCARGSHYFGHWHFAV WGQGTLVTVSSGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKAEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK **Light chain** DIQLTQSPSSLSASVGDRVTITCRASQSVDYDGDSYM NWYQQKPGKAPKLLIYAASYLESGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQSHEDPYTFGQGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNR
Mepolizumab[30] [30]	Humanized immunoglobulin-G1κ	N/A
Reslizumab[31]	Humanized immunoglobulin-G4κ	N/A

Table 1: Continued.

Biologic	Type	Fasta-sequence
Benralizumab[32]	Humanized immunoglobulin-G1κ	**Heavy chain** EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIHW VRQRPGQGLAWMGYINPYNDGTKYNERFKGKVTITS DRSTSTVYMELSSLRSEDTAVYLCGREGIRYYGLLGDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK **Light chain** DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQ QKPGKAPKLLIYHTSRLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQGYTLPYTFGQGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
Dupilumab[33]	Humane immuno-globulin-G4	**Heavy Chain** EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTW VRQAPGKGLEWVSSISGSGGNTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPRYYG LDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY TQKSLSLSLG **Light Chain** DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLD WYLQKSGQSPQLLIYLGSNRASGVPDRFSGSGSGTD FTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Listed are the biologics, biologic type and fasta-sequence. Abbreviation: N/A = not available

Table 2: Overview of outcome measures and treatment effects in phase III biological trials in severe asthma.

Biologic		**Response outcomes**	
Study	**N total (Treated – Placebo)**	**Primary outcome**	**Results Associations (treatment vs placebo)**
Omalizumab			
Busse 2001[40]	525 (268 - 257)	Number of asthma exacerbations after 16 wks (part I) and after ICS reduction phase of 12 wks (part II)	**Exacerbations per patient, mean:** Part I: 0.28 vs 0.54 p<0.01 Part II: 0.39 vs 0.66 p<0.01
Solèr 2001[41]	546 (274-272)	Asthma exacerbation rate after 16 wks (part I) and after ICS reduction phase of 12 wks (part II)	**Exacerbations per patient, mean (95% CI):** Part I: 0.28 (0.15-0.41) vs 0.66 (0.49-0.83) Part II: 0.36 (0.24-0.48) vs 0.75 (0.58-0.92)
Mepolizumab			
Bel 2014[42]	135 (69 - 66)	Chance on a reduction in OCS dose category at 24 wks	**OCS reduction chance, OR (95% CI):** 2.39 (1.25-4.56) p<0.01
Ortega 2014[43]	576 (385 - 191)	Asthma exacerbation rate at 32 wks	**Exacerbation rate, Reduction rate (95% CI)** 75 mg IV: 47% (28-60) p<0.01 100 mg SC: 53% (36-65) p<0.01
Reslizumab			
Castro 2015[44]	953 (477 - 476)	Asthma exacerbation rate at 52 wks 2 studies enclosed	**Exacerbation rate,** RR **(95% CI):** Study 1: 0.50 (0.37-0.67) p<0.01 Study 2: 0.41 (0.28-0.59) p<0.01
Bjermer 2016[45]	315 (210 - 105)	Change in pre-bronchodilator FEV_1 at 16 wks	**FEV_1 change, LSM-TD (95% CI):** 0.160 (0.060-0.259) p<0.01
Benralizumab			
Bleecker 2016[46]	1205 (798 - 407)	Asthma exacerbation rate at 48 wks	**Exacerbation rate, RR (95% CI):** Q4W: 0.55 (0.42-0.71) p<0.01 Q8W 0.49 (0.37-0.64) p<0.01

Table 2: Continued.

Biologic		Response outcomes	
FitzGerald 2016[47]	1306 (866 - 400)	Asthma exacerbation rate at 56 wks	**Exacerbation rate, RR (95% CI):** Q4W: 0.64 (0.49-0.85) p<0.01 Q8W 0.72 (0.54-0.95) p=0.02
Nair 2017[48]	220 (145 - 75)	Chance on a reduction in OCS dose category at 28 wks	**OCS reduction chance, OR (95% CI):** Q4W: 4.09 (2.22-7.57) p<0.01 Q8W: 4.12 (2.22-7.63) p<0.01
Dupilumab			
Castro 2018[49]	1902 (1264 - 638)	1. Asthma exacerbation rate at 52 wks, 2. Pre-bronchodilator change in FEV_1 at 12 wks	**Exacerbation rate, Relative Risk (95% CI):** 200 mg dose: 0.52 (0.41-0.66) 300 mg dose: 0.54 (0.43-0.68) **FEV_1 change (L),** LSM-TD (95% CI): 200 mg dose: 0.14 (0.08-0.19) p<0.01 300 mg dose: 0.13 (0.08-0.18) p<0.01
Rabe 2018[50]	210 (103 - 107)	Percentage OCS dose reduction at 24 wks	**OCS change, LSM±SE:** -70.1%±4.9% vs -41.9%±4.6% p<0.01

Listed are the studies, number of participating patients and comparator arms, primary outcomes, and reported associations (treatment vs placebo). Abbreviations: CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled corticosteroids, IV = intravenous dose, LSM-TD = least squares mean treatment difference, Q4W = treated every 4 weeks, Q8W = treated every 8 weeks, OCS = oral corticosteroids, OR = odds ratio, RR = rate ratio, SC = subcutaneous dose, SD = standard deviation, SE = standard error

2.2 Biologics: Outcome measures

Different outcome measures are used in the distinct randomized clinical trials (RCTs) and also regarding the timing of the treatment evaluation, there are considerable differences between studies. An overview of outcome measures and treatment effects for the different biologics in severe asthma was constructed, summarizing the results for the primary outcomes of the biologic pre-approval phase III trials (Table 2). Reduction of exacerbation rate (7 RCTs), OCS dose reduction (3 RCTs), and improvement in lung function (2 RCTs) were found as primary outcomes, indicating the different treatment targets in severe asthma. Study duration varied from 16 to 53 weeks, and 3 of these RCTs included an evaluation moment between study start and end.

3. PREDICTORS OF RESPONSE

The main objective of phase I-III clinical trials is the assessment of efficacy and safety. Knowing which patient will respond in real-life is a different objective and usually not established at the moment of market approval of the biologic. Prediction of treatment responses is not easy and has to deal with various problems: e.g. how to define a response or responder, what are clinically relevant outcome measures [51], and what should be the timing of the evaluation of response. Since currently an overview on the topic is lacking, a summary of the results from studies concerning predicting responses and responders to biological treatment in severe asthma is given. References were extracted from the MEDLINE and EMBASE database until 1 December 2019.

Several of these studies have defined responders to therapy, using different responder criteria and different time points of evaluation, mostly addressing positive outcomes in global evaluation of treatment effectiveness (GETE)[52], exacerbation rate, or lung function tests evaluated after 4 - 12 months of treatment. More often the possibility to predict separate outcomes was investigated using data collected at baseline (before start biologic) or at an early evaluation some months after start of therapy. The different studies will be discussed below. Table 3 gives an overview of the largest studies (≥100 participants) regarding predictors and outcomes, for responders as well as responses to biological treatment.

Table 3: Overview of studies on prediction of response to biological treatment in severe asthma.

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome
Omalizumab			
[54] Casale 2019	737	Gender Pos. allergen specific IgE Serum eosinophils ACT	Responder: at 48 weeks 1 AER reduction ≥ 50% or 2 ACT improvement to ≥20 or 3 point ACT improvement or 3 FEV_1 improvement ≥120 mL
[57] Gibson 2016	180	ACQ-5 Age	Responder at 26 weeks: ACQ-5 improvement ≥0.5
[61] Humbert 2018	723	Serum eosinophils	Responder: Combined: AER reduction ≥40% + GETE at 4-6 months
[62] Hanania 2013	850 (427 - 423)	FeNO Serum eosinophils Periostin	Exacerbation reduction at 48 weeks vs placebo
[72] Bousquet 2007	195 (118 - 77)	Physician's overall assessment at 16 weeks	Responder: at 16 weeks AER vs placebo
Mepolizumab			
[74] Pavord 2012	621 (462 - 159)	Serum eosinophils AER in the previous year FeNO	AER vs placebo
[78] Albers 2019	936 (468 - 468)	BMI	AER vs placebo
[80] Ortega 2016	1192 (846 - 346)	Serum eosinophils	AER vs placebo FEV_1 vs placebo ACQ-5 vs placebo

Conclusion	Association
Predictive	**Odds of being a responder, OR (95% CI)** To criteria 1, 2 and 3: Males: 0.49 (0.28-0.86) p=0.01; Spec. IgE: 4.36 (1.38-16.92) p=0.02 To criterion 2: Eosinophils ≥ 300 cells/μL: 1.65 (1.10-2.51) p=0.02 To criterion 3: ACT≥20: 0.49 (0.25-0.91) p=0.03
Predictive	**Coefficient (SE):** ACQ ≥ 2.0: -142.24 (44.29) p<0.01 Age: 1.52 (0.77) p=0.05
Not predictive	**Responders, N, n(%) (95% CI)** ≥300 cells/μL: 220 (58.4) (53.3-63.4) <300 cells/μL: 201 (58.1) (52.7-63.4)
High subgroups predictive	**Exacerbation: Percentage reduction vs placebo (95% CI)** FeNO: ≥19.5: 53% (37-70) p=0.001, <19.5: 16% (-32-46) p=0.45 Serum eosinophils:≥260/μL: 32% (11-48) p=0.005, <260/μL: 9% (-24-34) p=0.54 Periostin: ≥50 ng/mL: 30% (-2-51) p=0.07, <50 ng/mL: 3% (-43-32) p=0.94
Predictive	**Responders vs non-responders**, AE rate vs placebo (SD): 0.6 (1.31) vs 2.6 (6.39)
Eosinophils and exacerbations predictive	**AER: RR vs placebo (95% CI)** Serum eosinophils: ≤150 cells/μL: 0.92 (0.58-1.45); >150 cells/μL - ≤300 cells/μL: 0.45 (0.25-0.80); >300 cells/μL - ≤500 cells/μL: 0.69 (0.43-1.09); >500 cells/μL: 0.27 (0.19-0.39) Previous exacerbations: 2: 0.87 (0.59-1.30); 3: 0.43 (0.29-0.65); ≥4: 0.36 (0.25-0.54) FeNO: <50 ppb: 0.63 (0.47-0.84); FeNO ≥50 ppb: 0.43 (0.30-0.63)
Not predictive	**AER: RR vs placebo (95% CI)** BMI: ≤25 kg/m² 0.38 (0.26-0.56); >25-30 kg/m² 0.45 (0.32-0.63); >30kg/m² 0.51 (0.35-0.73)
More AER reduction in increasing eosinophil subgroups	**AER: RR vs placebo (95% CI)** Serum eosinophils: ≥150 cells/μL: 0.48 (0.39-0.58); ≥300 cells/μL: 0.41 (0.33-0.51) ≥400 cells/μL: 0.34 (0.27-0.44); ≥500 cells/μL: 0.30 (0.23-0.40) **Change in FEV_1 (mL) (95% CI)** Serum eosinophils: ≥150 cells/μL: 64 (1-127); ≥300 cells/μL: 68 (-10-146); ≥500 cells/μL: 106 (-2-214) **Change in ACQ-5 (95% CI)** Serum eosinophils: ≥150 cells/μL: -0.35 (-0.49- -0.20); ≥300 cells/μL: -0.49 (-0.67- -0.31); ≥500 cells/μL:- 0.61 (-0.85- -0.37)

Table 3: Continued.

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome
[81] Albers 2019	936 (468 - 468)	Serum eosinophils	AER vs placebo
[84] Shrimanker 2019	606 (455 - 151)	Combination FeNO and serum eosinophils	AER vs placebo
[87] Condreay 2017	820	Subset of asthma related genetic markers GWAS	Exacerbation rate Change in eosinophil count Change in IgE level
[88] Gunsoy 2018	263 (120 - 126)	At 16 weeks: Reduction in eosinophils PRTR ACQ-5 improvement FEV_1 improvement No change or reduction in exacerbations	AER vs placebo
Reslizumab			
[44] Castro 2015	953 (477 - 476)	AER in the last year	AER vs placebo
[89] Brusselle 2017	931 (465 - 446)	Age of onset	AER vs placebo FEV_1 vs placebo
[91] Nair 2019	953 (477 - 476)	AER in the last year Age, gender, race, BMI, age of onset, atopic status, chronic rhinosinusitis with nasal polyposis	AER vs placebo
[92] Corren 2016	492 (395 - 97)	Serum eosinophils	At 16 weeks: Change in FEV_1 vs placebo ACQ-7 vs placebo

Conclusion	Association
More AER reduction in increasing eosinophil subgroups	**AER: RR vs placebo (95% CI)** Serum eosinophils: <150 cells/μL: 0.55 (0.34-0.89); ≥150 cells/μL: 0.43 (0.34-0.54); ≥300 cells/μL: 0.36 (0.28-0.48); ≥400 cells/μL: 0.30 (0.22-0.41); ≥500 cells/μL: 0.29 (0.20-0.41); ≥750 cells/μL: 0.15 (0.08-0.29
FeNO not associated with AER, blood eosinophils is associated	**AER: RR (95% CI)** Serum eosinophils/FeNO: <150 cells/μL/<30 ppb: 0.86 (0.47-1.57); <150 cells/μL/≥ 30 ppb: 0.94 (0.37-2.40) ≥150 cells/μL/<30 ppb: 0.64 (0.42-0.99); ≥150 cells/μL/≥30 ppb: 0.38 (0.27-0.53)
Not predictive	N/A
Not predictive	**DREAM study reported AER: Placebo adjusted rate ratio (95% CI)** Reduction from baseline eosinophils: ≥20%: 0.73 (0.20-2.67); ≥40%: 0.84 (0.27-2.64) ≥60%: 0.90 (0.35-2.33); ≥80%: 0.66 (0.25-1.69) Physician-rated treatment response Moderate/significant improvement: 0.92 (0.44-1.91); Any improvement: 0.77 (0.36-1.61) ACQ-5: 0.69 (0.34-1.40) FEV_1 ≥10%: 0.96 (1.46-2.01) No change or reduction in exacerbations: 0.60 (0.28-1.29)
Stronger effect with more exacerbations	**AER: RR vs placebo (95% CI)** AER in last year: All: 0.46 (0.37-0.58); 1: 0.68 (0.49-0.95); 2: 0.44 (0.28-0.69) 3: 0.39 (0.21-0.70); ≥4: 0.36 (0.22-0.58)
Greater improvements with higher age of onset	**AER: RR vs placebo (95% CI)** Onset: ≥40 years: 0.25 (0.16-0.40); <40 years: 0.58 (0.44-0.76) **FEV_1 (mL) change from baseline (95% CI)** Onset: ≥40 years: 167 (89-245); <40 years: 88 (34-142)
Stronger effect with more exacerbations, other variables not predictive	**AER: risk reduction vs placebo (95% CI)** AER in last year: ≥2: 77.5% (58%-88%) 1:15.2% (-150.5%-71.2%) (p=0.028) Other variables N/A
No effect in low-eosinophil subgroups	**Treatment effect FEV_1 (L) change versus placebo (95% CI):** Eosinophils <400 cells/μL: 0.03 (-0.07-0.14) Eosinophils ≥400 cells/μL: 0.27 (0.01-0.53) **Treatment effect ACQ-7 change versus placebo (95% CI):** Eosinophils <400 cells/μL: -0.12 (-0.33-0.087) Eosinophils ≥400 cells/μL: -0.49 (-1.01-0.03)

Table 3: Continued.

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome
[93] Bateman 2019	321	Predictive model using: changes in ACQ, AQLQ, and FEV_1 at 16 weeks, asthma exacerbations (previous year and in first 16 weeks)	Responder at 52 weeks: Combination of exacerbation rate and FEV_1 improvement, ACQ-6 and AQLQ improvement at 52 weeks
Benralizumab			
[96] FitzGerald 2018	2295 (1518 - 777)	Serum eosinophils AER in the previous year	AER vs placebo
[97] Bleecker 2018	2295 (1518 - 777)	OCS-use Nasal polyposis FVC AER in the previous year Age at diagnosis	AER vs placebo FEV_1 improvement vs placebo
[98] Chipps 2018	2295 (1518 - 777)	Serum IgE Atopic status	AER vs placebo FEV_1 improvement vs placebo
Dupilumab			
[49] Castro 2018	1902 (1264 - 638)	Serum eosinophils FeNO	AER vs placebo FEV_1 improvement at 12 weeks vs placebo

Conclusion	Association
Predictive for response, not for non-response	**Model performance:** PPV: 89.9% (95% CI, 87.1-92.1%) NPV: 50.0% (95% CI, 33.7-66.3%)
Enhanced efficacy in higher eosinophil and previous AER subgroups	**8 weekly benralizumab** **AER: RR vs placebo (95% CI)** Eosinophils: ≥0 cells/μL: 0.64 (0.55-0.75); ≥150 cells/μL: 0.63 (0.53-0.74); ≥300 cells/μL: 0.57 (0.47-0.69); ≥450 cells/μL: 0.50 (0.38-0.64) 2 AER in previous year + eosinophils ≥300 cells/μL: 0.73 (0.55-0.95) ≥ 3 AER in previous year+ eosinophils ≥300 cells/μL: 0.45 (0.34-0.60)
Predictors were associated with response	**AER: RR vs placebo (95% CI)** OCS-use: 0.42 (0.29-0.60); No OCS-use: 0.69 (0.58-0.82) Nasal polyposis: 0.50 (0.35-0.72); no nasal polyposis: 0.68 (0.57-0.81) FVC <65% pred.: 0.53 (0.39-0.71); FVC≥65%pred: 0.69 (0.58-0.83) ≥3 AER: 0.54 (0.43-0.67); 2 AER: 0.74 (0.60-0.90) Age at diagnosis ≥ 18 yrs: 0.59(0.49-0.71); Age at diagnosis <18 yrs: 0.79 (0.61-1.02) **FEV_1 (L) improvement: LS (95% CI)** OCS-use: 0.19 (0.06-0.31) No OCS-use: 0.08 (0.02-0.13) Nasal polyposis: 0.29(0.17-0.41); No nasal polyposis: 0.06 (0.01-0.011) FVC <65% pred.: 0.21 (0.10-0.31); FVC≥65%pred: 0.06 (0.01-0.12) ≥3 AER: 0.17 (0.09-0.26); 2 AER: 0.05 (-0.01-0.11) Age at diagnosis ≥ 18 yrs: 0.14 (0.09-0.20); Age at diagnosis <18 yrs: -0.01 (-0.11-0.18)
No difference found	**8 weekly benralizumab** **AER: RR vs placebo (95% CI)** IgE≥150 KU/L: 0.58 (0.45-0.75); IgE<150 KU/L: 0.57 (0.41-0.78) Atopy: 0.60 (0.47-0.77); No atopy: 0.54 (0.39-0.74) **FEV_1 (L) improvement: LS mean difference vs placebo (95% CI)** IgE≥150 KU/L: 0.123 (0.041-0.205); IgE<150 KU/L: 0.138 (0.044-0.233) Atopy: 0.114 (0.033-0.194); No atopy: 0.181 (0.085-0.278)
Greater efficacy in higher eosinophil and FeNO subgroups	**Dupilumab 300 mg every 2 weeks** **AER: RR vs placebo (95% CI**) Serum eosinophils: ≥300 cells/μL: 0.33 (0.23–0.45); ≥150 - <300 cells/μL: 0.56 (0.35–0.89); <150 cells/μL: 1.15 (0.75–1.77) FeNO (ppb) RR (95% CI): ≥50: 0.31 (0.19–0.49); ≥25 - <50: 0.44 (0.28–0.69); <25: 0.79 (0.57–1.10) **FEV_1 (L) LS mean diff. vs placebo (95% CI)** Serum eosinophils: ≥300 cells/μL: 0.24 (0.16-0.32; ≥150 - <300 cells/μL: 0.00(-0.10, 0.10); <150 cells/μL: 0.09 (-0.01-0.18) FeNO (ppb) RR (95% CI) ≥50: 0.39 (0.26-0.52); ≥25 - <50: 0.12 (0.03-0.21); <25: 0.03 (-0.04-0.10)

Table 3: Continued.

Study	N Total (Treated–Placebo)	Predicting variable(s)	Response outcome
[50] Rabe 2018	210 (103 - 107)	Serum eosinophils	OCS reduction at 24 weeks vs placebo
[100] Corren 2019	465 (307 – 158)	AER in the previous year FEV_1	ACQ AQLQ
[101] Corren 2019	1902 (1264 - 638)	Allergic asthma	AER vs placebo FEV_1 improvement at 12 weeks vs placebo ACQ improvement at 24 weeks vs placebo
[103] Yang 2019	2992 (N/A)	FeNO	AER vs placebo FEV_1 at 12 weeks vs placebo

Presented are studies with ≥100 participants. Listed are the studies, number of participating patients and comparator arms, predicting variables, outcome measures, conclusions, and reported associations. Predicting parameters are baseline (status at biologic initiation) if not specified otherwise. Abbreviations: ACQ = asthma control questionnaire, ACT = asthma control test, AER = annualized exacerbation rate, AQLQ = asthma-related quality of life questionnaire, BMI = body mass index, CI = confidence interval, FeNO = Nitric Oxide in exhaled breath, FEV_1 = forced exhaled volume in 1 second, FVC = forced vital capacity, GETE = global evaluation of treatment effectiveness, GWAS = genome wide association study, IgE = Immunoglobulin E, N/A = not available, NPV = negative predictive value, OCS = oral corticosteroid, OR = odds ratio, PPV =positive predictive value, PRTR = physician-rated treatment response, Q8W = treated every 8 weeks, RR = rate ratio, SD = standard deviation, SE = standard error, TARC = thymus and activation regulated cytokine.

Conclusion	Association
Greater efficacy in higher eosinophil subgroups	**OCS reduction LS mean difference (95% CI)** Serum eosinophils: ≥300 cells/μL: -36.8 (-54.7- -18.9); <300 cells/μL: -21.3 (-38.8- -3.9) ≥150 cells/μL: -29.4 (-43.1- -15.7); <150 cells/μL: -26.9 (-54.5-0.7)
Greater efficacy with more exacerbations an lower FEV_1	**Dupilumab 300 mg every 2 weeks** **ACQ LS mean change (±SE)** AER in previous year: ≤1: -1.12 (0.10): >1: -1.70 (0.11) p<0.01 FEV_1 (L): ≤1.75: -1.50 (0.11); >1.75: -1.44 (0.11) p=0.10 **AQLQ LS mean change (±SE)** AER in previous year: ≤1: 0.92 (0.11); >1: 1.51 (0.12) p<0.01 FEV_1 (L): ≤1.75: 1.31 (0.12); >1.75: 1.19 (0.12) p<0.05[95]
Outcomes improved regardless of allergic asthma	**Dupilumab 300 mg every 2 weeks** **AER reduction vs placebo % (95% CI**): With allergies:36.9% (13.4-54.0); Without allergies: 60.0% (42.7-72.1) **FEV_1 improvement LS mean (L) (95% CI)** With allergies: 0.16 (0.09-0.23); Without allergies: 0.09 (0.01-0.16) **ACQ LS mean change (95%** CI) With allergies:-0.26 (-0.44 -0.08); Without allergies: -0.08 (-0.29 -0.12)[95]
Greater efficacy in higher FeNO subgroups	**AER, mean difference vs placebo, rate estimate (95% CI)** Baseline FeNO: ≥ 50 ppb: -0.78 (-1.08- -0.47); ≥25 ppb <50 ppb -0.62 (-0.88- -0.36) <25 ppb: -0.18 (-0.34- -0.01) **FEV_1 at 12 weeks, mean difference vs placebo, change from baseline (95% CI)** Baseline FeNO: ≥ 50 ppb: 0.35 (0.26-0.43); ≥25 ppb <50 ppb: 0.15 (0.09-0.22) <25 ppb: 0.07 (-0.01-0.14)

3.1 Omalizumab

Most experience has been gained with the prediction of response of omalizumab, since it was the first MAB that was introduced and registered for the treatment of asthma (2003). Omalizumab is given in 75-600 mg subcutaneous injections. Advantages of omalizumab are the long experience and expertise that have been gained over the years and the specific applicability for allergic patients. The dosing regime is based on baseline serum IgE-level and bodyweight. In selecting treatment eligible patients, an IgE cut-off value of ≥30 IU/mL is utilized.[53]

Omalizumab: Baseline characteristics to predict medium and long-term response

The PROSPERO trial is the only large, prospective, real-world observational trial in patients with asthma receiving biological treatment (omalizumab) which was aimed at prediction of response. Patients were evaluated after 48 weeks of omalizumab treatment and considered omalizumab responders when they achieved an annual exacerbation reduction ≥50%, asthma control test (ACT) improvement to ≥20 of 3-point improvement or Forced Expiratory Volume in 1 second (FEV_1) improvement ≥120 mL. 78% of 795 patients met at least one of these criteria and were characterized as responders, the majority of them by an exacerbation reduction of ≥50%, whereas 23% were responders in all categories. In the responder analysis, females and patients with a positive allergen-specific IgE test were more likely to be responders (using all 3 criteria). Patients with high eosinophil levels were more likely to be ACT-responders. Lung function responders had poorer asthma control (ACT<20) at baseline. And aside from female gender, an increased number of exacerbations 12 months before baseline was the only factor associated with being responder by exacerbation definition.[54]

Clinical and functional parameters

Two commonly used validated questionnaires in asthma-care are the Asthma Control Questionnaire (ACQ) and the Asthma-related Quality of Life Questionnaire (AQLQ).[55,56] An Australian registry study in 180 patients studied the omalizumab responder rate, assessed by an improvement of at least 0.5 in ACQ-5 after 6 months of treatment, and they found poor asthma control (baseline ACQ-5 ≥ 2.0) and older age to be predictive.[57] A small (n=41) Greek single centre study explored clinical and inflammatory characteristics that could predict response to omalizumab and divided patients into early responders (improved within 16 weeks), late responders (improved between 16-32 weeks), or non-responders (no improvement at 32 weeks). They used GETE as responder criterion, and found that lower baseline FEV_1 and higher IL-13 levels in induced sputum supernatant were predictors of response to

omalizumab. Only three patients came out as late-responder, making an analysis into predictors of late responders unfeasible.[58]

Inflammatory parameters

Several inflammatory markers have been supposed to be possibly predictive of omalizumab response. While several of these markers are only used experimentally, some of them are parameters that are used in daily practice, i.e. blood eosinophils, IgE, fraction of exhaled nitric oxide (FeNO), and (in specified centres) periostin. Nitric oxide is produced by endothelial nitric oxide synthases in case of airway-inflammation and FeNO is used as a non-invasive biomarker of type 2 airway inflammation.[59] Periostin is induced by airway epithelial cells and fibroblasts in response to IL-13 and is therefore considered a biomarker for IL-13 driven inflammatory processes.[60]

To determine the importance of pre-treatment blood eosinophil count as a predictive measure for response to omalizumab, the retrospective STELLAIR study included 723 adult patients and compared omalizumab effectiveness in patients with high (≥300 cells/μL) and low (<300 cells/μL) baseline serum eosinophil counts. Response to omalizumab was assessed by three criteria: physician evaluation, reduction of ≥40% in annual exacerbation rate (AER) or a combination of both. The observed effectiveness was similar in both eosinophil groups, and the authors suggest that omalizumab effectiveness is similar in "high" and "low" eosinophil subgroups.[61] This contrasts with the before-mentioned PROSPERO trial, in which patients with high baseline serum eosinophil counts were more likely to be ACT responders.[54] Also, a post-hoc analysis of biomarkers in the EXTRA study suggests more benefit for patients with higher levels of baseline blood eosinophils. In this study the authors explored the potential of type 2 inflammatory biomarkers (blood eosinophils, FeNO and serum periostin) to serve as baseline predictors of therapeutic benefit of omalizumab treatment. Patients were divided into baseline low- and high-biomarker subgroups with cutoff values: FeNO <19.5 ppb or ≥19.5 ppb, eosinophils <260 cells/μL or ≥260 cells/μL and periostin <50 ng/mL or ≥50 ng/mL. It turned out that the reduction in exacerbations was larger in all three high baseline biomarker subgroups as compared with the low biomarker subgroups, indicating that these patients may achieve greater benefit from omalizumab therapy.[62] In addition, FEV_1 normalization after a year of omalizumab therapy was found to be associated with higher baseline values of FeNO and serum eosinophil count.[63] Though the evidence may not be fully consistent, the Global Initiative for Asthma added the criteria FeNO ≥20 ppb or serum eosinophils ≥260 cells/μL as factors that may predict good asthma response to anti-IgE.[64] Interestingly, from a recent pilot

study, the authors report that omalizumab is possibly inadequate to control sputum eosinophilia, and therefore may not have a steroid-sparing effect, especially in those maintained on oral corticosteroids daily.[65]

Total serum IgE-level is a sum of active and inactive (omalizumab-bound) IgE. After initiating omalizumab treatment, the serum IgE-level increases due to the binding of omalizumab to IgE, increasing the IgE half-life. Thus, measuring the total IgE-level is not an applicable tool to measure therapy-response while receiving omalizumab. The diagnostic value of monitoring free IgE-levels in the omalizumab response-evaluation has been studied, but only in small studies and results are indecisive. [66,67]

The aforementioned potential of periostin as predictive biomarker is further supported by a small prospective study in 30 patients who had been treated with omalizumab for at least 1 year. This study showed an association between high baseline levels of periostin and omalizumab induced absence of exacerbations and improved AQLQ-scores.[67] Currently, periostin assays are commercially available, but used for research purposes only.

Exploratory biomarkers

Several small studies investigated the predictive capabilities of different explorative biomarkers and found that patients responding to omalizumab had significant higher baseline levels of serum IL-12 and sputum IL-13.[58,68,69] In addition, associations with markers of airway remodeling and physicians assessment scores were found for galectin-3 levels in bronchial tissue and degree of syk expression with associated IgE-mediated histamine release, respectively.[70,71] Though very interesting and sometimes promising, these results are not yet applicable in common care and future studies are awaited to test their predictive capacity.

Early evaluation parameters to predict long-term omalizumab response

In addition to baseline characteristics, evaluation parameters after short-term treatment might have added value to predict long-term treatment response. A post-hoc analysis of the INNOVATE study deemed the physician's overall assessment after 16 weeks of therapy predictive for annual exacerbation risk.[72] This finding was confirmed in a pooled analysis of seven omalizumab RCTs, whereas no other individual parameters, nor baseline serum IgE level predicted long-term response. [72] As a result, the 16 week evaluation moment is included in the Xolair® Summary of Product Characteristics to decide whether to continue omalizumab therapy or not.[73].

Conclusions omalizumab

Baseline characteristics predicting omalizumab benefit include a history of frequent exacerbations, poor asthma control and the presence of a positive allergen-specific IgE test. Higher levels of blood eosinophils or FeNO further add to the expectation of better outcomes. The relative early assessment of treatment response at 16 weeks is already adopted in clinical practice and shown to be helpful in the prediction of future benefit.

3.2 Anti-IL-5 biological treatment

In the last years, three biologics targeting IL-5 were registered in the EU and USA for the treatment of severe eosinophilic asthma. Since these biologics are relatively new, there are no large prospective trials primarily aimed at prediction of response for these drugs yet.

Mepolizumab: Baseline characteristics to predict medium and long-term treatment response

Mepolizumab was the first registered anti-IL-5 biologic (2015) and is given subcutaneous (SC) every 4 weeks in a fixed dose of 100 mg. Since mepolizumab was the first available anti-IL-5 biologic, relatively much therapeutic experience has been gained. In selecting treatment eligible patients, an eosinophil cut-off value of ≥150 cells/μL is utilized.[35]

Clinical and functional parameters

Only a few studies explored baseline clinical or functional parameters as potentially predictors of response. In the Dose Ranging Efficacy And safety with Mepolizumab (DREAM) phase 2 study, an exploratory modelling of baseline characteristics indicated that efficacy of mepolizumab increases with increasing baseline eosinophil counts and numbers of exacerbations in the previous year, but not with atopic status, gender, weight, or FEV_1.[74] A retrospective review of 52 patients with OCS dependent asthma found 73% of the patients to be responder (≥50% reduction in OCS dose by 12 months). At baseline, responders had significantly lower daily OCS dose, better asthma control, were more often non-atopic and tended to have a lower body mass index (BMI).[75] Another small study with 32/42 responders, found no baseline parameters (gender, BMI, smoking history, allergies, and blood eosinophil levels) that predicted treatment response.[76]. Two meta-analyses combining the MENSA and MUSCA RCT data investigated the relationship between baseline percentage predicted FEV_1 or BMI and mepolizumab induced reduction in exacerbation rate, but no association was found.[77,78] This suggests that baseline

airway obstruction nor BMI are factors that predict treatment response, in line with the covariate modelling analysis in DREAM.[74]

Inflammatory parameters

Several other studies confirmed the increased efficacy of mepolizumab with increasing baseline blood eosinophil counts.[43,74,79,80] Large post-hoc analyses of data from the mepolizumab RCTs (DREAM, MENSA, MUSCA) revealed similar results: there is a close positive relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab, consistently regarding exacerbation reduction, and with less conclusive evidence considering improvement in FEV_1 and asthma control.[78,80,81] At less than 150 cells/μL, predicted efficacy was reduced, particularly for the DREAM study. Interestingly, blood eosinophil counts appear to be a better predictor of response than sputum eosinophil counts.[74]

In addition to eosinophils, other biomarkers have been investigated. In a proof of concept trial, FeNO levels were not responding to mepolizumab treatment, neither were baseline FeNO levels predictive of response.[82] This was confirmed in the DREAM trial were exacerbation rate reduction was similar in the high (≥50 ppb) and low (<50 ppb) FeNO subgroups[74], suggesting that FeNO is not responsive to IL-5 modulation, but might be more relevant in different aspects of the type 2 inflammatory process.[83] Yet, when both blood eosinophils and FeNO levels are increased, mepolizumab seems to be most effective. A post-hoc analysis of the DREAM trial divided 606 participants in four groups: high or low peripheral blood eosinophils combined with high or low FeNO. It was found that patients in the high serum eosinophil subgroups had a reduced exacerbation rate compared to the low eosinophil subgroup, regardless of having high or low FeNO. However, patients with the combination of high FeNO and high serum eosinophil counts had the most benefit of mepolizumab treatment.[84] Though caution is needed when interpreting such post-hoc analyses, this suggests that a combined biomarker profile might have greater prognostic value.

Exploratory biomarkers

Assessment of serum IL-5 is not commercially available for diagnostic means and is therefore not extensively investigated. A small study in 5 patients found that non-responders, according to OCS-use and exacerbation frequency, had an increase in IL-5 concentrations at 12 weeks, but these results need to be confirmed in larger studies.[85] Siglec-8, a transmembrane receptor on eosinophils, may act as a surrogate parameter, since it is regulated by IL-5. In a study in 12 patients, it was found that patients with low serum Siglec-8 had a trend towards better FEV_1 and

AQLQ improvements, but no correlation with serum eosinophil counts was found. [86]

An emerging aspect of modern healthcare is the utilization of a patient's genetic profile in medical decision making. A post-hoc analysis of the DREAM and MENSA trial data tested the association between asthma-specific genetic markers and mepolizumab efficacy in 820 patients, but found no association.[87]

Early evaluation parameters to predict long-term mepolizumab response

Currently there is only 1 study available using early evaluation parameters. This post-hoc analysis assessed to what extent clinical markers and biomarkers measured 16 weeks after treatment initiation might predict long-term treatment response based on exacerbation reduction, and could be used as a continuation rule. The authors analyzed data from the DREAM and MENSA trials and found only a marginal influence of changes in blood eosinophils after 16 weeks of treatment. No evidence was found for a continuation rule based on physician-rated response, ACQ-5 score, or lung function.[88]

Reslizumab: Baseline characteristics to predict medium and long-term treatment response

Reslizumab was the second available anti-IL-5 biologic, registered in 2016 for the treatment of severe eosinophilic asthma. As opposed to mepolizumab, reslizumab is administered intravenously every 4 weeks and is dosed based on bodyweight (3 mg/kg). The intravenous administration has to be performed in the clinic, warranting the patient adherence. The dosing based on bodyweight leads to a personalized treatment. In selecting treatment eligible patients, an eosinophil cut-off value of ≥400 cells/μL is utilized.[36]

Clinical and functional parameters

Only a few studies address the topic of predicting reslizumab response using baseline clinical characteristics. Exploratory analyses in phase 3 trials suggested that previous exacerbations exerted a strong effect on the reduction of clinical asthma exacerbation rate by reslizumab.[44] In a post-hoc analysis using phase 3 trial data, reslizumab efficacy was compared in 658 patients with early-onset asthma versus 273 with late-onset asthma (cut-off 40 years). Though beneficial in both groups, larger reslizumab induced reductions in asthma exacerbations and improvements in lung function were found in patients with late-onset asthma.[89] This is in line with results from a pooled analysis of 477 patients from two phase 3 reslizumab trials assessing characteristics of non-, moderate-, high-, and super-responders.

Comparing non-responders and super-responders, super-responders tended to have later age of onset, as well as lower BMI, higher baseline ACQ and a history of nasal polyps, with no significant differences in age, gender, baseline lung function, or baseline medications.[90] The same trials were used in a post-hoc analysis using patients on daily OCS. To determine predictors of asthma exacerbation response, several parameters were used: age, gender, race, BMI, weight, number of exacerbations in the previous year, late-onset asthma, atopic status, chronic rhinosinusitis with nasal polyps, and blood eosinophil count. The only characteristic associated with reduced exacerbation risk with reslizumab, was having 2 or more versus 1 clinical asthma exacerbation in the previous 12 months.[91]

Inflammatory parameters

To assess whether baseline serum eosinophil count has an effect on reslizumab outcomes, a study was conducted in a population unselected for baseline blood eosinophil level, in contrast to the previous reslizumab RCTs that used a cut-off value of ≥400 eosinophil cells/μL to include patients. The results showed that reslizumab did not meaningfully improve asthma outcomes, including both lung function and measures of symptom control, in patients with blood eosinophil counts <400 cells/μL.[92]

Early evaluation parameters to predict long-term reslizumab response

A large study was conducted to predict long-term response and non-response in patients after 16 weeks of reslizumab treatment. The authors used an algorithm they developed based on clinical indicators from pivotal clinical trials, including change from baseline to 16 weeks in ACQ and AQLQ scores and FEV_1, and number of asthma exacerbations. The algorithm was evaluated for its ability to predict response at 52 weeks, based on AER, FEV_1 improvement, ACQ-6 improvement or AQLQ-improvement. The algorithm had 95.4–95.5% sensitivity and 40.6–54.1% specificity, and was successful at predicting response at 52 weeks, but failed regarding the potentially more important prediction of long-term non-responders.[93]. So unfortunately the algorithm might add little to routine practice, as it will not change the need for a 12-month trial of treatment, and this would ideally be the outcome of such a prediction model.[94]

Benralizumab: Baseline characteristics to predict medium and long-term treatment response

Benralizumab was registered in the EU and USA in 2018 for the treatment of severe eosinophilic asthma. Benralizumab is given in 30 mg SC injections, initially every 4 weeks and after three gifts every 8 weeks. The dosing interval of 8 weeks is the

longest of the five biologics, which is an advantage of benralizumab therapy. In selecting treatment eligible patients, an eosinophil cut-off value of ≥150 cells/μL is utilized.[95]

Clinical and functional parameters

For benralizumab, the impact of baseline factors on treatment efficacy has been investigated in 3 post-hoc analyses using data from benralizumab phase 3 trials (SIROCCO and CALIMA).[96-98] These studies contained a total of 2295 patients: 756 received 4-weekly 30 mg benralizumab (Q4W), 762 8-weekly 30 mg benralizumab (Q8W) and 777 placebo.

Several clinical and functional baseline factors that might influence benralizumab efficacy were evaluated, including OCS use, nasal polyposis, pre-bronchodilator forced vital capacity (FVC), prior year exacerbations and age at diagnosis. Efficacy outcomes included AER and change in pre-bronchodilator FEV_1 at treatment end relative to placebo. Patients with any of abovementioned factors had greater reduction in AER, and more improvement in lung function with benralizumab Q8W versus placebo compared with the efficacy in the overall population and those with blood eosinophil counts ≥300 cells/μL. For the overall population, OCS use and nasal polyposis had the greatest influence on improvement of AER, whereas nasal polyposis and pre-bronchodilator FVC <65% of predicted had the greatest influence on increasing FEV_1.[97] In another analysis, benralizumab treatment was found to decrease exacerbations and improve lung function regardless of serum IgE concentrations and atopic status.[98]

Inflammatory parameters

When focusing on the impact of different baseline blood eosinophil thresholds (≥0, ≥150, ≥300, or ≥450 cells/μL) and number of exacerbations (two vs three or more) in the previous year, the Fitzgerald study showed that the degree of improvement in AER increased with increasing baseline blood eosinophil counts, and enhanced efficacy was observed for patients with increased blood eosinophils combined with a history of three or more exacerbations per year.[96] Though efficacy was reported in the patients with eosinophil levels ≥0 cells/μL, the absence of significant effect in the subgroup of patients with eosinophils <150 cells/μL requires restraint with regard to treatment with benralizumab in the patients with low eosinophil numbers.

To our knowledge, there is no study available using evaluation parameters after some months of treatment to assess longer-term benralizumab benefit.

Conclusion anti-IL-5 biologics

A history of frequent exacerbations and higher levels of blood eosinophils are consistently identified in the different IL-5 targeting trials as baseline characteristics that predict treatment response regarding exacerbation reduction and lung function improvement. The presence of late-onset asthma, OCS dependency, impaired lung function and nasal polyposis might further increase the chance of good response. So far, the added value of early evaluation parameters to predict future treatment response is still debatable.

3.3 Dupilumab: Baseline characteristics to predict medium and long-term treatment response

Dupilumab is an anti-IL-4 receptor antagonist, preventing the function of both IL-4 and IL-13 in the type 2 inflammation cascade (Figure 1). Dupilumab was first registered in the treatment of moderate-to-severe atopic dermatitis. In 2019 the indication for severe eosinophilic asthma was added. Dupilumab is given in 200mg or 300 mg SC injections every 2 weeks after a 400mg or 600 mg loading dose, based on OCS use or concomitant atopic dermatitis. Recently, the FDA approved dupilumab for treatment of chronic rhinosinusitis with nasal polyposis.[99] This relatively large range of indications, some of which are common comorbidities in patients with severe asthma, is a major advantage of dupilumab.

Clinical and functional parameters

Since dupilumab has only recently been registered for use in severe asthma, studies on clinical or functional characteristics predicting response are limited. In a post-hoc analysis of a phase 2b trial, patients with a history of >1 exacerbation in the prior year or baseline $FEV_1 \leq 1.75$ L, showed a better response to dupilumab in asthma control and quality of life scores.[100]

Inflammatory parameters

A post-hoc analysis of the phase 3 study LIBERTY ASTHMA QUEST, found that dupilumab reduced severe exacerbation rates, improved FEV_1 and asthma control, and suppressed type 2 inflammatory biomarkers in both allergic and non-allergic asthma.[101] Reductions in severe exacerbation rates and improvement in FEV_1 were greater in patients with higher baseline levels of type 2 inflammatory biomarkers. These findings are consistent with previous dupilumab studies, showing that dupilumab treatment results in a lower AER and a higher FEV_1 across the whole spectrum of baseline blood eosinophil counts, however these benefits are more pronounced in patients with higher levels of baseline blood eosinophils or FeNO. [49,50,102,103]

Explorative biomarkers

In addition to blood eosinophils and FeNO, other type 2 associated biomarkers have been explored, such as serum IgE, thymus and activation regulated chemokine, and eotaxin-3, but so far none defined a subpopulation more responsive to treatment. [49,103,104]

Currently, there is no study available using evaluation parameters after some months of treatment to assess longer-term dupilumab benefit in severe asthma.

Conclusion dupilumab

Baseline characteristics predicting dupilumab benefit are still far from clear and mainly concern inflammatory parameters. Though efficacy is shown regardless of baseline eosinophil levels, the magnitude of response seems to increase with increasing levels of baseline blood eosinophils or FeNO.

3.4 Exclusion of the use of biologics in severe asthma

This manuscript focuses on parameters for the initiation of MABs. However, there are some reasons for excluding the use of biologics in severe asthma. Obviously, failing to meet the inclusion criteria is the main reason for not starting a biologic. The main inclusion criteria are uncontrolled asthma despite optimized inhalation therapy and evidence of type 2 inflammation.[64] For the individual biologics, serum eosinophils <150 cells/μL excludes the use of anti-IL-5 biologics. Pre-treatment serum IgE <30 IU/L or >1300 IU/L falls outside the omalizumab dosing table and excludes the use of omalizumab. Dupilumab is applicable for all patients with evident type 2 inflammation. Furthermore, the biologics are contraindicated in patients with hypersensitivity to the biologic and patients with a helminth infection. The components of type 2 inflammation (IgE, IL-4, IL-5, IL-13 and eosinophils) are involved in the immune response against helminths. Interfering with this immune response using biologics, while a helminth infection is present, might lead to life-threatening infections.[105] Using biologics during pregnancy is currently contra-indicated due to the lack of experience in pregnant women.

4. FUTURE PERSPECTIVES

New perspectives in response prediction of the MABs used in severe asthma may present themselves in the near future. Four possible aspects will be highlighted below.

4.1 Breatheomics

Breatheomics, the analysis of biomarkers in exhaled breath, is an emerging aspect in lung disease diagnostics. Interestingly, profiling of volatile organic compounds (VOCs) was selected by a group of severe asthma experts as one of the most important potential biomarkers for the future.[106] Examples of VOCs are ethane and pentane, which are shown to be related to oxidative stress. However, there is a wide range of exhaled biomarkers that are yet to be explored.[107] Identification of distinct VOC profiles has been shown to be successful in discriminating asthma from controls or chronic obstructive pulmonary disease (COPD), and early- from late-onset asthma.[108,109] Interestingly, exhaled breath profiling was also effective in predicting steroid responsiveness in asthma.[110] Detecting the optimal subgroup of patients for biologic response by means of VOC profiling may be a future phase in biological treatment in severe asthma.[111,112]

4.2 Genetic aspects

The last decade's insight in genomic predictors of asthma phenotypes and treatment response is growing.[113] A few pharmacogenetic studies have recently evaluated the response to asthma therapies with monoclonal antibodies.[87,114] In a GWAS using DREAM and MENSA data of mepolizumab-treated patients, a trend towards association was found between exacerbation prevention and 2 loci found on chromosomes 6 and 9, respectively UTRN, EPM2A, IFNA14 and IFNA22P. However, the biologic link to enhanced mepolizumab response is not clear for these loci.[87] Though so far only suggestive associations with MAB response are reported, the possibility of genetic screening before therapy initiation may be a next step towards personalized medicine.

4.3 Therapeutic drug monitoring (TDM)

Mechanisms underlying response or non-response not only include disease characteristics, but also drug- (immunogenicity, pharmacodynamics, and pharmacokinetics) and treatment strategy (dosing regimen) related factors.[115,116] There is a wide inter-individual variability in MAB exposure due to target burden and other factors affecting their pharmacokinetics, including the development of anti-drug antibodies (ADA).[117] TDM of MABs can be used, measuring total (free, soluble target bound and ADA bound) MAB concentration, to optimize clinical outcomes in patients in various clinical situations. [117,118] Evidence regarding the utility of TDM for MABs in the treatment of inflammatory diseases is growing steadily. In the treatment of inflammatory bowel disease and ulcerative colitis, emerging data indicate a strong relationship between drug exposure and efficacy of anti-Tumor Necrosis Factor-α (TNF-α) agents.[119-121] Different expert groups in this field

suggest a role for TDM of anti-TNF-α agents in guiding treatment changes [122,123], in particular upon treatment failure, following successful induction, and in clinical remission. Also in Rheumatoid Arthritis, TDM for adalimumab and infliximab plasma levels has been widely established over the past few years[124-126], based on the relationship between low MAB serum levels and non-response or ADA development. [125,127] In asthma, research into the role of TDM in optimizing MAB use is still in its infancy[128] and its utility in early detection of non-response needs to be assessed. Yet, in line with developments in other inflammatory disease, therapeutic drug monitoring may be considered a promising tool to increase the efficacy, patient safety and cost-effectiveness of MABs in severe asthma treatment.

4.4 Data science approaches

Another option to enable evaluation of response to biological treatment in patients with severe asthma lies in the utilization of large population databases. Standardized international severe asthma registries, such as SHARP [129] and ISAR [130], may help to identify the right endotypes and biomarkers, predictive of response to specific drugs.[131]

5. CONCLUSION

This article summarizes the current state of knowledge on response prediction of biological treatment in severe asthma. Studies that explore the predictability of biological efficacy are mainly based on post-hoc analyses of the large registration trials or small exploratory studies with a limited number of patients. Although these studies provide some insight, there are still several issues that require further evidence. For example, what is the best timing to assess biologic response or when can a patient be classified as non-responder? Should we keep on focusing on general response criteria or might an individualized approach be preferable, considering treatment responses on a case-by-case basis?[106] Further research should incorporate real-world data and investigate whether detailed algorithms, using baseline as well as early evaluation parameters, might improve the monitoring of treatment response and the prediction of long-term benefits. New tools have potential to contribute to response prediction, and may prove their value in the near future. Decisions on initiation and continuation of biological therapy in severe asthma are still challenging, indicating the need to better recognize the clinical relevance of phenotypes and biomarkers, both those currently available as well as those to be expected.

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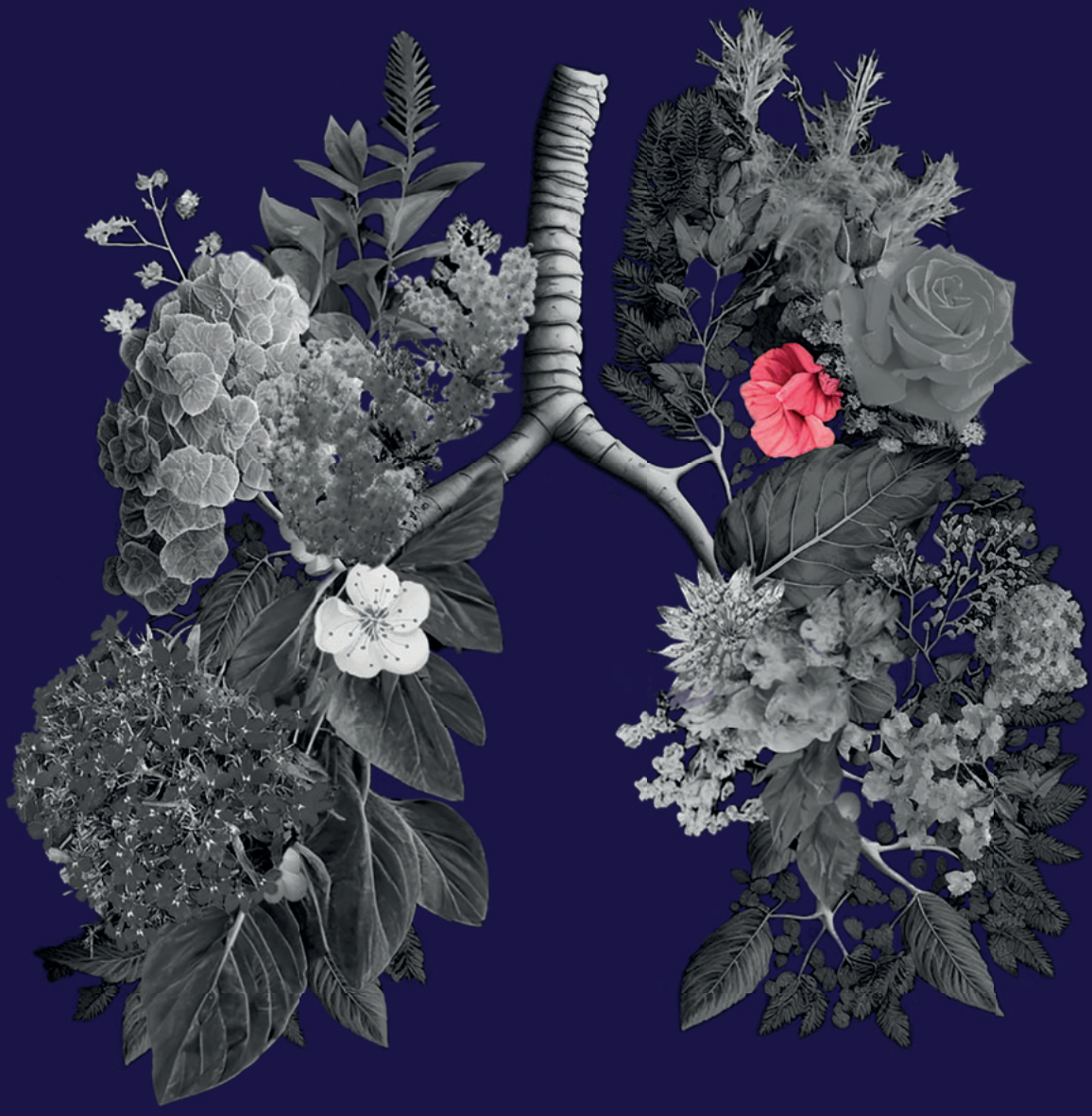

Chapter 8

Patient-reported outcome measures after 8 weeks of mepolizumab treatment and long-term outcomes in patients with severe asthma: an observational study.

J.A. Kroes, S.W. Zielhuis, A.N. van der Meer, K. de Jong, A. ten Brinke, E.N. van Roon

Short Research Report
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ABSTRACT

Background

The novel anti-IL-5 drug mepolizumab improves asthma outcomes in the majority but not all patients with severe eosinophilic asthma. Currently it is difficult to predict an individuals' chance of being a responder. Early changes in patient-reported outcome measures may contribute to the prediction of long-term outcomes.

Aim

To compare early changes in patient-reported outcome measures after 8 weeks and long-term response to mepolizumab treatment.

Method

22 patients with severe eosinophilic asthma starting mepolizumab therapy in a severe asthma centre in the Netherlands were evaluated on baseline, 8 weeks and 52 weeks, collecting questionnaire scores and asthma-related parameters. Well-controlled asthma was defined as an asthma control questionnaire score ≤0.75. Long-term treatment response was defined as continuing mepolizumab therapy at 52 weeks.

Results

Nine patients (41%) had well-controlled asthma at 8 weeks and all were mepolizumab responders at 52 weeks (positive predictive value = 100%, 95%CI 66-100), versus only 5 responders out of 13 patients with not well-controlled asthma at 8 weeks (negative predictive value = 62%, 95%CI 32-86).

Conclusion

The results in this study suggest that patients receiving mepolizumab therapy with an ACQ-score ≤0.75 at 8 weeks are unlikely to need extensive monitoring, for they are very likely to be long-term responders.

INTRODUCTION

The novel anti-IL-5 drug mepolizumab improves asthma outcomes in the majority but not all patients with severe eosinophilic asthma [1]. Baseline patient characteristics may influence mepolizumab-induced outcomes, but currently it is difficult to predict an individuals' chance of being a responder to treatment with mepolizumab [2]. Frequently used patient-reported outcome measures (PROMs) in severe asthma care are the Asthma Control Questionnaire (ACQ) and the Asthma-related Quality of Life Questionnaire (AQLQ). A low ACQ-score indicates good asthma control, and a high AQLQ-score indicates better quality of life [3, 4]. Early changes in these PROMs may contribute to the prediction of long-term outcomes, as shown in a study on the prediction of asthma exacerbations [5]. We hypothesize that early changes in the ACQ and AQLQ are associated with long-term response to mepolizumab treatment for patients with severe asthma.

Aim

The aim of this study was to compare ACQ and AQLQ scores 8 weeks after starting mepolizumab for patients with or without long-term response to mepolizumab treatment. Furthermore, in patients who already achieved well-controlled asthma in week 8, we evaluated the chance of becoming a mepolizumab responder in week 52.

Ethics approval

Ethical approval was waived by the local Ethics Committee of the Medical Centre Leeuwarden in view of the retrospective nature of the study and all the performed procedures were part of the routine care.

METHOD

Patients with severe eosinophilic asthma starting mepolizumab therapy in a severe asthma centre in the Netherlands were evaluated on baseline, 8 weeks and 52 weeks as part of regular care. Eosinophilic asthma was diagnosed according to GINA guidelines for severe asthma (ICD-10 code J82.83)[6]. All patients starting mepolizumab treatment in the inclusion period (January 2017 to August 2018) were selected for this study. Inhalation technique and adherence to inhalers were optimized before and during mepolizumab treatment. Spirometry, forced expiratory nitric oxide (FeNO), serum eosinophil count, daily oral corticosteroid dose (OCS), and questionnaires were recorded at each evaluation. Well-controlled asthma was defined as an ACQ≤0.75 [7]. All patients used prednisolone as their maintenance OCS. Long-term treatment response was defined as continuing mepolizumab

therapy at 52 weeks, based on the decision by the healthcare professionals. This decision was made using a predefined protocol, based on exacerbation rate, OCS use, lung function, and patient's well-being. All participants signed informed consent before participating in this study. Patients discontinuing mepolizumab treatment due to side effects and patients with missing questionnaire data at baseline, 8 weeks or 52 weeks were excluded from the study.

Continuous variables were expressed as medians (IQR) and categorical variables as numbers and percentages. Differences between subgroups were analysed using Mann-Whitney U, $\chi 2$, or Fisher exact tests when applicable. A P-value <0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 24.0.

RESULTS

Twenty-five patients initiated mepolizumab in the study period. Two were excluded due to incomplete data, and 1 patient discontinued mepolizumab due to side effects. Baseline characteristics are described in table 1.

Table 1. Baseline characteristics.

Characteristic	Population (N=22)		Non-responder (N=8)		Responder (N=14)		P-value
Age (y)*	52	(46-61)	49	(37-61)	53	(49-61)	0.305
Gender; male, N (%)	11	(50)	5	(63)	6	(43)	0.659
Body mass index (kg/m²)*	26.0	(24.3-28.6)	25.8	(24.5-31.6)	26.8	(23.9-28.6)	0.885
Former smoker, N (%)	10	(46)	4	(50)	6	(43)	1.000
Late onset asthma, N (%)	15	(68)	3	(38)	12	(86)	0.052
Non-atopic asthma, N (%)	17	(81)	7	(88)	10	(77)	1.000
OCS dose (mg/day)*	8.8	(2.5-10.0)	10	(8.8-12.5)	5	(0.0-10.0)	0.028
OCS maintenance, N (%)	17	(77)	8	(100)	9	(64)	0.115
Annualized exacerbation rate (# per year)*	2	(1-3)	2	(2-3)	2	(1-3)	0.416
Serum eosinophil count (*10^9/L)*	0.3	(0.1-0.5)	0.3	(0.0-0.5)	0.3	(0.1-0.5)	0.779
FEV_1 pre-bronchodilator (%predicted)*	70	(58-78)	63	(48-73)	72	(63-82)	0.151
FeNO (ppb)*	53	(23-73)	43	(11-99)	55	(23-70)	0.941

The table describes patient characteristics at baseline and compares non-responders to responders. Abbreviations: FeNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, OCS oral corticosteroids. *Median (IQR)

Of the 22 included patients, 14 patients (64%) continued mepolizumab therapy at 52 weeks after initiation, classifying them as long-term responders. Patient characteristics are compared in table 1. A statistically significant difference was found in OCS dose at baseline between non-responders and responders.

Table 2. Asthma-related parameters at baseline, 8 weeks and the change in these parameters.

		Non-responder (N=8)		Responder (N=14)		P-value
ACQ	Baseline	2.57	(2.09-3.33)	2.33	(1.17-2.50)	0.204
	8 Weeks	1.69	(1.25-2.25)	0.67	(0.50-1.50)	0.018
	Delta	-1	(-1.32 - -0.40)	-0.66	(-1.66 - -0.37)	0.800
AQLQ	Baseline	5	(3.90-5.15)	5.21	(4.89-5.89)	0.168
	8 Weeks	5.16	(4.20-5.49)	6.39	(5.77-6.63)	0.009
	Delta	0.35	(0.28-0.45)	0.78	(0.10-1.22)	0.128
OCS dose (mg/day)	Baseline	10	(8.8-12.5)	5	(0.0-10.0)	0.028
	8 Weeks	6.3	(5.0-12.5)	2.5	(0.0-7.5)	0.081
	Delta	-1.25	(-5.0-0.0)	0	(-2.5-0.0)	0.451
Serum eosinophil count (*10^9/L)	Baseline	0.3	(0.0-0.5)	0.3	(0.1-0.5)	0.779
	8 Weeks	0.0	(0.0-0.1)	0.0	(0.0-0.0)	0.017
	Delta	-0.2	(-0.5 - 0.0)	-0.3	(-0.6- -0.1)	0.596
FEV_1 pre-bronchodilator (%pred)	Baseline	63	(48-72.5)	72	(63-82)	0.151
	8 Weeks	71	(44-91)	91	(67-97)	0.116
	Delta	3	(-3-86)	10	(-5-21)	0.590
FEV_1 post-bronchodilator (%pred)	Baseline	66	(45-86)	81.5	(70.5-86.5)	0.204
	8 Weeks	76	(51-96)	93	(71-103)	0.160
	Delta	0	(-4-3)	4	(2-14)	0.130
PEF (%pred)	Baseline	58	(47-92)	78	(61-89)	0.246
	8 Weeks	72	(49-95)	86	(76-95)	0.310
	Delta	3.5	(-4-15)	6	(-4-15)	0.968
FeNO (ppb)	Baseline	43	(11-99)	55	(23-70)	0.941
	8 Weeks	38	(17-72)	44	(28-55)	0.710
	Delta	-9	(-22-8)	2	(-9-12)	0.297

The table describes asthma-related parameters at baseline, 8 weeks and the change in these parameters. All values are medians (IQR). Abbreviations: ACQ asthma control questionnaire, AQLQ asthma-related quality of life questionnaire, FeNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, OCS oral corticosteroids, PEF peak expiratory flow.

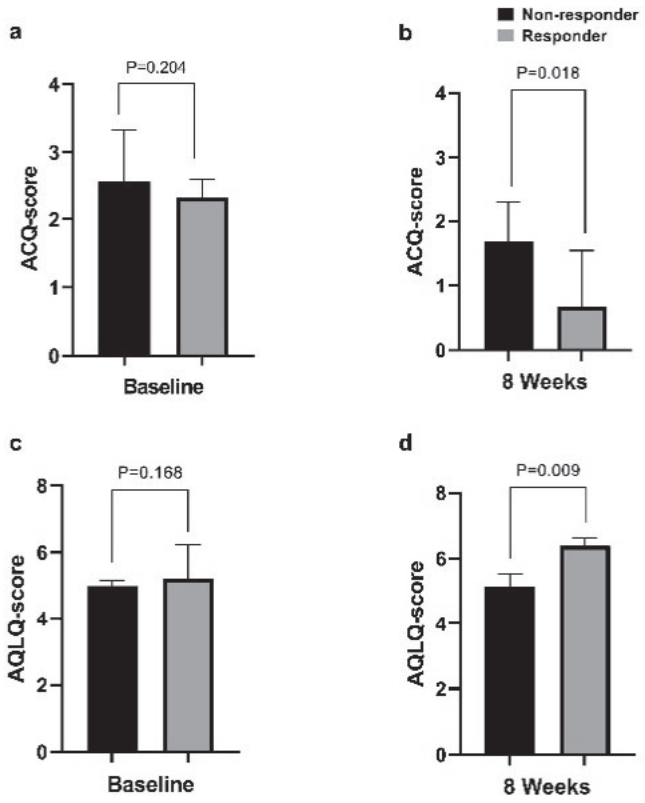

Figure 1. Median and interquartile range of patient-reported outcome measures at baseline and 8 weeks for non-responders (black) and responders (grey). Panel a: ACQ-score at baseline. Panel b: ACQ-score at 8 weeks. Panel c: AQLQ-score at baseline. Panel d: AQLQ-score at 8 weeks. Abbreviations: ACQ Asthma Control Questionnaire, AQLQ Asthma-related Quality of Life Questionnaire

For the total study cohort, median ACQ score decreased from 2.33 (IQR 1.50–2.83) at baseline to 1.09 (IQR 0.67-1.70) after 8 weeks of therapy (p<0.001) and median OCS dose decreased from 8.8 (IQR 2.5-10) to 5 mg/day (IQR 0-7.5) (p=0.004). Median AQLQ score increased from 5.09 (IQR 4.20-5.36) to 5.82 (IQR 4.96-6.46) (p<0.001). The asthma-related parameters for responders and non-responders are described in table 2. At baseline, there was no statistically significant difference in ACQ and AQLQ for the long-term responders and non-responders, while at 8 weeks a statistically significant difference between responders and non-responders was found for both parameters (Fig. 1). The OCS dose, while different at baseline, did not differ at the 8 week mark.

Nine patients (41%) had well-controlled asthma at 8 weeks and were also mepolizumab responders at 52 weeks (positive predictive value=100%, 95%CI 66-100), versus 5 responders out of 13 patients without well-controlled asthma at 8 weeks (negative predictive value=62%, 95%CI 32-86). Consequently, the relative risk for being a responder at 52 weeks for patients with well-controlled asthma compared to the patients without well-controlled asthma at 8 weeks was 2.6 (95%CI 1.307-5.171; P=0.004).

DISCUSSION

In this explorative study in patients initiating mepolizumab therapy, we found a statistically significant difference in PROMs at 8 weeks between long-term responders and non-responders, whereas these did not differ at baseline. This occurred despite a statistically significant reduction of the daily OCS dose in the population. Furthermore, all patients with well-controlled asthma at 8 weeks were long-term responders. The results in this study suggest that incorporation of early changes in asthma-related parameters could help in the early detection of long-term responders to mepolizumab treatment.

A strength of this study is the real-world character, giving detailed information about the first period of mepolizumab treatment in a severe asthma centre. A limitation of the current study is the number of patients and the single-centre data, warranting caution when interpreting these results, and limiting the statistical power. Due to the small sample size, multivariable analysis, correcting for possible confounders, and exploration of the optimal ACQ cut-off using a ROC-curve were deemed unfeasible.

In the DREAM study, one of the mepolizumab phase II clinical trials, the first observed reduction in serum eosinophil counts occurred 4 weeks after the initial mepolizumab injection [8]. The early improvement in asthma control might be related to the fast eosinophil reduction. However, in the current study, no association between asthma control at 8 weeks and eosinophils was found. Recently, Numata et al. also explored predictors for mepolizumab response after 52 weeks in 24 Japanese patients. In this small study, multivariable analysis indicated that lower baseline BMI predicted response to mepolizumab treatment. This was not found in our study, and elucidating the influence of BMI on mepolizumab outcomes remains an objective for future studies. Numata et al. also found improvement after 3 months of treatment in eosinophil count, FeNO, and ACT-score, indicating the rapid onset of effects of mepolizumab treatment. In contrast to our study, differences at 3 months between responders and non-responders were not reported[9]. The

summary of product characteristics of mepolizumab demands annual treatment evaluation, while the Global Initiative for Asthma (GINA) advises 16 weekly response evaluations, resulting in several evaluations before long-term treatment response is established[6]. The results in our study suggest that patients receiving mepolizumab therapy with an ACQ-score ≤0.75 at 8 weeks are unlikely to need this extensive monitoring, for they are very likely to be long-term responders. Objective clinical measurements, like spirometry data, did not improve after 8 weeks in our study, while we did observe a reduction of the OCS maintenance dose. Severe asthma is associated with airway remodeling and while the PROMs improve very rapidly, this rapid improvement can possibly not be expected in lung function[10]. Patients requiring higher OCS maintenance doses at baseline were less likely to be long-term responders. These patients might experience more severe asthma, decreasing their capability to be long-term responders. Therefore, the baseline OCS dose should be taken into account in the prediction of long-term response. However, while different at baseline, the OCS dose was not different at 8 weeks between non-responders and responders, as opposed to the PROMs. This may indicate that the OCS dose is less suitable to evaluate treatment response at 8 weeks. This advocates the use of PROMs in the therapy evaluation after initiating mepolizumab treatment. The decision at 8 weeks to identify patients that require less follow-up, leads to personalized follow-up, enabling pulmonologists to shift their focus to patients less likely to be long-term responders to mepolizumab therapy.

Future studies should include more patients from different centres to explore the consistency of the results in other populations, and to enable statistical stratification for baseline values. Furthermore, these studies should explore whether response after 52 weeks endures or decreases, to what extent neutralizing antibodies develop and how this influences long-term response. The results in this study show a strong relationship between early improvement in PROMs and long-term therapy continuation. However, it might be more in the doctors' and patients' interest to identify non-responders at an early moment. Whether the addition of early changes in PROMs could help in the early identification of non-responders, remains an objective for future studies.

CONCLUSION

Expert groups and policy makers around the world attempt to achieve consensus about the evaluation of biological therapy in severe asthma and prediction of response on the long-term. In our study we found that early changes in ACQ and AQLQ may contribute to the prediction of mepolizumab response. This encourages

further exploration of the applicability of early changes in PROMs in the clinical process. An early decision about personalized follow-up enables pulmonologists to allocate their valuable time to the patients that actually need close monitoring, improving the healthcare process concerning biological treatment of severe asthma.

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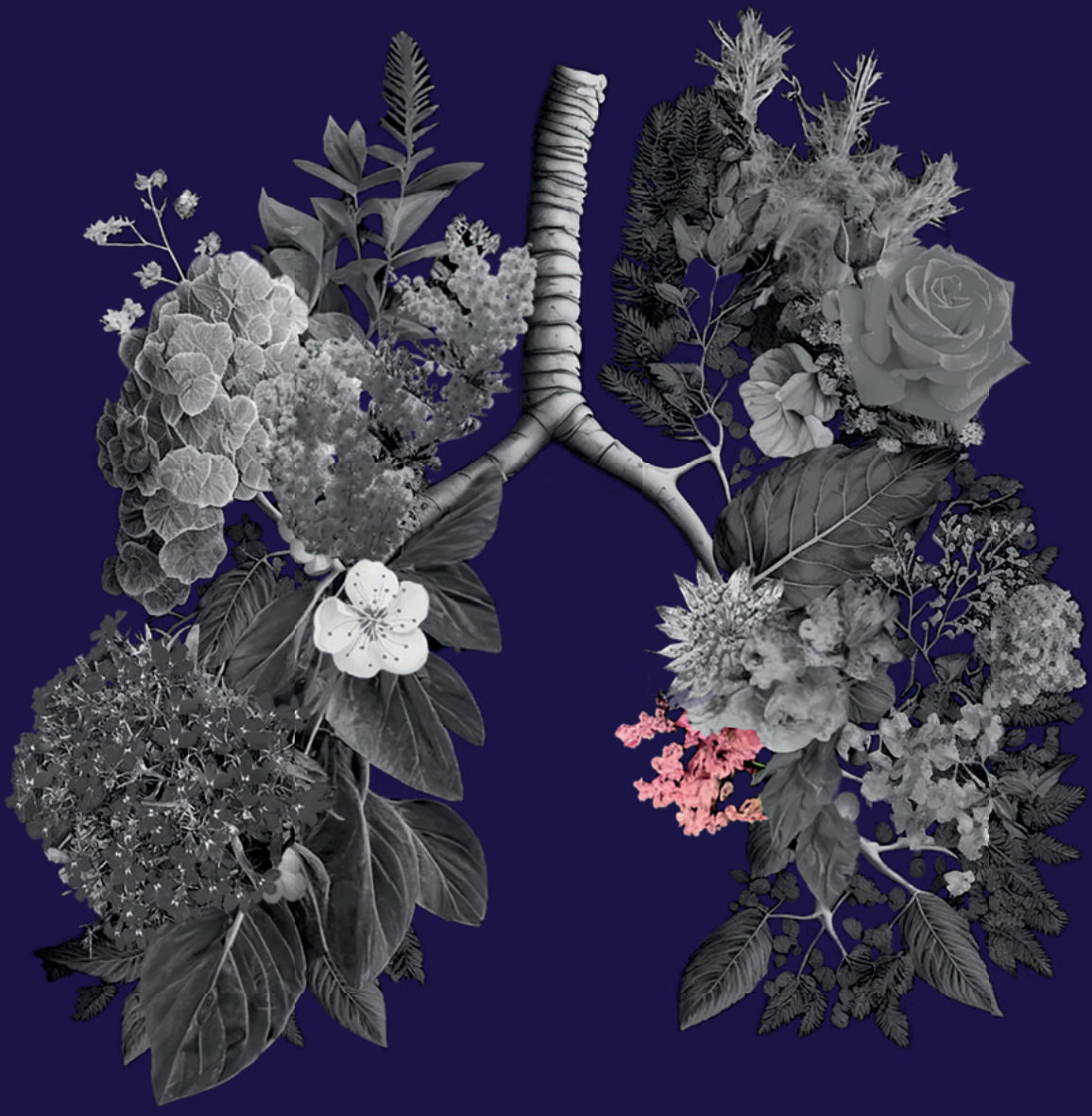

Chapter 9

Early treatment outcomes add in predicting long-term benralizumab response in severe asthma

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ABSTRACT

Background
Benralizumab is highly effective in many, but not all, patients with severe asthma. Baseline characteristics alone are insufficient to predict an individual's probability of long-term benralizumab response.

Objectives
To (1) study whether parameters at 3 months – in addition to baseline characteristics - contribute to the prediction of benralizumab response at 1 year and to (2) develop an easy-to-use prediction tool to assess an individual's probability of long-term response.

Methods
We assessed the effect of benralizumab treatment in 220 patients from the Dutch severe asthma registry (RAPSODI). To investigate predictors of long-term benralizumab response (defined as continuation of benralizumab at 12 months) we used logistic regression, including baseline characteristics and 3-month Asthma Control Questionnaire (ACQ-6) score and maintenance oral corticosteroid (OCS) dose.

Results
Benralizumab treatment significantly improved several clinical outcomes and 168 (76.4%) patients were classified as long-term responders. Response prediction improved significantly when 3-month outcomes were added to a predictive model with baseline characteristics only (area under receiver-operating characteristic 0.86 vs 0.70, $p<0.001$). Based on this model, a prediction tool using gender, prior biologic use, baseline blood eosinophils, and at 3 months OCS dose and ACQ-6 was developed which classified patients into 3 categories with increasing probability of long-term response (95%CI): 30%(10-56), 77%(66-85) and 95%(89-99) respectively.

Conclusion
In addition to baseline characteristics, treatment outcomes at 3 months contribute to the prediction of benralizumab response at 1 year in patients with severe eosinophilic asthma. Prediction tools as proposed in this study may help physicians optimize the use of costly biologics.

INTRODUCTION

Severe eosinophilic asthma is associated with impaired quality of life, uncontrolled asthma symptoms,[1-3] and severe exacerbations that, until recently, could only be controlled by recurrent bursts or daily use of oral corticosteroids (OCS) putting patients at risk for serious long-term side effects.[4] This undesirable situation changed remarkably with the availability of biologics, especially biologics targeting Interleukin (IL)-5, a cytokine responsible for the recruitment and activation of eosinophils.[5]

One of these biologics is benralizumab, targeting the IL-5-receptor alpha subunit (IL-5Ra), which has been shown to be very effective in the treatment of severe eosinophilic asthma. In phase 3 randomized controlled trials (RCTs) benralizumab treatment has shown to induce a reduction in maintenance OCS dose and exacerbation rate and an improvement in pulmonary function and patient-reported outcome measures (PROMs).[6-8] In addition, results of the recent open-label PONENTE study showed that the majority of patients initiating benralizumab were able to reduce or completely eliminate maintenance OCS.[9]

While benralizumab is highly effective in most patients, some patients have no response or only a partial response, resulting in discontinuation or switching to another biologic.[10-12] Given the high burden of disease and treatment costs, there is an urgent need for (bio)markers to predict long-term response to benralizumab.[13, 14]

To date, a few studies have addressed the prediction of benralizumab response. Certain baseline characteristics, such as higher exacerbation rate or higher blood eosinophil counts, are associated with more favorable benralizumab-induced outcomes, but it remains difficult to predict an individuals' probability of being a responder.[12, 15] Next to baseline characteristics, early treatment effects may contribute to the prediction of long-term outcomes, as shown by a few studies that focused on predicting future asthma exacerbations or therapy response.[16-18] Whether the prediction of long-term response to benralizumab improves with the addition of early treatment outcomes to baseline characteristics is not yet known.

Therefore, we assessed the effects of benralizumab treatment using real-world patient data from the Dutch Severe Asthma Registry RAPSODI.[19] The primary aim of this study was to assess whether treatment outcomes at 3 months –in addition to baseline characteristics– contribute to the prediction of benralizumab response at 1 year. We further, exploratively, developed an easy-to-use prediction tool to

enable clinicians to assess an individual patient's probability of long-term response to benralizumab treatment.

METHODS

Study design and patient population

This was a nationwide, multicenter observational registry-based real-world population study. The study population consisted of patients with severe asthma included in the Dutch Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI). In RAPSODI, patient-level data are captured annually in a CASTOR EDC® eCRF from patients with severe asthma in 19 Dutch hospitals. Furthermore, patients are asked to fill in 3-monthly electronic questionnaires (PatientCoach®, Leiden University Medical Center, Leiden, The Netherlands.[20]

All patients ≥18 years old who initiated benralizumab for severe eosinophilic asthma between 1 April 2018 and 1 October 2020 were included in this study. All patients were diagnosed with severe asthma according to the ERS/ATS guidelines.[21] Anti-IL-5Ra eligibility was based on serum eosinophils $\geq 0.3*10^9$ cells/L or $\geq 0.15*10^9$ cells/L for patients using OCS maintenance treatment.[22] Patients were excluded if they were lost to follow-up. Informed consent for this study was collected at registry-enrolment. For the current study, a formal approval from a medical ethics committee was waived according to Dutch legislation. The study was registered in the Netherlands Trial Register (registration number: NL8885).

Measurements

The Asthma Control Questionnaire (ACQ-6) at baseline, 3 months and 12 months after initiating benralizumab was collected using the application PatientCoach®. Other baseline characteristics at the moment of benralizumab initiation and clinical outcomes after 12 months were collected from the RAPSODI registry and included: patient demographics, asthma characteristics, medication (inhaled corticosteroids (ICS) dose, OCS use, OCS maintenance dose, previous biologic), number of exacerbations in the 12 months before benralizumab initiation, lung function measurements (FEV_1), inflammatory markers (peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO)), and comorbidities (nasal polyposis, chronic rhinosinusitis, bronchiectasis). OCS maintenance dose after 3 months of benralizumab treatment was collected from the patients' records. Clinical outcomes after 12 months were: continuation of benralizumab, number of exacerbations in the previous 12 months, OCS use, OCS maintenance dose, ACQ-6, and FEV_1.

Study definitions

A positive response to benralizumab treatment was defined as continuation of benralizumab after 12 months (responders).[23] If benralizumab was discontinued at or before the 12 months mark, the patients were classified as non-responders.

Asthma exacerbations were defined by at least one of the following criteria: 1) patient-reported use of OCS courses; 2) doubling of maintenance dose of OCS for at least 3 days; 3) unscheduled emergency visits or hospitalizations for asthma deterioration.

Statistical analysis

Assessment of clinical outcomes

Continuous variables are expressed as means (SD) or medians (IQR) whatever applicable and categorical variables as percentages. Baseline differences between responders and non-responders to benralizumab treatment were compared using t-tests and Mann-Whitney U-tests whatever applicable for continuous variables and Chi^2-tests for categorical variables. Changes in clinical outcomes pre- and (3 or 12 months) post benralizumab initiation in the total group and within responder group were assessed using Wilcoxon signed-rank tests.

Predicting response

To investigate predictors of benralizumab response at 12 months, we used logistic regression, including commonly available baseline characteristics and clinical outcomes after 3 months as potential predictors. Variables with >20% missing data were considered not commonly available from clinical practice and were hence left out of the analysis. Variables univariately associated with benralizumab response ($P<0.20$) were selected for multivariable logistic regression, following a full model approach in order to avoid predictor selection bias and overfitting.[24, 25] Effect-sizes were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). Discriminative ability was assessed with the area under the receiver-operating characteristic (AUROC) and calibration with the Hosmer-Lemeshow test and calibration plots. Based on AUROCs, a choice was made between incorporating either variables at baseline and 3 months or the change in these variables between baseline and 3 months. To assess the added value of the variables at 3 months in the prediction of long-term response, 2 multivariable models predicting long-term response were compared: a model with only baseline variables and a model with baseline variables combined with 3-months data. AUROCs of both regression models were compared using the DeLong-test. Sensitivity analyses were performed to examine the robustness of the results. The multivariable regression analyses were

repeated with another outcome measure for long-term response, incorporating ≥50% exacerbation reduction or ≥50% OCS dose reduction in the definition of response (Supplementary materials).

Development of a prediction tool

Based on the univariately selected predictors, an easy-to-use tool was developed in order to predict an individual's probability of being a benralizumab responder. First, continuous variables were categorized according to clinically relevant cut-offs and a multivariable regression model was constructed. In order to construct a parsimonious model, variables that contributed marginally to the AUROC were excluded from the model. The model was internally validated and corrected for optimism using internal bootstrap resampling (1000 bootstrap samples).[26] Finally, score points were assigned to the variables based on the regression coefficients. Individual prediction scores were calculated to assess the performance of the model in the study population. Risk categories based on the absolute risk for response were established in order to make the model clinically applicable.

A P-value <0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 26.0 and STATA version 16.0.

RESULTS

Patient characteristics at baseline

Two hundred twenty out of 814 patients included in the RAPSODI registry at 1st October 2020 initiated benralizumab between 1 April 2018 and 1 October 2020. All 220 patients had follow-up data for at least 12 months and were included in the analysis (Figure 1). Table 1 summarizes the characteristics of the study population at benralizumab initiation. Forty-nine percent of the participants were male, the majority of patients had adult-onset asthma, and almost half of the patients were previous smokers. Fifty-six percent of the patients received maintenance OCS when initiating benralizumab and 60% of them had previously used another biologic.

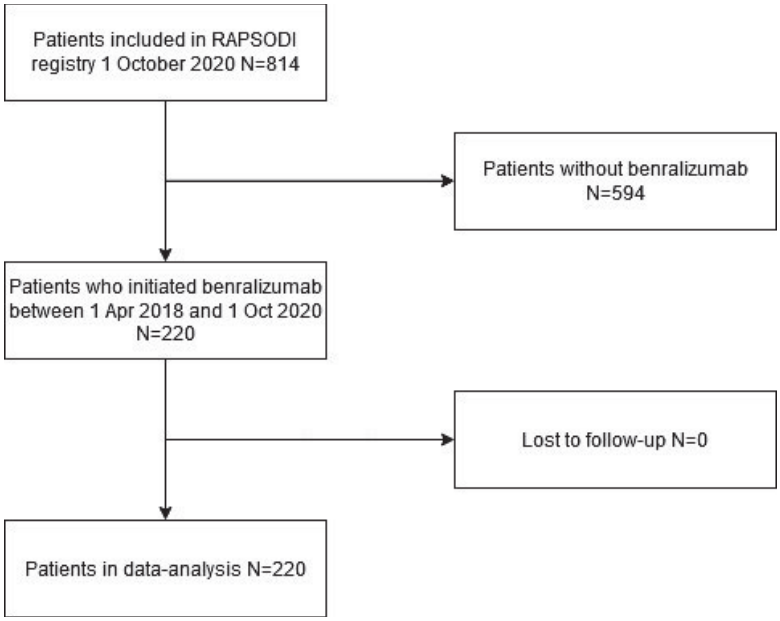

Figure 1: Flow chart of selected patients.

Real-world effectiveness of benralizumab

The effect of benralizumab treatment on several asthma-related outcomes is demonstrated in Figure 2 and Table E1 in the supplementary materials. In the total population, initiating benralizumab led to a statistical significant improvement at 1 year of exacerbation rate (median (IQR) 3 (2-4) exacerbations per year to 0 (0-1) exacerbations per year, p<0.01) and OCS maintenance dose (5 (0-10) mg/day to 0 (0-2.5) mg/day, p<0.01). In addition, ACQ-6-score significantly improved from 2.17 (1.5-3.17) at baseline to 1.0 (0.33-1.8) at 1 year, p<0.01, and FEV_1 (%predicted) from 73% (59-87) to 80% (66-95), p<0.01. A statistical significant improvement of OCS maintenance dose and ACQ-6-score was observed as early as 3 months after initiating benralizumab treatment.

Table 1: Baseline characteristics for the total population, and stratified for non-responders and responders.

	Total population (N=220)	Non-responders (N=52)	Responders (N=168)	P-value
Age (y)*	57 (13)	56 (14)	58 (13)	0.42
Male gender (%)	49.1	38.5	52.4	0.079
Body mass index (kg/m²)*	28.5 (10.9)	28.5 (5.8)	28.5 (12.1)	0.97
Former smoker (%)	48.6	44.2	50.0	0.64
Pack years (y)† ˜	10 (5-20)	10 (5-20)	11 (6-21)	0.62
Age of asthma onset (y)*	40 (19)	36 (17)	41 (20)	0.15
Non atopic asthma (%)	64.5	63.3	64.8	0.87
Late asthma onset (%)	79.9	80.8	79.6	0.86
Exacerbation number last year (exacerbations per year)†	3 (2-4)	3 (1-4)	3 (2-4)	0.75
ICS daily dose (mg, fluticasone equivalents)†	1000 (750-1250)	1000 (750-1500)	1000 (750-1000)	0.77
OCS maintenance on baseline (%)	55.9	55.8	56.0	0.98
OCS dose baseline (mg/day)†‡	10 (5-15)	10 (10-20)	10 (5-12.5)	0.011
Previous biologic for severe asthma (%)	59.5	78.8	53.6	0.001
Ever use of omalizumab (%)	12.7	19.2	10.7	
Ever use of mepolizumab (%)	49.1	61.5	45.2	
Ever use of reslizumab (%)	14.5	25	11.3	
Ever use of dupilumab (%)	1.8	1.9	1.8	
FEV_1 pre-bronchodilator (%pred)*	72.8 (22.7)	69.4 (22.8)	73.8 (22.6)	0.23
FeNO (ppb)†	44 (24-77)	34 (18-60)	45 (26-74)	0.044
Serum eosinophils (*10^9 cells/L)†	0.3 (0.1-0.6)	0.1 (0.1-0.4)	0.3 (0.1-0.7)	0.46

Table 1: Continued.

		Total population (N=220)	Non-responders (N=52)	Responders (N=168)	P-value
Serum eosinophils (*10^9 cells/L)	<0.3 (%)	51.5	62.8	48.4	0.095
	≥0.3 (%)	48.5	37.2	51.6	
Bronchiectasis (%)		14.1	17.3	13.1	0.68
Nasal polyposis (%)		47.7	52.9	46.1	0.65
Chronic rhinosinusitis (%)		58.1	60.8	57.3	0.51

* Mean SD, † Median IQR, ˜ Calculated for former smokers, ‡ Calculated for patients receiving OCS maintenance treatment on baseline, N=123.
Abbreviations: FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced Expiratory Volume in 1 second, ICS: Inhaled Corticosteroids, IQR: interquartile range, OCS: Oral corticosteroids (prednisone equivalents)

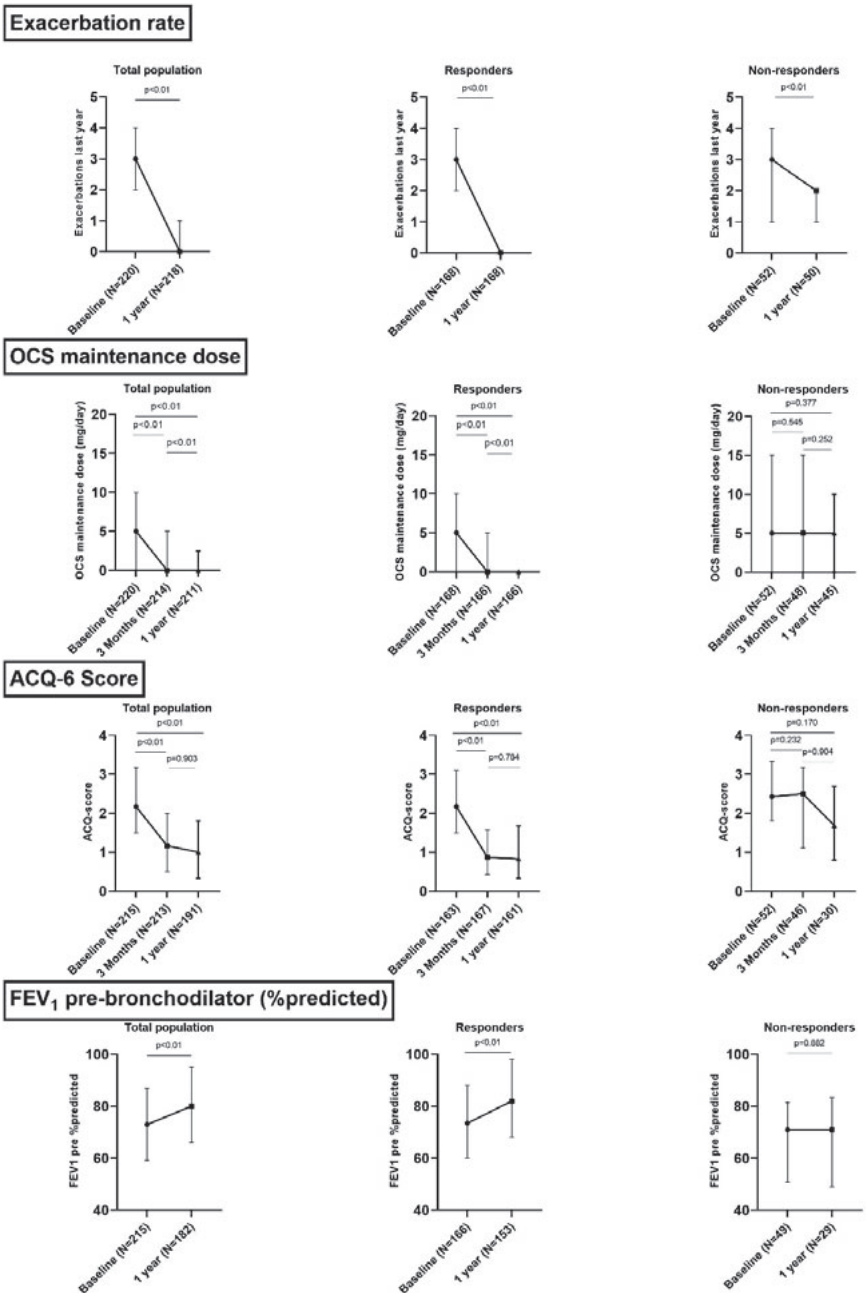

Figure 2 (on the right): Benralizumab effectiveness after 12 months. The figure describes the effect of benralizumab after 12 months on exacerbation rate, maintenance OCS-dose, ACQ-6-score, and pre-bronchodilator FEV_1 (%predicted) for the total population (N=220), responders (N=168) and non-responders (N=52). The available number of patients per time point is shown on the X-axes in brackets.

One hundred sixty-four (76.4%) patients continued benralizumab after 12 months, classifying them as responders. Of the 52 (23.6%) patients that discontinued benralizumab within 12 months (non-responders), the reasons for stopping were: failure to reduce symptoms (N=36), failure to reduce OCS (N=25), insufficient effect on pulmonary function (N=22), side effects (N=7), and other (N=2). Multiple reasons for discontinuing benralizumab were possible. No patients discontinued benralizumab solely based on insufficient effect on pulmonary function. The median (IQR) duration of treatment for patients discontinuing benralizumab was 4 (4-8) months.

Baseline characteristics of responders and non-responders are shown in Table 1. Responders differed from non-responders in that they were less likely to report the use of a prior biologic and were more often male. Responders had higher levels of FeNO and tended to have blood eosinophil levels above 0.3 x 10^9 cells/L. Data on the effect of benralizumab on clinical outcomes for responders and non-responders are illustrated in Figure 2 and Table E1 in the supplementary materials.

Predicting long-term benralizumab response

To explore whether 3 months data can improve prediction of benralizumab response at 1 year, we used univariate logistic regression analyses (Table 2). Male gender, no previous biologic use, lower OCS dose at baseline, lower ACQ-6-score at baseline, baseline blood eosinophils ≥0.3*10^9 cells/L, lower OCS dose at 3 months and lower ACQ-6 at 3 months were univariately associated with benralizumab response (P<0.20) and included in the multivariable analyses. 189 patients had complete data for all characteristics.

Table 2: Univariate logistic regression analysis predicting long-term benralizumab response.

Variables at baseline	OR (95%CI)	P-value
Male gender	**1.76 (0.93-3.30)**	**0.081**
Body mass index (kg/m²)	1.00 (0.97-1.00)	0.97
Age (years)	1.01 (0.99-1.00)	0.42
Former smoker	1.28 (0.68-2.40)	0.46
Non-atopic asthma	1.07 (0.55-2.10)	0.84
Adult onset asthma	0.93 (0.42-2.00)	0.86
Exacerbation rate year before start (exacerbations per year)	1.03 (0.92-1.15)	0.61
ICS dose (mg, fluticasone equivalents)	1.00 (1.00-1.00)	0.66
OCS dose (mg/day)	**0.97 (0.94-1.00)**	**0.049**
No previous biologic	**3.23 (1.56-6.71)**	**0.002**
ACQ-6 score	**0.80 (0.60-1.07)**	**0.13**
FEV_1 pre-bronchodilator (%predicted)	1.01 (1.00-1.02)	0.23
Serum eosinophils (*10^9 cells/L)	1.37 (0.74-2.52)	0.32
Serum eosinophils ≥0.300 *10^9 cells/L	**1.80 (0.90-3.60)**	**0.097**
Bronchiectasis	0.67 (0.28-1.66)	0.39
Nasal polyposis	0.72 (0.37-1.43)	0.35
Chronic rhinosinusitis	0.755 (0.37-1.52)	0.42
Variables at 3 months	**OR (95%CI)**	**P-value**
OCS dose (mg/day)	**0.89 (0.85-0.94)**	**<0.001**
ACQ-6 score	**0.35 (0.24-0.50)**	**<0.001**

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV_1: Forced Expiratory Volume in 1 second, ICS: Inhaled Corticosteroids, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio.

Table 3 demonstrates the multivariable logistic regression analyses of two models, the first model using only predictive parameters at baseline and the second model with predictors at baseline and 3 months. The model with only baseline predictors corresponded to an AUROC of 0.70 (95%CI 0.62-0.79), the Hosmer Lemeshow-test did not indicate bad fit (p=0.39). The model using baseline parameters combined with 3 months parameters corresponded to a higher AUROC than baseline predictors alone, namely 0.86 (95%CI 0.79-0.94). The Hosmer Lemeshow-test showed no indication of bad fit (p=0.69); for the calibration plots, see Figure E1 in the supplementary materials. The AUROCs of both models were statistically significant different (p<0.001). Two exploratory analyses with only outcomes at 3 months and only the ACQ-6 at 3 months, are performed in the supplementary materials, Table E3. Both analyses yielded lower AUROCs than the model using baseline parameters combined with 3 months parameters. The sensitivity analysis incorporating ≥50% exacerbation reduction or ≥50% OCS dose reduction in the definition of response did

not find other predicting variables and yielded comparable AUROCs (Supplementary materials, Tables E4 and E5).

Table 3: Multivariable logistic regression analysis, including baseline and 3 months characteristics (right), predicting long-term benralizumab response, as compared to a model including baseline characteristics only (left).

	Baseline only		**Baseline and 3 months**	
Variable	OR (95%CI)	P-value	OR (95%CI)	P-value
Male gender	1.46 (0.70-3.03)	0.31	1.55 (0.61-3.95)	0.36
OCS dose at baseline (mg/day)	0.97 (0.94-1.01)	0.10	0.98 (0.92-1.04)	0.46
No previous biologic	3.25 (1.33-7.92)	0.010	2.02 (0.69-5.93)	0.20
ACQ-6 score at baseline	0.80 (0.56-1.14)	0.22	1.60 (0.90-2.84)	0.11
Serum eosinophils ≥0.300 *10^{9}cells/L	1.09 (0.48-2.48)	0.83	1.04 (0.38-2.85)	0.94
OCS dose at 3 months (mg/day)	-	-	0.92 (0.84-1.00)	0.047
ACQ-6 score at 3 months	-	-	0.27 (0.15-0.46)	<0.001
Area under ROC (95%CI)	**0.70 (0.62-0.79)**		**0.86 (0.79-0.94)**	

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.

Clinical assessment of long-term response

Based on the multivariable logistic regression model from Table 3, including both baseline and predictors at 3 months, we proposed an easy-to-use response prediction tool in Table 4 and Figure 3. Removal of the ACQ-6 at baseline and OCS dose at baseline had a minimal effect (-0.03) on the AUROC. Internal validation yielded a correction for optimism of 0.01 decrease in the AUROC. Three score categories for probability of long-term benralizumab response were established: low (score 0-3), intermediate (score 4-10) and high (score ≥11). Patients with a score ≥11 at 3 months had a very high probability (95%, 95%CI 88-99%) of still receiving benralizumab after 12 months and 92% of these patients had a ≥50% reduction of either exacerbation rate or maintenance OCS dose after 12 months. The number of patients per score (0-16) and the proportion of patients and likelihood ratios per prediction category are described in Table E2 in the supplementary materials.

Table 4: Development of a prediction tool, predicting long-term benralizumab response.

Variable		Rounded points	OR (95%CI)	P-value
Female gender		0	Ref.	
Male gender		2	1.5 (0.65-3.6)	0.33
Previous biologic		0	Ref.	
No previous biologic		2	2.1 (0.77-5.8)	0.15
Serum eosinophils <0.300 *10^{9}cells/L		0	Ref.	
Serum eosinophils ≥0.300 *10^{9}cells/L		1	1.2 (0.46-3.1)	0.72
OCS dose at 3 months >7.5 mg/day		0	Ref.	
OCS dose at 3 months ≤7.5 mg/day		4	4.2 (1.6-10.5)	0.003
ACQ-6 score at 3 months	≤0.75	7	7.4 (2.3-23.7)	0.001
	0.76-1.5	4	4.2 (1.4-12.8)	0.01
	>1.5	0	Ref.	
Area under ROC curve (95%CI)		**0.81 (0.74-0.89)**	**0.82 (0.74-0.90)**	

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.

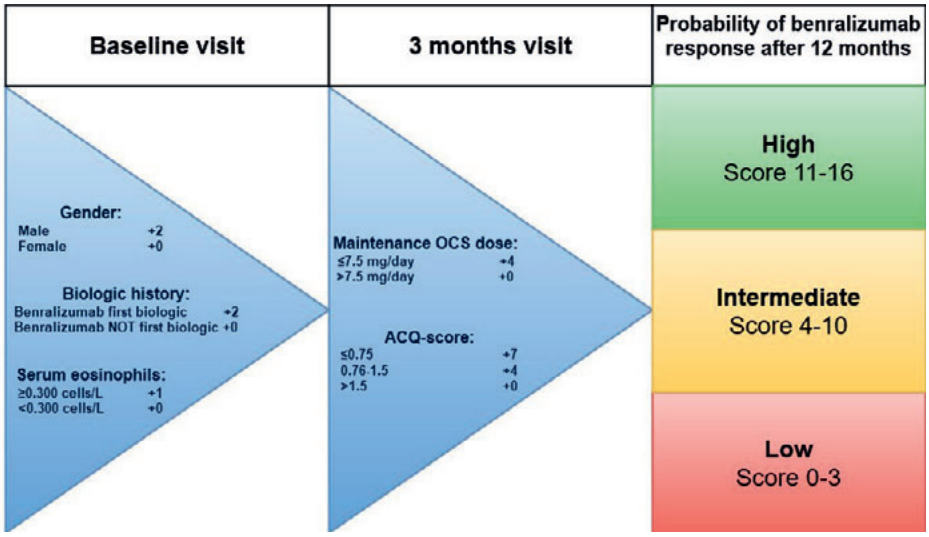

Figure 3: Benralizumab response score. The prediction tool combines baseline characteristics and outcomes at 3 months to predict long-term benralizumab response. Based on the score, the individual patient has a high (95% (95%CI 88-99)), intermediate (77% (95%CI 66-85)) or low (30% (95%CI 10-56)) probability of benralizumab response after 12 months.

DISCUSSION

The present study shows that treatment outcomes at 3 months –in addition to baseline characteristics– contribute to the prediction of benralizumab response at 1 year in patients with severe eosinophilic asthma. In this large nationwide real-world population, benralizumab treatment significantly improved exacerbation rate, OCS maintenance dose, ACQ-6 and FEV_1. The majority (76.4%) of the 220 included patients still received benralizumab 1 year after initiation, identifying them as responders. The prediction of response to benralizumab was significantly improved by adding two easy-to-assess parameters at 3 months (OCS dose and ACQ-6) to a set of baseline parameters, resulting in a predictive model with a higher AUROC and hence a higher discriminative capability. These results suggest that combining baseline data and short-term treatment outcomes and incorporating them into a simple tool, such as the one we propose, could help clinicians predict future response to benralizumab and thus promote the efficient use of costly biologics.

The beneficial effects of benralizumab, as well as its rapid onset, which we demonstrate in this study are in line with previous findings from randomized controlled trials and real-world studies.[6-9, 18] However, in terms of response rate, we identified 23.6% non-responders, which is higher than the 13-14% reported in

two UK studies.[11, 18] This may be due to the higher number of patients with prior biologic use in our study, or to the different definitions of response, but also the very strict eligibility criteria used in the UK and in these British studies which may have selected a more exacerbation-prone population resulting in lower rates of non-responders than experienced in other real-world settings.

The prediction of response to benralizumab has been studied before. Studies predicting response based on baseline characteristics found higher blood eosinophils, more frequent exacerbations, use of maintenance OCS, nasal polyposis, adult-onset asthma and higher levels of FEV_1 as important predictive parameters.[11, 12, 15, 27] Early treatment outcomes as a parameter in predicting future response to benralizumab was studied in a single study in which an ACQ-6-improvement of ≥0.5 units 4 weeks after initiating benralizumab predicted response at 48 weeks.[18] Our study confirms and extends these findings, as we showed that a combination of baseline characteristics and early treatment outcomes was most successful in identifying patients that are most likely to respond to benralizumab.

We found that 87.6% of biologic naive patients were responders *vs.* 68.7% in patients with a previous biologic. No prior use of a biologic emerged as an important predictor of long-term response to benralizumab. In a recent study it was stated that benralizumab is effective in severe asthma independent of previous biologic use.[18] Also in the present population, patients with or without previous treatment with a biologic for severe asthma significantly benefited from benralizumab treatment (data not shown). However, the individual probability of responding to benralizumab treatment was significantly higher in patients without previous biologic use, justifying its inclusion in the predictive model.

A major strength of this study is that it analyzes the largest real-world population of benralizumab-treated patients, using the Dutch RAPSODI registry, which collects longitudinal data in a standardized way, both by clinicians and 3-monthly by patients themselves. This unique registry allowed us to include treatment outcomes at 3 months in the analysis of predictors of long-term response to benralizumab. This study also has limitations inherent to the real-world character and observational design of the study, such as lack of a control group and possible unnoticed confounders in the comparison of clinical outcomes. Further, incompleteness of some data meant that certain parameters, such as FeNO, could not be used in the prediction model. As limiting as this may seem, it reflects real-world practice and ultimately we are looking for predictive parameters that are easy to assess in every clinical practice and a prediction tool that is widely applicable, as presented in our

study. We have optimized our predictive model through internal validation, but realize that external validation in another severe asthma population is required to confirm the applicability of our model and tool. Unfortunately, we do not have access to such an independent second population. Finally, we conducted our study at a time when the COVID-19 pandemic increasingly dominated the world. This likely reduced both the rate of exacerbations and the willingness of clinicians or patients to discontinue or switch biologics and may therefore have resulted in fewer patients with non-response. Nevertheless, the number of non-responders in our study is still higher than observed in other studies[11, 18], suggesting that the results were unlikely to have been significantly influenced in this regard, although we cannot exclude such an effect.

Our results have both clinical and research implications. We demonstrated a predictive model and developed a simple clinical scoring tool to help clinicians assess whether a patient is likely to respond to benralizumab treatment on the long-term. Where baseline characteristics alone are insufficient to predict an individual's probability of being a responder, our addition of parameters at 3 months succeeds in identifying patients with 95% probability on long-term benralizumab response. These patients may require less intensive monitoring, helping clinicians to allocate their valuable time. Further research will need to determine whether clinical tools integrating biomarkers, phenotypic features and clinical outcomes, such as the one proposed in our study, are a valuable addition to clinical practice, not only in predicting response to benralizumab or other biologics, but -even more challenging- in predicting non-response.

In conclusion, this nationwide real-world study confirms the beneficial effects of benralizumab treatment on several clinical outcomes in patients with severe eosinophilic asthma. The prediction of long-term response to benralizumab was clearly improved by adding treatment outcomes at 3 months to baseline characteristics and long-term response could be determined using an easy-to-use scoring tool. Prediction tools, such as the one proposed in our study, are promising additions to clinical practice, assisting clinicians in their clinical decision-making and further optimizing treatment with costly biologics.

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SUPPLEMENTARY MATERIALS

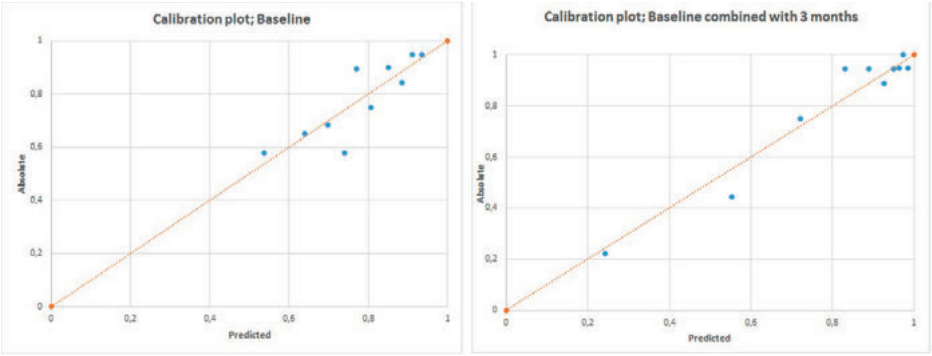


Figure E1. Calibration plots for the logistic regression model with baseline characteristics and baseline characteristics combined with 3 months.

Table E1: Clinical outcomes to benralizumab treatment

Variable	Total population (N=220)	Non-responders (N=52)	Responders (N=168)	P-value
Annual exacerbation rate at baseline*	3 (2;4)	3 (1;4)	3 (2;4)	0.75
Annual exacerbation rate after 1 year*	0 (0;1)	2 (1;2)	0 (0;0)	<0.001
Change in annual exacerbation rate after 1 year*	-2 (-3;0)	-1 (-2;0)	-2 (-4;-1)	<0.001
Maintenance OCS dose at baseline (mg/day)*	5 (0;10)	5 (0;15)	5 (0;10)	0.29
Maintenance OCS dose after 3 months (mg/day)*	0 (0;5)	5 (0;15)	0 (0;5)	0.001
Change in maintenance OCS dose after 3 months (mg/day)*	0 (-5;0)	0 (-3.75;0)	0 (-5;0)	0.015
Maintenance OCS dose after 1 year (mg/day)*	0 (0;2.5)	5 (0;12.5)	0 (0;0)	<0.001
Change in maintenance OCS dose after 1 year (mg/day)*	0 (-5;0)	0 (-5;0)	0 (-5;0)	0.004
ACQ-6-score baseline*	2.17 (1.5;3.17)	2.43 (1.82;3.33)	2.17 (1.5;3.1)	0.11
ACQ-6-score after 3 months*	1.17 (0.5;2)	2.5 (1.14;3.17)	0.87 (0.43;1.57)	<0.001
Change in ACQ-6-score after 3 months*	-0.83 (-1.5;-0.16)	-0.16 (-0.72;0.43)	-1 (-1.67;-0.33)	<0.001
ACQ-6-score after 1 year*	1 (0.33;1.8)	1.69 (0.83;2.6)	0.83 (0.33;1.67)	<0.001
Change in ACQ-6-score after 1 year*	-0.88 (-1.63;-0.17)	0.05 (-0.83-0.34)	-1 (-1.67;-0.33)	<0.001
FEV_1 baseline (%predicted)*	73 (59;87)	71 (51;81)	73.5 (60;88)	0.15
FEV_1 after 1 year (%predicted)*	80 (66;95)	71 (50;82)	82 (68;98)	0.004
Change in FEV_1 after 1 year (%predicted)*	4 (-2;12)	-1 (-4;5)	5 (-1;15)	0.008

*: Median (IQR) Abbreviations: ACQ: Asthma Control Questionnaire, FEV_1: Forced Expiratory Volume in 1 second, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio.

Table E2: Performance of the prediction tool in the population.

		Number of patients (N=189)*		
Prediction score		**Non-responders (N=36)**	**Responders (N=153)**	
0		4	2	
1		1	1	
2		4	2	
3		3	0	
4		4	14	
5		3	2	
6		5	8	
7		3	10	
8		2	9	
9		1	13	
10		2	9	
11		2	16	
12		0	5	
13		1	28	
14		1	15	
15		0	2	
16		0	17	
Prediction category	**Prediction score**	**Non-responders (N=36)**	**Responders (N=153)**	**Likelihood ratio (LR)**
Low	**0-3**	12 (70%, 95%CI 44-90)	5 (30%, 95%CI 10-56)	0.10
Intermediate	**4-10**	20 (23%, 95%CI 15-34)	65 (77%, 95%CI 66-85)	0.76
High	**11-16**	4 (5%, 95%CI 1-11)	83 (95%, 95%CI 88-99)	4.88

* N=189; complete cases in the data set.
Abbreviations: CI: Confidence Interval; LR: Likelihood Ratio, defined as the probability of this prediction category occurring, given being responder, divided by the probability of this prediction category occurring, given being non-responder.

Predicting response with only variables at three months.

Table E3: Multivariable logistic regression analysis, 3 months characteristics (left), predicting long-term benralizumab response, as compared to a model including only the ACQ-6 at 3 months (right).

	3 months only		**ACQ at 3 months only**	
Variable	OR (95%CI)	P-value	OR (95%CI)	P-value
OCS dose at 3 months (mg/day)	0.92 (0.87-0.97)	0.004	-	-
ACQ-6 score at 3 months	0.39 (0.27-0.57)	<0.001	0.35 (0.24-0.50)	<0.001
Area under ROC (95%CI)	**0.79 (0.71-0.88)**		**0.78 (0.70-0.86)**	

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.

SENSITIVITY ANALYSIS

We performed a sensitivity analysis using a separate outcome measure to examine the robustness of the results. In this analysis, long-term response was defined as:

Continuing benralizumab treatment AND (1) ≥50% reduction in exacerbation rate OR (2) ≥50% reduction in maintenance oral corticosteroid dose. In this analysis, the few patients who had no exacerbations and used no OCS maintenance treatment at benralizumab initiation (all switchers from another biologic) were considered responders if they had no exacerbations in the follow-up year and no OCS maintenance use at 1 year.

This approach found 162 patients with long-term response and 56 non-responders. The tables below show the same predicting variables as our initial analysis and comparable AUROCs.

Table E4: Univariate logistic regression analysis predicting long-term benralizumab response.

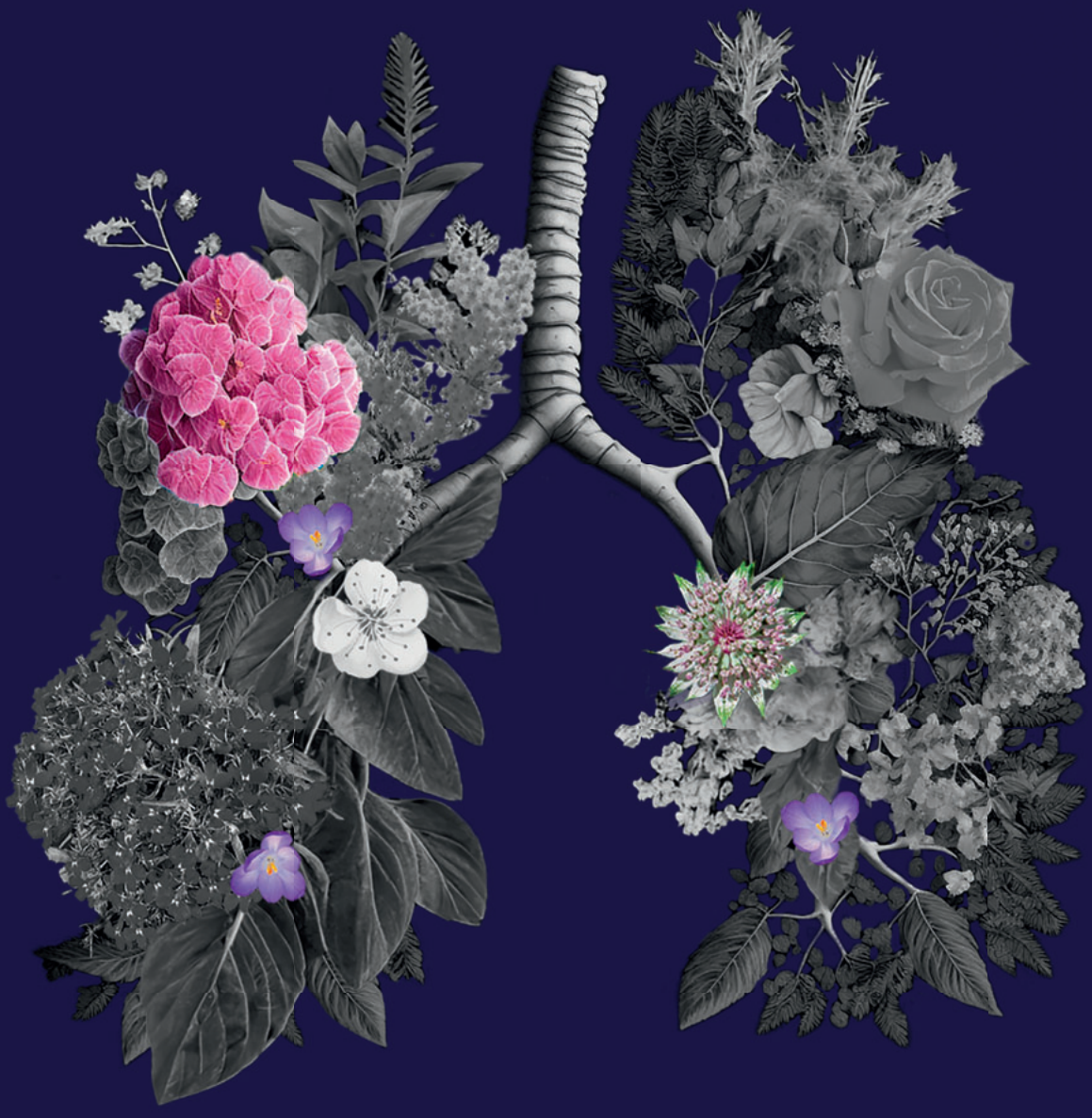
Variables at baseline	OR (95%CI)	P-value
Male gender	**2.04 (1.09-3.82)**	**0.026**
Body mass index (kg/m²)	0.97 (0.92-1.03)	0.31
Age (years)	1.01 (0.98-1.03)	0.55
Former smoker	1.26 (0.68-2.32)	0.47
Non-atopic asthma	1.01 (0.53-1.91)	0.98
Adult onset asthma	1.1 (0.52-2.32)	0.80
Exacerbation rate year before start (exacerbations per year)	1.07 (0.95-1.20)	0.27
ICS dose (mg, fluticasone equivalents)	1.00 (0.99-1.00)	0.84
OCS dose (mg/day)	**0.98 (0.95-1.01)**	**0.16**
No previous biologic	**3.80 (1.84-7.87)**	**<0.001**
ACQ-6 score	**0.82 (0.61-1.09)**	**0.16**
FEV_1 pre-bronchodilator (%predicted)	1.01 (0.99-1.02)	0.23
Serum eosinophils (*10^9 cells/L)	1.48 (0.77-2.84)	0.24
Serum eosinophils ≥0.300 *10^9 cells/L	**1.96 (0.99-3. 68)**	**0.050**
Bronchiectasis	0.66 (0.28-1.57)	0.35
Nasal polyposis	0.79 (0.41-1.53)	0.48
Chronic rhinosinusitis	0.93 (0.47-1.85)	0.85
Variables at 3 months	**OR (95%CI)**	**P-value**
OCS dose (mg/day)	**0.91 (0.86-0.96)**	**<0.001**
ACQ-6 score	**0.39 (0.28-0.54)**	**<0.001**

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV_1: Forced Expiratory Volume in 1 second, ICS: Inhaled Corticosteroids, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio.

Table E5: Multivariable logistic regression analysis, including baseline and 3 months characteristics (right), predicting long-term benralizumab response, as compared to a model including baseline characteristics only (left).

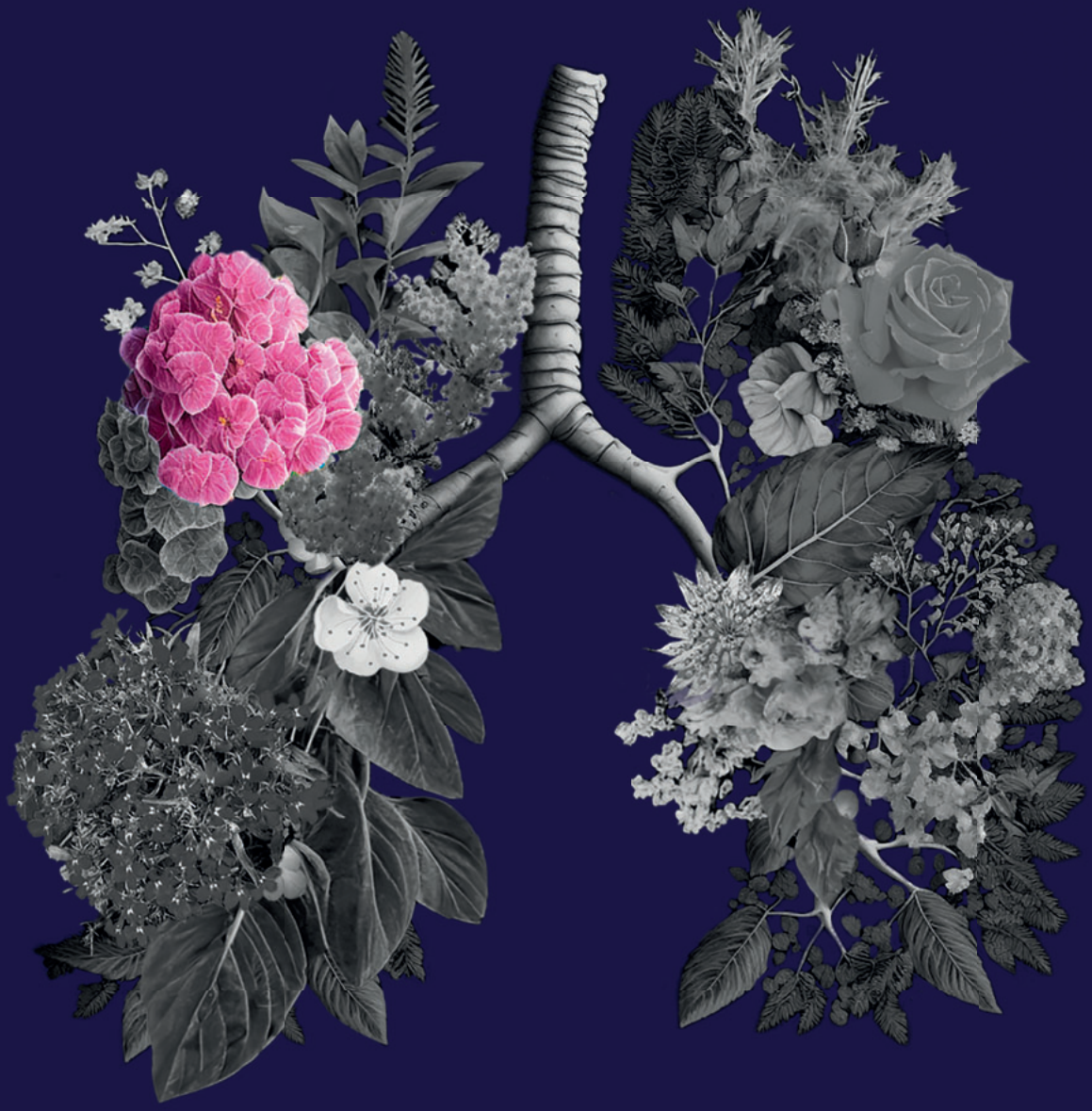
	Baseline only		**Baseline and 3 months**	
Variable	OR (95%CI)	P-value	OR (95%CI)	P-value
Male gender	1.60 (0.78-3.27)	0.200	1.63 (0.67-3.97)	0.28
OCS dose at baseline (mg/day)	0.98 (0.94-1.02)	0.26	1.00 (0.94-1.05)	0.85
No previous biologic	3.91 (1.62-9.42)	0.002	2.77 (0.98-7.82)	0.054
ACQ-6 score at baseline	0.78 (0.55-1.11)	0.16	1.39 (0.83-2.36)	0.21
Serum eosinophils ≥0.300 *10^9cells/L	1.09 (0.49-2.43)	0.83	1.04 (0.40-2.72)	0.94
OCS dose at 3 months (mg/day)	-	-	0.92 (0.85-1.00)	0.050
ACQ-6 score at 3 months	-	-	0.32 (0.19-0.52)	<0.001
Area under ROC (95%CI)	**0.72 (0.64-0.80)**		**0.85 (0.78-0.92)**	

Abbreviations: ACQ: Asthma Control Questionnaire, CI: Confidence Interval, FEV_1: Forced Expiratory Volume in 1 second, ICS: Inhaled Corticosteroids, OCS: Oral corticosteroids (prednisone equivalents), OR: Odds ratio, ROC: Receiver-Operating Characteristic.



Part III

Patient-tailored outcomes



Chapter 10

Optimizing omalizumab dosing in severe asthma – the exploration of therapeutic drug monitoring

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Clinical Communication
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Therapeutic drug monitoring (TDM), measuring drug concentrations to adjust dosing and optimize treatment outcomes, is commonly applied to personalize costly biological treatment in rheumatoid arthritis and inflammatory bowel disease (IBD).[1] Currently, TDM is not used for the biologics applied in severe asthma, but might likewise help to optimize therapy efficacy, safety and cost-effectiveness.[2] Studies evaluating variability in biologic serum levels in long-term responders, combined with clinical asthma outcomes, are lacking.

Omalizumab has been used in the treatment of severe allergic asthma since 2003. Therapy is evaluated after 16 weeks and continued in patients with good response.[3-5] In early dose-finding trials, it was found that to achieve sufficient immunoglobulin E (IgE) suppression, omalizumab serum levels should be in serum-excess over baseline IgE of at least 15:1.[6] This approach translated to the currently applied dosing table, incorporating baseline IgE and bodyweight.[7] It is unknown to what end this 15:1 ratio is achieved or surpassed in patients receiving long-term (≥1 year) omalizumab therapy and what variability is seen in these ratios.

Despite being characterized by their pulmonologist as 'omalizumab responders' based on achieved improvements in clinical parameters, some patients still suffer from lack of control and need their next dose sooner that the standard dosing interval. On the other hand, some patients can maintain control with extended dosing intervals. Inadequate or excessive biologic trough levels (the serum level before the next administration) might be related to this phenomenon.

Therefore, the variability in excess of omalizumab trough level over baseline IgE was determined in a real-world responder population, receiving long-term (≥1 year) omalizumab therapy for the treatment of severe asthma. In addition, the relationship between omalizumab trough levels and patient-reported need for the next administration was examined.

Patients recruited from a severe asthma centre in the Netherlands, all of whom were receiving long-term (≥1 year) omalizumab therapy for the treatment of severe allergic asthma by June 2019 were selected and informed consent was collected. In addition to the standard 6-monthly evaluation, recording questionnaires (Asthma Control Questionnaire (ACQ), Asthma-related Quality of Life Questionnaire (AQLQ)) and spirometry, omalizumab trough levels in serum were determined at the end of the dose interval. We used a modified patient-reported outcome measure BORG-scale ranging from 'no need' (score 0) to 'extreme need' (score 10) to quantify the patient-reported need for the next omalizumab administration.[8] Patients were

divided in subgroups with none to low need (0-2) and higher need (3-10). Inhalation medication was optimized before starting omalizumab treatment and monitored during the treatment.

27 patients with severe asthma (GINA step 5) were included. Baseline characteristics are displayed in table 1.

Table 1: Baseline characteristics.

Characteristic	N=27
Age (y), median (IQR)	54 (33-59)
Sex (male), N (%)	10 (37)
Bodyweight (kg), median (IQR)	88 (76-95)
BMI, median (IQR)	27.7 (25.1-33.6)
Inhaled fluticasone equivalents (mg/d), median (IQR)	1000 (500-1000)
Inhaled formoterol equivalents (mg/d), median (IQR)	24 (24-24)
Treatment duration (mo), median (IQR)	38 (24-58)
Omalizumab dose (mg), range	150-600
Omalizumab interval (wk), range	2-6
Dose per 4 wk (mg), median (IQR)	450 (300-750)
Annual exacerbation rate, median (IQR), (range)	0 (0-1), (0-1)
ACQ-score, median (IQR)	0.83 (0.50-2.17)
AQLQ-score, median (IQR)	6.07 (5.26-6.35)
FEV_1 pre-salbutamol (%predicted), median (IQR)	79 (73-94)
FeNO (ppb), median (IQR)	20 (13-40)

Abbreviations: ACQ = Asthma control questionnaire, AQLQ = Asthma-related quality of life questionnaire, FeNO = Fractional exhaled nitric oxide, FEV_1 = Forced expiratory volume in 1 second, IQR = Interquartile range.

The median omalizumab excess over baseline IgE was 72.5:1, ranging from 14.1:1 to 511.3:1 (Figure E1, Supplementary materials). All patients except one (96.3%) had an excess ≥15:1. Median omalizumab trough-level was 50 µg/mL (IQR 20-64), ranging from 9 µg/mL to 100 µg/mL.

14 patients reported a low need for the next administration versus 13 with a high need for the next administration. Higher patient-reported need was associated with lower omalizumab trough levels (β=-5.11, 95%CI= -10.16 to -0.06, p=0.048). Patients in the high need group had significantly lower median omalizumab trough levels as compared to the low need group (Figure 1A and 1B). No significant associations were found between omalizumab trough levels and other clinical parameters

(exacerbation rate, ACQ, AQLQ, FEV_1, FeNO). No significant associations were found between patient-reported need and gender, BMI, omalizumab interval, inhaled corticosteroid dose and reliever medication.

In this explorative study in long-term omalizumab treated patients, we found a large variability in omalizumab to baseline IgE ratios as well as omalizumab through levels, suggesting an opportunity to individualize treatment. These findings encourage to further explore the potential of TDM in omalizumab treatment.

The 15:1-excess mentioned in early omalizumab dose-finding trials is achieved in almost all patients. This implies that the currently applied dosing table probably succeeds in achieving sufficient IgE suppression. However, the excess generously surpasses the ratio found in early trials in most patients, indicating possible overtreatment with omalizumab in these long-term responders. Inter-individual trough levels varied greatly, as was the case in a similar study evaluating infliximab levels in IBD patients. In the latter study, an association between remission and infliximab trough levels was found.[9] These and similar results led to the incorporation of TDM in the application of biologics for IBD, personalizing the treatment and optimizing clinical outcomes. The large variability we observed in this explorative study in omalizumab responders after at least 1 year of treatment encourages to exploring whether inadequate omalizumab levels are associated with different levels of response to therapy in a more diverse population with responders, partial responders and non-responders.

The observed association between patient-reported need and omalizumab trough level is remarkable. Despite being an 'omalizumab responder', some patients indicate that the applied dosing regime is not optimal. A possible explanation might be that patients with higher blood levels clear omalizumab more slowly, resulting in more stable and adequate omalizumab levels and smaller fluctuations in unbound IgE. Fluctuations in unbound IgE might lead to a relative loss of control, leading to the feeling of needing the next administration. We were not able to test this hypothesis since no assay for measuring unbound IgE was available. However, the excess of omalizumab to baseline IgE found in our population seems to negate this explanation.

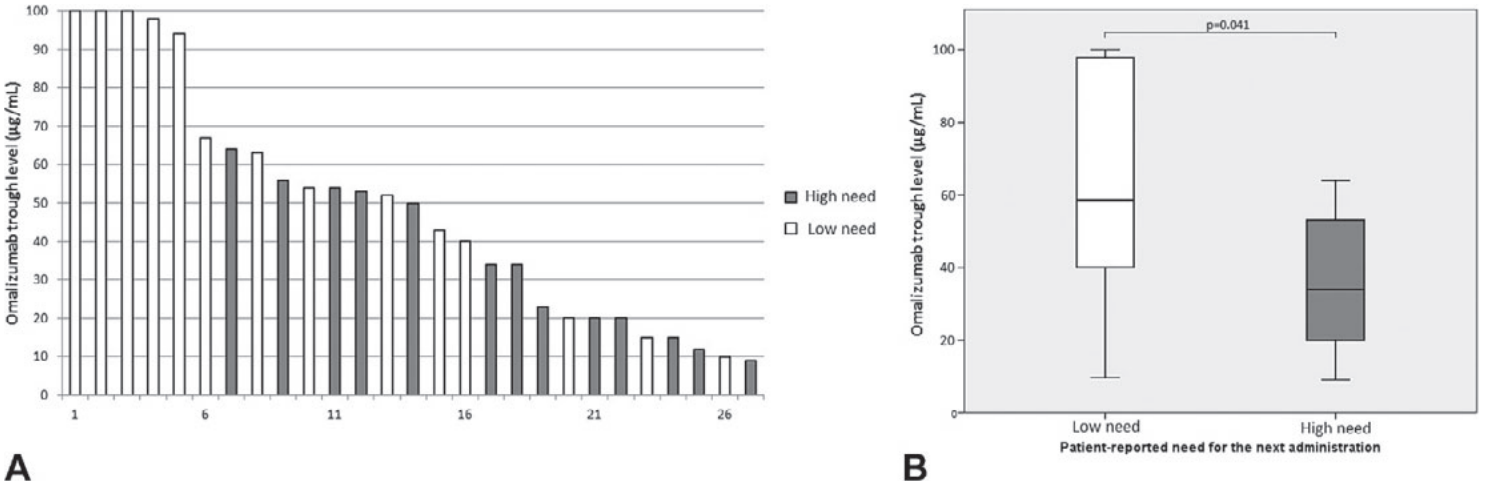

Figure 1: A, Omalizumab trough levels ranging from high to low. Each bar represents a trough level of a patient. The high or low patient-reported need for the next gift is represented by the respective gray and white bars. B, Boxplot of the omalizumab trough levels and patient-reported need subgroups. Patients in the low need group had significantly higher omalizumab trough levels as compared with the high need group: 59 µg/mL (IQR, 40-98 µg/mL) vs 34 µg/mL (IQR, 20-53 µg/mL), *P* = .041. *IQR*, Interquartile range.

This proof of principle study is the first to evaluate the variability of omalizumab trough levels in patients with severe asthma treated for more than one year and patient-reported need for the next administration and provides an opportunity to individualize treatment, adjusting the currently applied dosing schedule. The focus on therapeutic drug monitoring is an innovative approach towards personalized medicine in severe asthma care. The study includes a complete single centre responder population, but the number of participants remains limited. Data on the variability in serum levels of other biologics used in the treatment of severe asthma are currently lacking. Therefore, larger studies are warranted in more diverse populations, focusing on the applicability of TDM in the recently approved biologics for severe asthma. The incorporation of serum level measurements of biological therapy has led to successful individualization of medicine in other diseases, increasing efficacy, patient wellbeing, patient safety and cost-effectiveness, an addition which undoubtedly will be welcomed in severe asthma clinical care.

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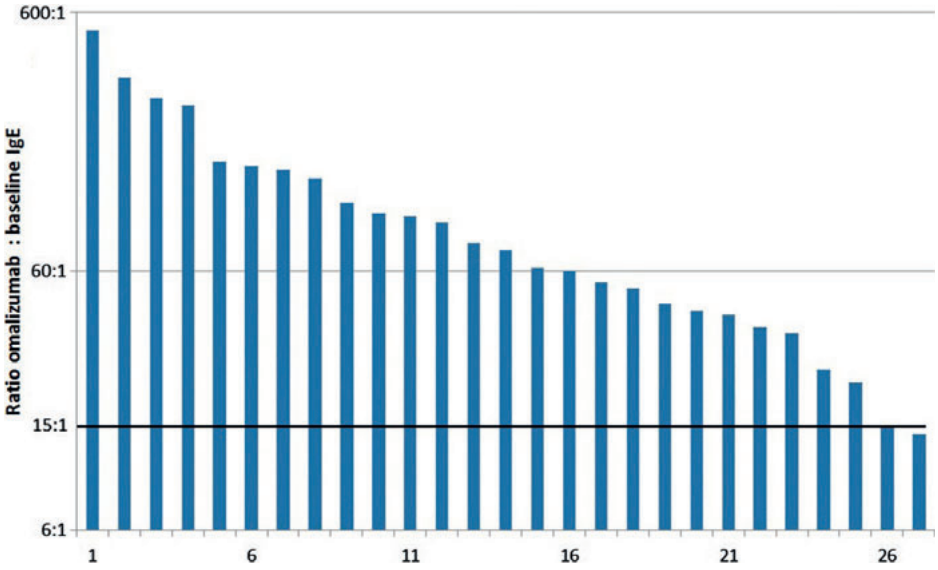
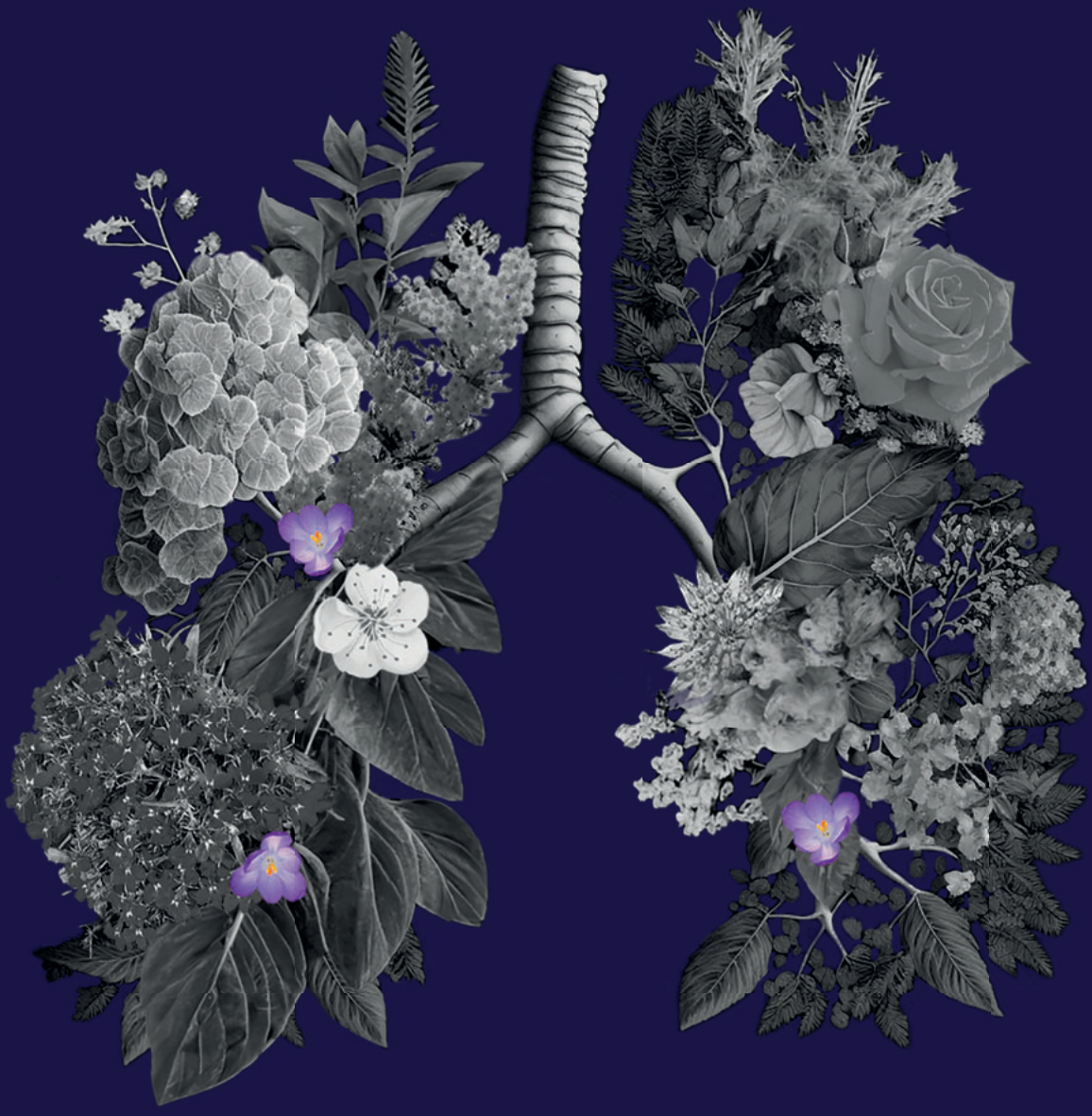
SUPPLEMENTARY MATERIAL



Supplementary figure E1: Ratios of omalizumab to baseline IgE ranging from high to low. Each bar represents a ratio of a patient. The 15:1 threshold found in early dose-finding trials is indicated by the black horizontal line.



Chapter 11

“That last week is drama” - The perceived waning of biologics in severe asthma

J.A. Kroes, L.H.G. van Hal, L. van Dijk, S.W. Zielhuis, A.N. van der Meer, E.N. van Roon, A. ten Brinke

Submitted

ABSTRACT

Background

Biologics are highly effective in severe asthma and used at fixed dosing intervals. However, in clinical practice, dosing intervals are sometimes shortened if patients perceive a decreased biologic effect before the next administration. The occurrence and clinical relevance of this perceived waning of biological effect is unknown.

Objective

To explore (1) the frequency, severity and conditions, (2) associated symptoms and (3) relationship with clinical characteristics of the patient-perceived waning effect of biologics before the next administration.

Methods

Patients with severe asthma receiving biological treatment ≥4 months were included. Based on 17 semi-structured patient interviews, we developed a questionnaire focusing on the waning effect of biologics before the next administration, which was distributed among 129 patients. Clinical characteristics, including asthma control (ACQ) and quality of life (AQLQ) scores, were collected from patient files.

Results

65/101 patients who completed the questionnaire reported a waning of biological effect, graded as severe (median (IQR) 6.5 (5-7.5) on a 0-10 BORG-scale). Waning manifested in a broad spectrum of symptoms. Patients reporting waning had higher ACQ and lower AQLQ scores versus those without ($p<0.05$) and higher BORG-scores were associated with higher exacerbation rate ($\rho=0.309$, $p=0.013$). A third of all patients were in favor of extending or shortening their dosing interval.

Conclusion

Many patients with severe asthma perceive waning of biologic effect at the end of the dosing interval, which is associated with poorer asthma control and quality of life. The diversity in observed waning of effect opens the way for research into more individualized dosing of biologics.

INTRODUCTION

The recent approval of biologics to treat patients with severe asthma has led to major changes in severe asthma care. These biologics target type 2 inflammatory pathways and have been shown to markedly reduce asthma exacerbations and oral corticosteroid (OCS) use, as well as improve asthma symptoms, lung function and quality of life [1-6]. However, there is considerable heterogeneity in clinical response to biologics and not all patients respond equally well [7]. Treatment is therefore evaluated after 4-6 months and discontinued or switched to another biologic if the response is deemed insufficient [8].

Within responders, there are also degrees of response. Some patients demonstrate a super-response to the biologics, while other patients have only a partial response with residual disease manifestations [7,9]. In clinical practice, this sometimes leads to adjustment of the dosing intervals, despite the fact that the summaries of product characteristics state that the biologics need to be prescribed in fixed dosing intervals. For example, there are patients with an excellent response in whom prolongation of the dosing interval is possible without loss of asthma control [10]. On the other hand, some patients feel that their asthma symptoms worsen towards the end of their dosing interval, sometimes leading to dose escalation by shorter dosing intervals [11].

These signals from clinical practice suggest that individualized dosing of biologics may be possible and desired for a subset of patients. Such a personalized approach, in which the maintenance of asthma control and healthcare costs are essential, could contribute to an optimal application of the costly biologics. However, guidelines or objective parameters for dose adjustments are lacking and adjustment of dosing intervals, if any, is performed empirically based on the subjective experiences of patients. Currently, data on these patient's experiences are lacking. We have no insight into the frequency and severity of the perceived waning of biological effect at the end of the dosing interval, nor do we know what characterizes this perception and whether it is clinically relevant.

Therefore, the aim of this study is to explore in patients with severe asthma (1) the frequency, severity and conditions of the patient-observed waning effect of biologics prior to the next administration. In addition, we evaluated the (2) characteristics and (3) association with asthma-related outcomes of this perceived waning biological effect.

METHODS

Study design and patients

This was a cross-sectional, observational study performed in the severe asthma centre of the Medical Centre Leeuwarden, the Netherlands. The study population consisted of all adult patients receiving biological treatment (omalizumab, mepolizumab, reslizumab, benralizumab or dupilumab) for severe asthma ≥4 months.

The study included two phases. In the first phase, a sample of 20 patients from the total study population was selected, taking into account differences in sex, age and type of biologic (Supplementary Table S1), in which semi-structured interviews were conducted for the purpose of developing a structured questionnaire. In the second phase of the study, the developed questionnaire was distributed over the rest of the study population in order to quantify the items that were derived from the interviews.

All participants signed informed consent before participating to this study. A medical ethics committee waived the necessity to comply with the Medical Research Involving Human Subjects Act.

Data collection

Interviews

An interview guide was developed with input from a pulmonary physician, a specialized pulmonary nurse and knowledge from a previous study [12]. Qualitative semi-structured interviews then were conducted to gather information from patients to explore what, in the patients' own words, are their experiences with biological treatment for severe asthma, whether these patients perceive a waning of the biological effect at the end of the dosing interval, and what symptoms are associated with this phenomenon.

Conducting the interviews was an iterative process, where new topics and answers from previous interviews were introduced to upcoming interviews [13]. New topics were introduced during the first few interviews and could be discussed during later interviews. All interviews were conducted by two researchers (JAK and LVH), recorded using ZOOM software and transcribed, coded and analyzed using ATLAS.ti, version 22.

Questionnaire

Based on the results from the interviews, a questionnaire was developed in order to quantify the findings from the interviews in the rest of the population. This questionnaire was tested for comprehensibility and legibility by approaching two patients that were not part of the interviewed sample. Any feedback was incorporated in the final version of the questionnaire (Supplementary file 1). This questionnaire was distributed over the remaining non-interviewed patients with severe asthma by post. After 3 weeks, patients were reminded by telephone if no reaction was received. After another 3 weeks, data collection was halted and data analysis commenced.

Measurements

In addition to the questionnaire, study characteristics were collected from the nearest (max. 3 months before/after taking the questionnaire) standard evaluation moment in the patients' files. These included: patient demographics, asthma characteristics, medication (biologic dose, biologic dosing interval, OCS use, OCS maintenance dose, previous biologic), number of exacerbations in the last 12 months, lung function measurements (FEV_1), inflammatory markers (peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO)), and comorbidities (nasal polyposis, chronic rhinosinusitis, bronchiectasis). Inhalation therapy was optimized before and during the treatment.

Statistical analysis

Continuous variables were expressed as means (SD) or medians (IQR) when applicable and categorical variables as percentages. Differences between the interviewed group and the questionnaire group were analysed using t-tests and Mann-Whitney U-tests or Chi^2-tests when applicable. The outcomes from the questionnaire were analysed using descriptive statistics. The association of waning of the biological effect and patient characteristics was analysed using t-tests and Mann-Whitney U-tests. The association between the BORG-scale (ranging from 0 (no need) to 10 (extreme need for the next administration)) was analysed using the Spearman Rank Correlation. A P-value <0.05 indicated statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 26.0.

RESULTS

Patients and development of the questionnaire

We identified 146 patients receiving biological treatment for severe asthma for at least 4 months. Of the 20 patients selected for the interviews, 17 patients agreed to be interviewed. Table 1 shows several themes and quotes that were found in the interviews. Based on these findings, the questionnaire in Supplementary File 1 was drafted.

Table 1: Findings from patient-interviews, themes (in bold) and quotes (in italics).

Patients were generally very satisfied with their biological treatment.
"It was a one-hit. I have not been sick [since initiating biological treatment], I feel super, I can do all sorts of things and I have no symptoms whatsoever. Sometime I think: I do not have asthma anymore."
Several patients mentioned that the final week(s) of the dosing interval is associated with asthma symptoms in different gradations and conditions, while some patients reported the opposite.
"That last week is a drama. I am demolished [that last week] and something has to be done. I either end up in the hospital or nebulize more. And then you do nothing on a day, you undertake nothing. Socially, you do not have anything. That is difficult."
"I do not feel that I need the [biological] medication. I do take the medication because I know what happens if I don't, but I do not feel anything else towards the end of the interval."
When asked what symptoms contribute to the perceived waning, a variety of symptoms was mentioned.
"I feel less energy and less stamina, more tired, towards the end of the dosing interval."
"It usually starts with shortness of breath and if that develops, I start coughing."
Patients reported several solutions when symptoms occurred.
"I nebulize more when I feel symptoms."
"I then need [towards the end of the dosing interval] to take my Foster more often, I then go to 3x2 instead of 2x2 daily."
Finally, several patients expressed the wish for an adjusted dosing interval, either prolonging due to good asthma control or shortening due to waning of the biological effect.
"I do not require the administration sooner. A week later might be possible. If my doctor would like to experiment with an administration every 9 weeks, I would be open to that."
"If I could take the gift on the, let's say, tenth or eleventh day [of a two-week interval], that would be better for me."

This questionnaire was distributed to the remaining 129 patients and completed by 101 of them (78.3%) (Figure 1). Table 2 summarizes the characteristics of the patients responding to the questionnaire. Fifty-seven percent of the 101 participants were male, 63% of patients had adult-onset asthma, and the fast majority of the patients had no asthma exacerbations in the previous year. As compared to the interviewed patients, the patients responding to the questionnaire were more often former smokers with lower levels of FEV_1 (Supplementary Table S2).

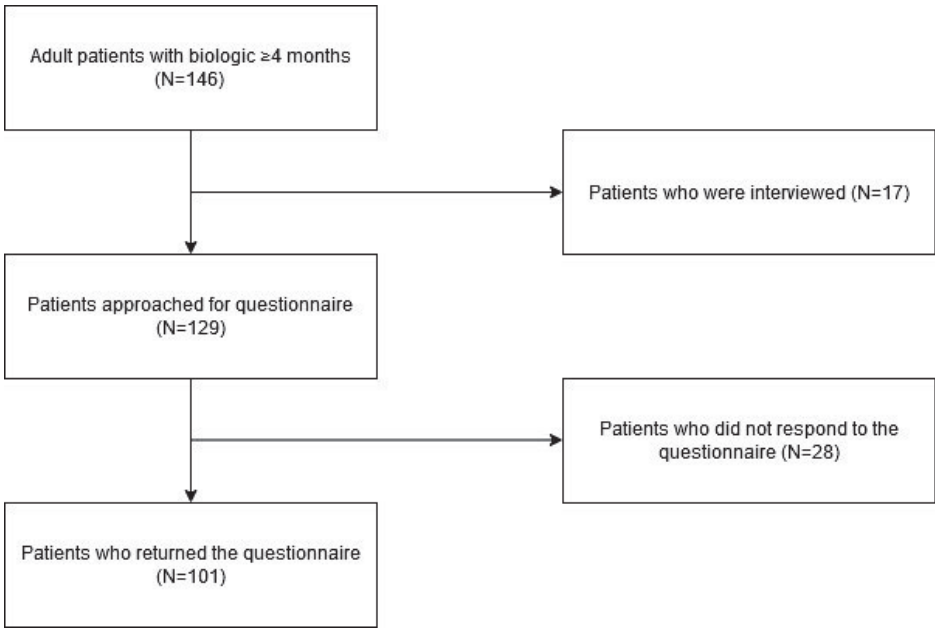


Figure 1: Flow chart of selected patients.

Table 2: Baseline characteristics for the total population, and stratified for patients with and without perceived waning of biological effect.

Patient characteristic	All patients (N=101)	With waning of effect (N=65)	Without waning of effect (N=36)	P-value
Age* (y)	60.0 (53.0-67.0)	60.0 (52.0-67.0)	60.0 (54.5-67.0)	0.94
Male gender, N (%)	58 (57.4)	40 (61.5)	18 (50.0)	0.26
BMI* (kg/m^2)	26.1 (23.6-30.2)	26.3 (24.1-30.5)	25.8 (23.5-28.6)	0.31
Former smoker, N (%)	46 (45.5)	30 (46.2)	16 (44.4)	0.82
Pack years*	8.0 (3.0-15.0)	9.0 (5.0-14.7)	5.5 (2.0-16.0)	0.35
Late asthma onset, N (%)	64 (63.4)	41 (63.1)	23 (63.9)	0.94
Age of asthma onset* (y)	47.0 (27.0-55.0)	50.0 (30.0-55.0)	43.0 (20.0-54.0)	0.23
Atopy, N (%)	47 (46.5)	28 (43.1)	19 (52.8)	0.39
Exacerbations last year*	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.73
Prescribed daily OCS dose* (mg/day)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.82
Previous biologic, N (%)	35 (34.7)	19 (29.2)	16 (44.4)	0.12
ACQ-score*	1.00 (0.50-1.83)	1.17 (0.67-2.00)	0.75 (0.33-1.42)	**0.015**
AQLQ-score*	6.08 (5.27-6.59)	5.69 (4.98-6.52)	6.44 (5.93-6.70)	**0.005**
FEV_1 pre-bronchodilator (%pred)*	83.0 (70.0-95.0)	82.0 (70.0-91.0)	87.0 (70.0-98.0)	0.35
FeNO (ppb)*	26.0 (16.0-46.0)	27.0 (18.0-43.0)	24.0 (15.0-59.0)	0.84
Serum eosinophils (10^9/L)*	0.02 (0.00-0.10)	0.01 (0.00-0.07)	0.08 (0.00-0.30)	0.11
Bronchiectasis, N (%)	21 (20.8)	12 (18.5)	9 (25.0)	0.44
CRSwNP, N (%)	39 (38.6)	25 (38.5)	14 (38.9)	

Table 2: Continued.

Patient characteristic		All patients (N=101)	With waning of effect (N=65)	Without waning of effect (N=36)	P-value
Biologic, N (%)	Omalizumab	13 (12.9)	6 (9.2)	7 (19.4)	0.088
	Mepolizumab	19 (18.8)	9 (13.8)	10 (27.8)	
	Reslizumab	5 (5.0)	4 (6.2)	1 (2.8)	
	Benralizumab	47 (46.5)	36 (55.4)	11 (30.6)	
	Dupilumab	17 (16.8)	10 (15.4)	7 (19.4)	
Dosing interval, N (%)†	2 weekly	17 (19.1)	10 (17.5)	7 (21.0)	0.180
	4 weekly	30 (33.7)	16 (28.1)	14 (43.8)	
	8 weekly	42 (47.2)	31 (54.4)	11 (34.4)	
Treatment duration (months)*		33.1 (17.8-46.0)	29.5 (17.3-41.5)	40.0 (25.4-64.2)	**0.039**

* Median, IQR
† Percentages calculated over patients with 2, 4 or 8 weekly dosing intervals.
Abbreviations: ACQ: Asthma control questionnaire, AQLQ: Asthma-related quality of life questionnaire, BMI: Body mass index, CRSwNP: Chronic rhinositis with nasal polyps, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced exhaled volume in 1 second, OCS: Oral corticosteroids.

Frequency, severity and conditions of waning of biological effect

Sixty-five patients (64.4%) gave a positive answer to the question "Do you notice that the effect of the biologic wears off before you take/receive the next injection/infusion?" (Figure 2.a). On a BORG-scale ranging from 0 (no need) to 10 (extreme need for the next administration) these 65 patients rated the severity of the need for a next administration with a score of 6.5 (5.0-7.5) (median (IQR)) (Figure 2.b). Nearly half (47.7%) of patients experienced this effect with every administration, and 12 (18.4%) in specific seasons (Figure 2.c).

Symptoms experienced with waning of biological effect

Patients were asked: "What symptoms do you experience in the period of waning of effect?". A wide variety of symptoms was reported, with reduced stamina, shortness of breath and fatigue being the most common (Figure 3). Patients reported that symptoms improved within 2 (2-4) days (median; IQR) after the next biologic administration.

Waning and asthma-related characteristics

Characteristics of the patients with or without a perceived waning of effect are compared in Table 2. Patients experiencing waning of the biological effect used biological treatment shorter compared to those not experiencing waning. The annual exacerbation rate and maintenance OCS use did not differ between both subgroups. However, patients perceiving waning of effect had higher ACQ-scores and lower AQLQ-scores than those without a need for early administration (Figure 4).

Within the 65 patients who perceived waning of biological effect, a higher BORG-score for severity of waning was associated with lower AQLQ scores (ρ=-0.292, p=0.031) and a higher rate of exacerbations (ρ=0.309, p=0.013), but no significant association was observed with ACQ and FEV_1.

Coping and preferences

When asked what actions are being taken by the patients when perceiving the waning of effect, 42 patients (64.6%) state that they slow down and undertake fewer activities and 36 patients (55.4%) indicate that they increase the frequency of their inhaled controller medication.

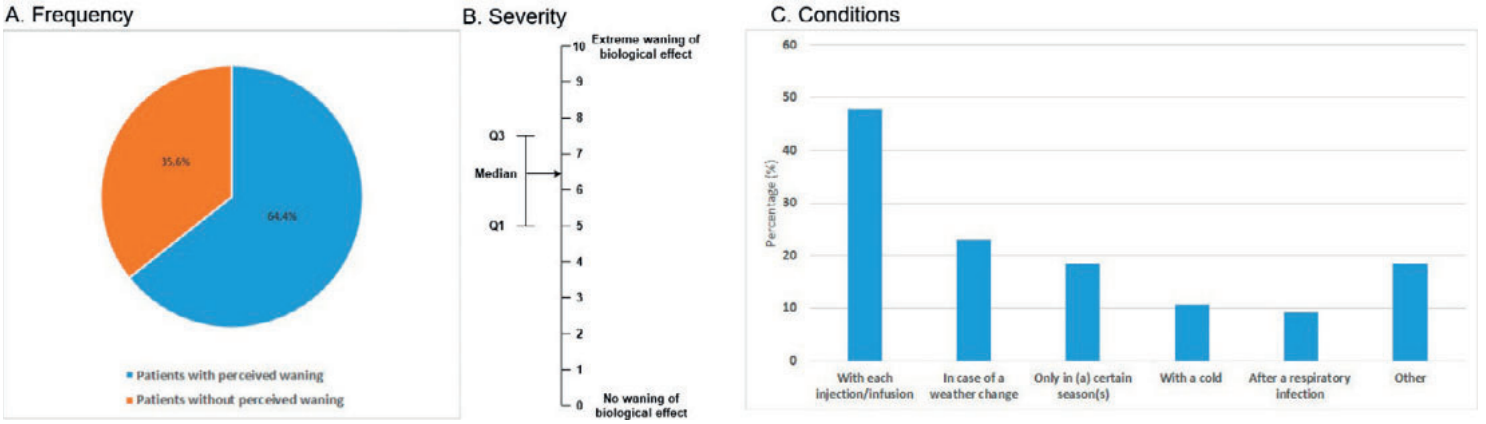


Figure 2: Frequency, severity and conditions of perceived waning of biological effect. These figures show the frequency (panel a, N=101), severity (panel b, N=65) and conditions (panel c, N=65) of perceived waning of biological effect in patients with severe asthma.

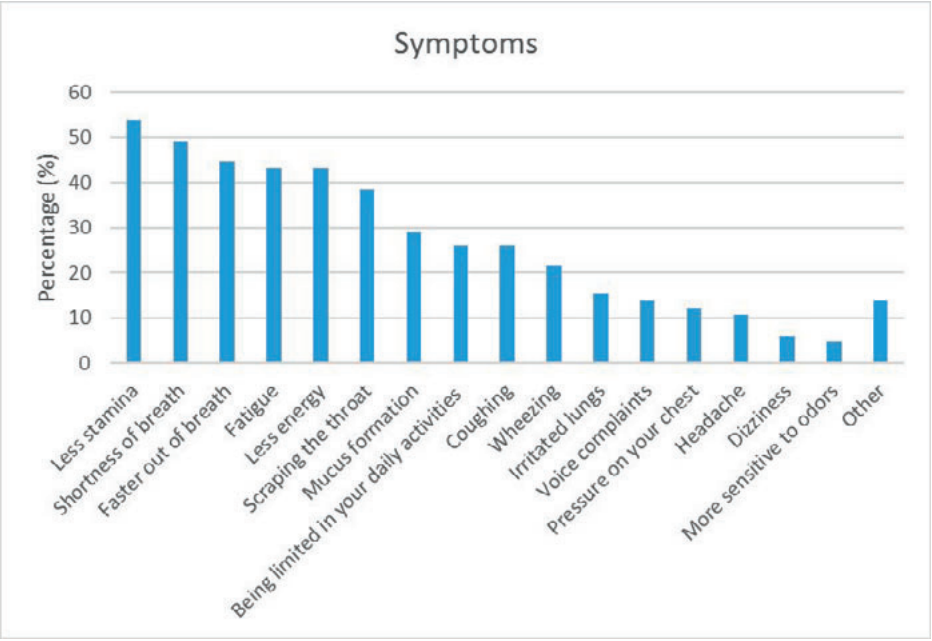


Figure 3: Symptoms experienced with waning of biological effect. This figure shows the reported symptoms when patients (N=65) experience waning of biological effect.

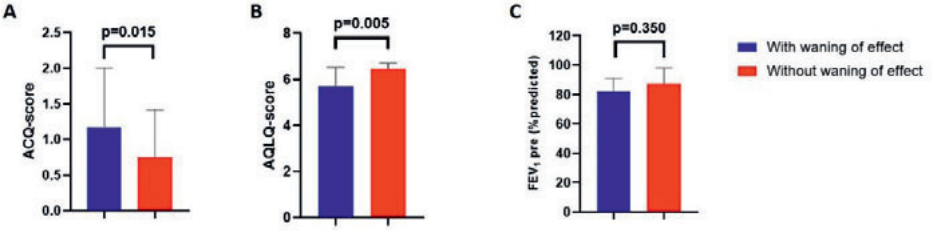


Figure 4: Perceived waning of biologic effect and asthma control (panel a), quality of life (panel b) and lung function (panel c). This figure shows asthma-related outcomes for patients with and without perceived waning of biological effect. Abbreviations: ACQ: Asthma Control Questionnaire, AQLQ: Asthma-related Quality of Life Questionnaire, FEV_1: Forced Expiratory Volume in 1 second.

Finally, when focusing on the wishes regarding dosing interval adjustment, 35 (34.6%) of the total population indicated that they were in favor of such an adjustment, either extending or shortening the interval: Twenty-eight of 65 patients with perceived waning of biologic effect indicate that they wish to shorten their dosing interval. The median (IQR) number of days they would like to receive the injection/infusion earlier is 4 (3-5), 7 (6-7) and 7 (7-14) for biologics dosed at 2, 4

and 8 weekly intervals, respectively. Seven of 36 patients with no observed waning effect indicate that they would be willing to extend their dosing interval if suggested by their physician.

DISCUSSION

This study shows that two-thirds of patients with severe asthma perceive a waning of biological effect at the end of the dosing interval, the majority of whom report this as severe. Patient-reported waning manifested in a wide variety of symptoms, with reduced stamina, shortness of breath and fatigue being the most common. Compared to those without, patients with perceived waning had poorer asthma control and quality of life, and higher exacerbation rates with increasing severity of perceived waning. Several of these patients indicated a wish to shorten their dosing interval, whereas, on the other hand, a subset of the patients with no perceived waning effect were willing to increase their dosing interval. These findings encourage further research into the effectiveness and costs of a more personalized dosing of biologics for severe asthma.

This is the first study investigating the perceived waning of biological effect in a large severe asthma population. While little is known about the patient-observed decreasing effect of their biological treatment over the course of the dosing interval, this phenomenon was recently mentioned in an international study involving focus-groups and underpinned the interval adjustment in a case report [11,14]. In addition, in a small proof-of-principle study it was shown that patient-reported need for the next omalizumab administration was associated with lower serum levels of omalizumab. The suggestion was made that combining patient-reported signals and objective biologic trough levels could provide healthcare professionals with the tools to successfully personalize biological treatment [12]. Our study, which quantifies and qualifies our patients' signs of a declining effect, can be seen as a first step in such an approach.

A strength of this study is that interviews were conducted in a broad representation of the patient population to ensure that all topics brought up by patients were covered in the questionnaire. Furthermore, not only was the willingness to participate in the interviews good, but especially the response rate of 78.3% to the questionnaire was very high. In addition to the questionnaire, patient- and asthma characteristics were systematically collected in clinical practice and therefore well-described, further contributing to the quality of this study. Our study has some limitations as well. First, this was a single-centre study, which may limit the

generalizability of our results to other patient populations. Second, there is no validated questionnaire to assess the perceived waning of biological effect and although we have tried to cover all aspects in our newly-made questionnaire, we cannot rule out that using a different questionnaire would have yielded different results. Nevertheless, we believe that the findings of our exploratory study give a clear signal which provides an important objective for future research. Furthermore, patients experiencing a waning of biological effect might be more interested in completing the questionnaire, possibly leading to a selection bias. Though patients who did not respond to the questionnaire were generally younger and had more often early-onset atopic asthma (data not shown), we do not expect this to have a major impact on our results, especially given the high response rate, although we cannot rule this out completely. Finally, a drawback of our study is the lack of more objective outcomes to explain our findings, for example assays to determine biological serum levels. However, our findings will hopefully convince multiple parties to investigate the effectiveness and costs of a more personalized dosing of biologics for severe asthma, using patients' perceptions and objective measures such as biological serum levels.

How can the patient-observed waning of biological effect and the difference between patients in this regard be explained? First, pharmacokinetic variabilities may be considered. Here we may learn from diseases such as inflammatory bowel disease and rheumatoid arthritis where biologics have been used for a long time. For example, in rheumatoid arthritis, due to inter-patient variability in clearance, infliximab trough levels varied and low through levels were associated with decreased disease control approaching the end of the dosing interval [15]. Thus, inadequate serum levels and enhanced clearance of the biologics could explain the findings in our study. In addition, biologic administration may lead to an endogenous antibody response, which may alter the pharmacokinetics and efficacy of the biologics [16]. These associations are however not yet explored for the biologics used in severe asthma. Third, we also cannot exclude the possibility of coincidence or a nocebo effect explaining our findings [17]. However, the association found between the perceived waning effect and poorer scores of the validated and commonly used questionnaires ACQ and AQLQ could also indicate a subgroup with more uncontrolled disease in which there is undertreatment, and which could benefit from dose escalation by shortening of dosing intervals. Finally, on the other side of the palette we see patients who do not experience any decrease in biological effect and opt for extending the dosing interval, which may be a manifestation of their super-response or even asthma remission [18].

Our results have several implications. The majority of the patients reported a waning of biological effect. Whether this is due to undertreatment with biologics and might improve with dose escalation is currently unknown. Therefore, future studies confirming our findings in a wider population and elucidating the mechanism behind this phenomenon are warranted. In other inflammatory diseases, such studies included dose escalation or de-escalation trials and led to development of therapeutic drug monitoring (TDM), which provides objective tools to improve biological treatment [19-24]. Such objective tools could be a welcome addition to severe asthma clinical care, because they could help optimize treatment with the costly biologics and improve patient satisfaction. Consequently, studies on the clinical added value and cost-effectiveness of adjusting dosing intervals based on objective parameters and patient-perception are warranted, pursuing shared decision-making and personalized medicine.

In conclusion, this study finds that many patients with severe asthma perceive a waning of biological effect at the end of the dosing interval, which results in a wide variety of symptoms and is associated with poorer asthma control and quality of life. The diversity in perceived waning of biological effect opens the way for research into more individualized dosing of biologics in severe asthma.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1: Interview sampling strategy.

Biologic: Omalizumab Gender: Male Age: <60 years	Biologic: Mepolizumab Gender: Male Age: <60 years	Biologic: Reslizumab Gender: Male Age: <60 years	Biologic: Benralizumab Gender: Male Age: <60 years	Biologic: Dupilumab Gender: Male Age: <60 years
Biologic: Omalizumab Gender: Male Age: ≥ 60 years	Biologic: Mepolizumab Gender: Male Age: ≥ 60 years	Biologic: Benralizumab Gender: Male Age: ≥ 60 years	Biologic: Benralizumab Gender: Male Age: ≥ 60 years	Biologic: Dupilumab Gender: Male Age: ≥ 60 years
Biologic: Omalizumab Gender: Female Age: <60 years	Biologic: Mepolizumab Gender: Female Age: <60 years	Biologic: Reslizumab Gender: Female Age: <60 years	Biologic: Benralizumab Gender: Female Age: <60 years	Biologic: Dupilumab Gender: Female Age: <60 years
Biologic: Omalizumab Gender: Female Age: ≥ 60 years	Biologic: Mepolizumab Gender: Female Age: ≥ 60 years	Biologic: Reslizumab Gender: Female Age: ≥ 60 years	Biologic: Benralizumab Gender: Female Age: ≥ 60 years	Biologic: Dupilumab Gender: Female Age: ≥ 60 years

Supplementary Table S2: Comparison interviewed and questionnaire patients.

	All patients (N=118)	**Interview (N=17)**	**Questionnaire (N=101)**	**P-value**
Age* (y)	60.0 (51.0-67.0)	54.0 (38.0-65.0)	60.0 (53.0-67.0)	0.14
Male gender, N (%)	67 (56.8)	9 (52.9)	58 (57.4)	0.73
BMI* (kg/m^2)	26.2 (23.6-30.2)	26.3 (23.1-31.2)	26.1 (23.6-30.2)	0.79
Former smoker, N (%)	49 (41.5)	3 (17.6)	46 (45.5)	**0.028**
Pack years*	8.5 (4.0-15.0)	9.0 (4.0-22.0)	8.0 (3.0-15.0)	0.74
Late asthma onset, N (%)	74 (62.7)	10 (58.8)	64 (63.4)	0.72
Age of asthma onset* (y)	46.5 (22.5-54.5)	26.0 (16.0-51.0)	47.0 (27.0-55.0)	0.16
Atopy, N (%)	55 (46.6)	8 (47.1)	47 (46.5)	1.0

Supplementary Table S2: Continued.

		All patients (N=118)	Interview (N=17)	Questionnaire (N=101)	P-value
Exacerbations last year*		0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.43
Prescribed daily OCS dose* (mg/day)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.72
Previous biologic, N (%)		41 (34.7)	6 (35.3)	35 (34.7)	0.96
ACQ score*		1.00 (0.50-1.83)	1.33 (1.00-2.17)	1.00 (0.50-1.83)	0.12
AQLQ score*		6.03 (5.27-6.58)	5.70 (5.36-6.48)	6.08 (5.27-6.59)	0.34
FEV_1 pre-bronchodilator (%pred)*		85.0 (70.0-97.0)	92.0 (81.0-103.0)	83.0 (70.0-95.0)	**0.037**
FeNO (ppb)*		27.0 (17.0-46.0)	34.0 (19.0-40.0)	26.0 (16.0-46.0)	0.70
Serum eosinophils (10^9/L)*		0.02 (0.00-0.10)	0.03 (0.01-0.40)	0.02 (0.00-0.10)	0.37
Bronchiectasis, N (%)		23 (19.5)	2 (11.8)	21 (20.8)	0.52
CRSwNP, N (%)		47 (39.8)	8 (47.1)	39 (38.6%)	0.511
Biologic, N (%)	Omalizumab	16 (13.6)	3 (17.6)	13 (12.9)	0.23
	Mepolizumab	23 (19.5)	4 (23.5)	19 (18.8)	
	Reslizumab	8 (6.8)	3 (17.6)	5 (5.0)	
	Benralizumab	51 (43.2)	4 (23.5)	47 (46.5)	
	Dupilumab	20 (16.9)	3 (17.6)	17 (16.8)	
Dosing interval, N (%)†	2 weekly	20 (19.2)	3 (20)	17 (19.1)	0.275
	4 weekly	38 (36.5)	8 (53.3)	30 (33.7)	
	8 weekly	46 (44.2)	4 (26.7)	42 (47.2)	
Treatment duration (months)*		34.0 (19.3-50.2)	37.6 (29.8-53.1)	33.1 (17.8-46.0)	0.12

*Median (IQR)
† Percentages calculated over patients with 2, 4 or 8 weekly dosing intervals.
Abbreviations: ACQ: Asthma control questionnaire, AQLQ: Asthma-related quality of life questionnaire, BMI: Body mass index, CRSwNP: Chronic rhinositis with nasal polyps, FeNO: Fractional exhaled Nitric Oxide, FEV_1: Forced exhaled volume in 1 second, OCS: Oral corticosteroids

Supplementary File 1: Questionnaire

Which biologic are you currently using? A biologic is the injection or infusion you receive for your severe asthma.

☐ Omalizumab (Xolair)
☐ Mepolizumab (Nucala)
☐ Reslizumab (Cinqaero)
☐ Benralizumab (Fasenra)
☐ Dupilumab (Dupixent)

How satisfied are you with your biologic? Draw a vertical line in the scale at that spot. You can choose a number between 0 and 10, where 0 is very unsatisfied and 10 is very satisfied.

In general, how would you describe your health? Color in the ball below.

Bad	Moderate	Good	Very good	Excellent
O	O	O	O	O

How has your health changed since you started your current biologic therapy? Color in the ball below.

Very much deteriorated	Deteriorated	Nothing changed	Improved	Very much improved
O	O	O	O	O

How often do you take/receive your biologic? <enter the number of weeks>

☐ Every ..... weeks

Is your biologic administered at home (by yourself or by someone close to you)?

☐ Yes
☐ No

If **No**, continue with **question 10.**

Do you ever deviate from the injection moment?

☐ Yes, I always take the injection earlier. Reason: .....
☐ Yes, I sometimes take the injection earlier. Reason: .....

☐ Yes, I always take the injection later. Reason: .....
☐ Yes, I sometimes take the injection later. Reason: .....
☐ No
☐ Other, namely: .....

How satisfied are you with being able to administer the biologic at home? Draw a vertical line in the scale at that spot. You can choose a number between 0 and 10, where 0 is very unsatisfied and 10 is very satisfied.

Does the self-injection ever go wrong? If yes, please indicate what is going wrong.
☐ Yes, namely: .....
☐ No

Do you ever experience any side effects from the biologic?
☐ Yes, tick the side effect(s) in the list below.
☐ No

Do you notice that the effect of the biologic wears off before you take/receive the next injection/infusion?
☐ Yes
☐ No

If **Yes**, go to **part A** of the questionnaire on page 5. You **only need to complete part A**.
If **No**, go to **part B** of the questionnaire on page 7. You **only need to complete part B**.

Part A: Need for the next dose

You have indicated that the effect of your biologic has worn off to some extent before you take/receive a new dose. Can you indicate how big that need is on the day before you take/receive the next dose? Draw a vertical line in the scale at that spot. Number 0 means no need for the next dose at all. Number 10 means an extreme need for the next dose.

How many days before the new dose do you notice that the previous dose is starting to wear off?
☐ ..... days

Please tick what symptoms you experience in the period under question 13. You may tick more than one answer.

What do you do when you have these complaints? You may tick more than one answer.
☐ Nothing
☐ Take more puffs
☐ Nebulize (more often)
☐ Slow down/undertake fewer activities
☐ Other, namely: .....

When do you notice that you are ready for your next injection/infusion? You may tick more than one answer.
☐ With each injection/infusion
☐ With a cold
☐ After a respiratory infection
☐ Only in (a) certain season(s), namely: .....
☐ In case of a weather change, namely: .....
☐ Other, namely: .....

How quickly do the complaints improve after the next dose?
☐ Within ..... days

Would you like to receive the injection/infusion sooner than you are receiving it now because you feel that the medicine is wearing off? (Your answer has no effect on your current treatment. Adjustments to your therapy are always made in consultation with your physician)
☐ Yes, ... days earlier
☐ No

If you have any comments, please state them below:

Thank you for completing the questionnaire!

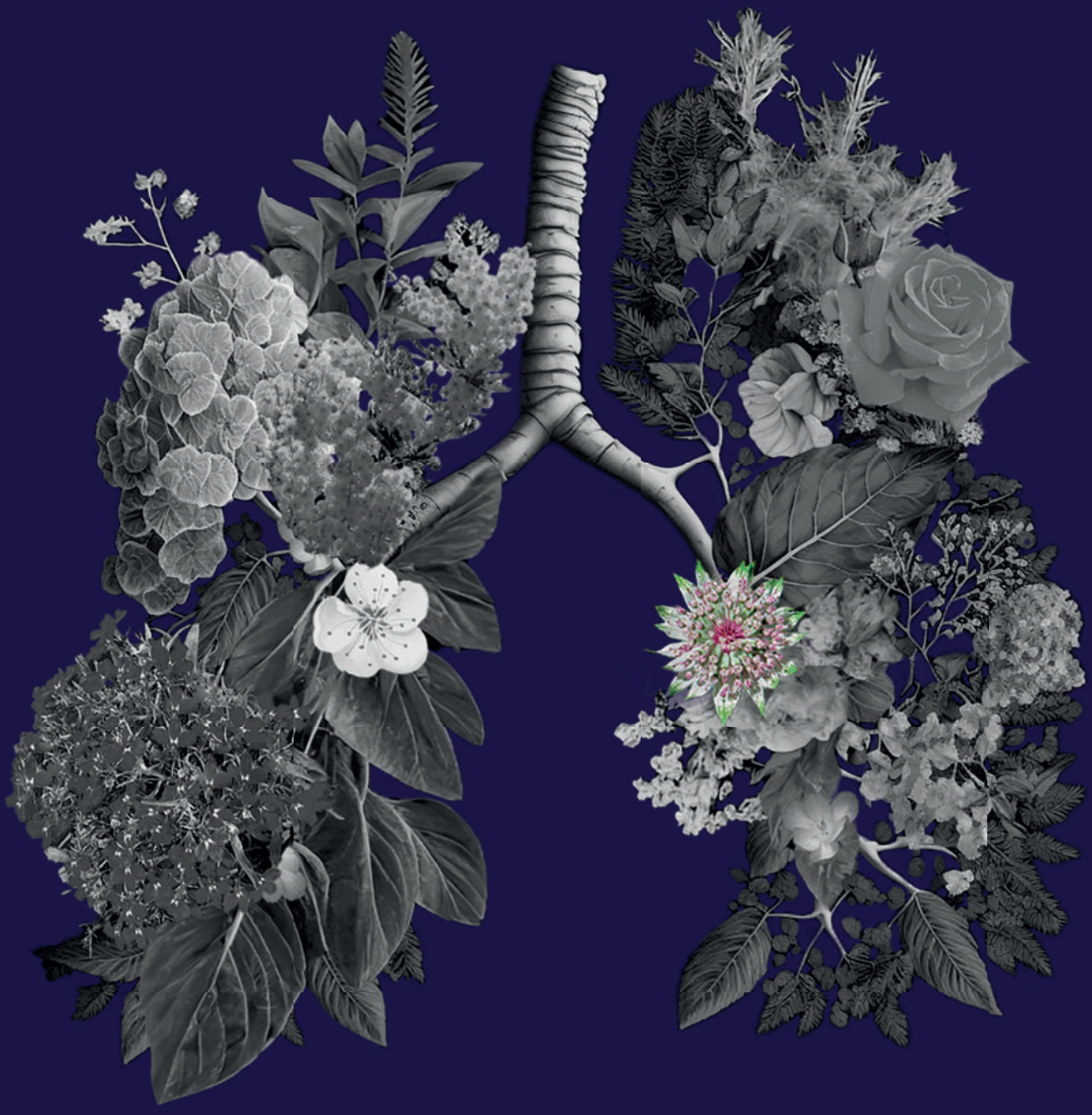
Part B: No need for the next dose

You have indicated that the effect of your biologic has not worn off before you take/receive a new dose. Can you indicate how small that need is on the day before you take/receive the next dose? Draw a vertical line in the scale at that spot. Number 0 means no need for the next dose at all. Number 10 means an extreme need for the next dose.

Would you be willing to take/receive the injection/infusion later? (Your answer has no effect on your current treatment. Adjustments to your therapy are always made in consultation with your physician)
☐ Yes, ... days later
☐ No

If you have any comments, please state them below:

Thank you for completing the questionnaire!



Chapter 12

Administration of benralizumab in a patient with severe asthma admitted to the intensive care unit with COVID-19 pneumonia: case report

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SUMMARY

A patient with severe asthma on benralizumab therapy was admitted to the intensive care unit (ICU) for a coronavirus disease 2019 (COVID-19) infection. At the end of the 8 week benralizumab dosing interval, discussion arose as to whether benralizumab should be administered or if treatment should be discontinued, due to the lack of experience with benralizumab in this situation. Severe broncho-obstruction developed, and the next injection of benralizumab was administered during ICU admission without detrimental symptoms. With this case report, we would like to share our experience with the safe administration of benralizumab during COVID-19 pneumonia, guiding doctors in future decision making.

BACKGROUND

To our knowledge, this is the first report of a patient with severe asthma with coronavirus disease 2019 (COVID-19) infection receiving benralizumab during intensive care unit (ICU) admission. The 'NICE COVID-19 rapid guideline: Severe Asthma' provides guidelines on biological treatment during the COVID-19 pandemic, but does not mention the use in patients with severe asthma on mechanical ventilation.(1)

CASE PRESENTATION

A 64-year-old obese woman (body mass index 38.5 kg/m2) with severe asthma, for which she had been receiving 8 weekly benralizumab (anti-interleukin-5Rα) injections since December 2019, presented to her general practitioner (GP) with migraine and myalgia. Three days later, she developed a fever and dyspnea. Azithromycin and a 30 mg/day prednisone course were initiated, but these failed to reduce the signs and symptoms. She was admitted to the hospital with a suspected COVID-19 infection 2 days later. PCR sequencing of the nasopharynx swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and a chest x-ray showed bilateral consolidation of the lungs in accordance with severe viral pneumonia. After a day on the isolation ward, her oxygen saturation decreased to 85% and she was admitted to the ICU. The prednisone prescribed by her GP was discontinued at admission.

Initially, at the presentation in the hospital and during the first days of ICU admission, the patient's asthma was controlled and no broncho-obstructive component was present. However, asthma-related broncho-obstruction developed on the 10th day of ICU admission with hypercapnia (partial pressure of carbon dioxide (PCO2) 10.6

kPa), a need for higher oxygen fractions (fractional inspired oxygen (FiO2) 50%, arterial oxygen pressure (PaO2)/FiO2 ratio 126) and an increase in peak airway pressure, but without signs of dynamic hyperinflation. During her stay, the patient received twice daily nebulized budesonide, but this failed to reduce the broncho-obstruction adequately. On day 11 of ICU admission, the 7th week of her 8 week benralizumab dosing interval, 30 mg/day prednisone injections were started and broncho-obstruction decreased over the next days. At the end of the 8 week benralizumab dosing interval, the next benralizumab administration was given at day 17 of ICU admission. The prednisone injections were reduced to 25 mg/day on days 17 and 18, 12.5 mg/day on days 19 and 20, and discontinued on day 21. Airway obstruction decreased 2 days after the benralizumab injection and the patient's pulmonary status stabilized 4 days after the injection. Eosinophil levels were measured a total of 15 times, but remained undetectable throughout ICU admission. This is in line with early clinical trials, in which the reported benralizumab-induced eosinopenia lasted for at least 8–12 weeks.(2) Before and during ICU admission, prednisone was administered several times, adding to the observed eosinopenia.

TREATMENT

Severe side-effects due to benralizumab have rarely occurred in clinical trials. Therefore, it was decided that the possible benefits of benralizumab treatment outweighed any possible adverse events.

OUTCOME AND FOLLOW-UP

The patient tested negative for SARS-CoV-2 by day 31 after which a tracheotomy was performed to facilitate weaning off the mechanical ventilation. She was able to leave the ICU on day 44 to start further physical and mental rehabilitation.

DISCUSSION

Since there is no evidence that biologics such as benralizumab suppress immunity for viral or bacterial infections, administration during a COVID-19 infection was considered a safe option for this patient with severe broncho-obstruction during mechanical ventilation. Acute hypersensitivity reactions to benralizumab have occurred rarely in clinical trials.(3) Two recent studies suggested the continuation of biological treatment during the COVID-19 pandemic, but also highlighted the lack of evidence on the subject.(4, 5)

Renner et al (6) described the consideration concerning biological treatment for eosinophilic asthma during the COVID-19 pandemic and reports two benralizumab-treated patients with severe asthma with COVID-19 infection. The COVID-19 infection was very mild in the described cases, as opposed to our case, which described a severe COVID-19 infection.

This is the first case report of benralizumab administration to a severely asthmatic patient on invasive mechanical ventilation. Only two previous cases have reported the administration of biologics in severe asthmatics during ventilation, one reporting the anti-IL-5 drug reslizumab and one reporting the anti-IgE drug omalizumab. In both cases, the administration appeared safe and each patient's ventilation improved shortly after the administration.(7, 8)

Learning points

Phase 2 and 3 trials with benralizumab were conducted in relatively small selected populations. Therefore, reports about the safe administration of benralizumab to specific patients are necessary, increasing the amount of real-world data on benralizumab. Our case adds evidence on the safety of benralizumab administration during ICU admission for a patient with severe COVID-19 pneumonia. Healthcare professionals may consider continuing biological treatment in patients with severe asthma admitted to the ICU with COVID-19 infection.

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Chapter 13

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The overall objective of this thesis was to gain insight in real-world outcomes of biological treatment for severe asthma. To this end, we utilized population-based registries, attempted to predict response to the novel biologics, and focused on patient-tailored approaches. Table 1 summarizes the aims, main findings and future perspectives of the chapters in this thesis.

Table 1. Overview of the aims, main findings and future perspectives of the chapters in this thesis.

Chapter 2	**Long-term therapy response to anti-interleukin-5 biologics in severe asthma – A real-life evaluation**	
Aims	*Main outcomes*	*Implication/Future perspectives*
Assess prevalences and predictors of super-, partial- and non-responders to long-term anti-IL-5 treatment. Assess frequency and reasons for switches. Assess the nature of residual disease manifestations.	The vast majority of patients with severe asthma respond favorably to anti-IL-5 biologics after 2 years of treatment. Residual disease manifestations are common. Incomplete response often causes physicians to switch between biologics.	Physicians should be wary of residual disease manifestations. Physicians should evaluate the therapeutic response in a systematic way.
Chapter 3	**Real-world effectiveness of reslizumab in patients with severe eosinophilic asthma – First initiators and switchers**	
Aims	*Main outcomes*	*Implication/Future perspectives*
Evaluate the real-world effectiveness of reslizumab, in biologic-naive patients and in those who switched from another type 2 biologic. Evaluate physicians' experience with reslizumab treatment.	Reslizumab reduces severe asthma exacerbations and oral corticosteroid use in patients with severe eosinophilic asthma, both in biologic-naive initiators and in those who switched from another type 2 biologic. The additional value of reslizumab was recognized by clinical severe asthma experts.	It may be worthwhile to switch patients who do not respond to one specific type 2 biologic to a second add-on biologic, even if this has a similar mechanism of action. Further research will have to determine the reasons for improved response after switching from one anti-IL-5 biologic drug to another.
Chapter 4	**Cumulative corticosteroid sparing effect of anti-interleukin-5/5Ra in eosinophilic asthma**	
Aims	*Main outcomes*	*Implication/Future perspectives*
Compare the cumulative oral corticosteroid exposure over a 2-year period before and after anti-IL-5/5Ra initiation. Investigate whether duration and cumulative oral corticosteroid exposure prior to anti-IL-5/5Ra influence the ability to discontinue oral corticosteroids.	Anti-IL-5/5Ra therapy leads to a significant reduction in cumulative oral corticosteroid exposure over a 2-year period. Patients with lower and shorter oral corticosteroid exposure were more likely to completely eliminate oral corticosteroids.	Early intervention with anti-IL-5/5Ra treatment may lead to a better long-term prognosis in patients with severe eosinophilic asthma. Clinicians should be aware of possible residual OCS exposure despite anti-IL-5/5Ra treatment and pursue further treatment optimization.

Chapter 5	**Blueprint for harmonizing non-standardized disease registries to allow federated data analysis – Prepare for the future**	
Aims Describe the harmonization process that SHARP has gone through. Provide a blueprint for how to successfully use real-world data from existing disease registries to perform federated analysis.	*Main outcomes* Setting up a federated data network is a complex process that requires thorough preparation.	*Implication/Future perspectives* Setting up a federated data network is a worthwhile investment for all clinical research collaborations.
Chapter 6	**Evaluation of real-world mepolizumab use in severe asthma across Europe – The SHARP experience with privacy-preserving federated analysis**	
Aims Harmonize data from 10 national severe asthma registries Assess the real-world mepolizumab effectiveness across Europe. Evaluate mepolizumab treatment patterns.	*Main outcomes* This study is a successful proof-of-concept of the SHARP federated analysis platform. Mepolizumab reduced asthma exacerbations and maintenance OCS use in real-world patients with severe asthma across Europe. Patients prescribed mepolizumab differed considerably between the different European countries.	*Implication/Future perspectives* This study paves the way for future pan-European real-world severe asthma studies using patient-level data in a privacy-proof manner. A revision of the international ERS/ATS definition of severe asthma may be required.
Chapter 7	**Prediction of response to biological treatment with monoclonal antibodies in severe asthma**	
Aims Summarize results from studies on predicting response and responders to biological treatment in severe asthma. Describe future perspectives on response prediction to biological treatment for severe asthma.	*Main outcomes* Studies that explore the predictability of biologic efficacy are mainly based on post-hoc analyses of the large registration trials or small exploratory studies with a limited number of patients.	*Implication/Future perspectives* There are still several issues regarding the prediction of response to the biologics for severe asthma that require further evidence.

Chapter 8	Patient-reported outcome measures after 8 weeks of mepolizumab treatment and long-term outcomes in patients with severe asthma: an observational study	
Aims	*Main outcomes*	*Implication/Future perspectives*
Compare early changes in patient-reported outcome measures after 8 weeks and long-term response to mepolizumab treatment.	All patients with well-controlled asthma at 8 weeks were long-term responders.	This study encourages further exploration of the applicability of early changes in patient-reported outcome measures in the clinical process.
Chapter 9	**Early treatment outcomes add in predicting long-term benralizumab response in severe asthma**	
Aims	*Main outcomes*	*Implication/Future perspectives*
Study whether parameters at 3 months contribute to the prediction of benralizumab response at 1 year. Develop an easy-to-use prediction tool to assess an individual's probability of long-term response.	In addition to baseline characteristics, treatment outcomes at 3 months contribute to the prediction of benralizumab response at 1 year in patients with severe eosinophilic asthma. We propose a prediction tool assessing an individual's probability of long-term response.	Prediction tools incorporating outcomes at 3 months, as proposed in this study, may help physicians to optimize the use of costly biologics. Future studies need to validate our results.
Chapter 10	**Optimizing omalizumab dosing in severe asthma – The exploration of therapeutic drug monitoring**	
Aims	*Main outcomes*	*Implication/Future perspectives*
Determine the variability in excess of omalizumab trough levels to baseline IgE in a real-world responder population. Examine the relationship between omalizumab trough levels and patient-reported need for the next administration.	A large variability in omalizumab to baseline IgE ratios as well as omalizumab through levels was found. An association between patient-reported need and omalizumab trough level was found.	Larger studies are warranted in more diverse populations, focusing on the applicability of TDM in the recently approved biologics for severe asthma.

Chapter 11	**"That last week is drama" – The perceived waning of biologics in severe asthma**	
Aims Explore the frequency, severity and conditions of the patient-perceived waning effect of biologics before the next administration. Explore symptoms associated with waning effect of biologics. Explore the relationship of clinical characteristics and the patient-perceived waning effect of biologics.	*Main outcomes* Many patients with severe asthma perceive waning of biologic effect at the end of the dosing interval. Waning manifests in a broad spectrum of symptoms. Waning of the biological effect is associated with poorer asthma control and quality of life.	*Implication/Future perspectives* The diversity in observed waning of effect opens the way for research into more individualized dosing of biologics.
Chapter 12	**Administration of benralizumab in a patient with severe asthma admitted to the intensive care unit with COVID-19 pneumonia: case report**	
Aims Share our experience with the administration of benralizumab during respiratory failure due to COVID-19 pneumonia.	*Main outcomes* Administration of benralizumab during ICU admission of COVID-19 pneumonia appeared safe.	*Implication/Future perspectives* Healthcare professionals may consider continuing biological treatment in patients with severe asthma admitted to the ICU with COVID-19 infection.

PART I: POPULATION-BASED REGISTRIES

Population-based registries are a fundamental part of collecting real-world evidence in the present age of digitalization.(1) In this thesis, we described several studies on the novel biologics for severe asthma that were based on population-based registries and attempted to close pending knowledge-to-care gaps.

One of these knowledge-to-care gaps is the effectiveness of the biologics in the real-world, or in other words: how many and which patients respond to the treatment? Not all patients are equal. As patients differ, so does their response to the biologics. The randomized controlled trials (RCTs) that led to the approval of the biologics were designed to evaluate the effect of the biologics on either exacerbation rate or oral corticosteroid (OCS) dose.(2-13) However, these RCTs do not provide actionable tools in order to quantify the degree of response in the individual patient. In addition, the patients in RCTs were highly selected on for example lack of comorbidities or smoking history and are therefore different from the patients that are treated in clinical practice.(14) This is called the 'gap' between RCTs and the real-world.(15)

In this thesis, we sought to quantify the degrees of response. Clinicians recognize patients with severe asthma in whom the biologics lead to a dramatic improvement, while other patients do not show any improvement of symptoms.(16) These patients with a perfect response are often called "super-responders". In **chapter 2**, we studied the effectiveness of anti-interleukin(IL)-5 biologics after 2 years of treatment and indeed found that a subset (14%) of patients was completely free of any disease manifestations after 2 years. We labeled these "super-responders". To be labeled as a super-responder, patients had to be free of OCS use, exacerbations over the last 3 months, have controlled asthma symptoms, adequate pulmonary function, low Fractional exhaled Nitric Oxide (FeNO) and complete control of comorbidities. The criteria in our study were relatively strict. Other studies used other criteria and found a higher (20%-65.1%) number of super-responders.(17-19) These studies all used different definitions of super-response, measured at different time points. In order to gain international consensus on the definition of super-response, a Delphi-study was conducted, involving 81 healthcare professionals across 24 countries.(16) The experts established that, in order to be labeled a super-responder, patients had to achieve improvement in three or more criteria over 12 months. Major and minor criteria for super-response were also established and super-responders had to have at least 2 major criteria. These major criteria were: elimination of exacerbations, major improvement in asthma control, and cessation of maintenance OCS. Minor criteria were 75% exacerbation reduction, well-controlled asthma, and ≥500 mL

improvement of Forced Exhaled Volume in 1 second (FEV_1). These criteria are to some extent similar to the relatively strict criteria used in our study, therefore the findings in our study are applicable to clinical practice when these criteria are adopted.

Currently, the treatment goals of the biologics focus on control of symptoms and exacerbations after 12 months. Interestingly, the recent paper by Thomas et al. described the concept of clinical asthma remission. Remission is similar to super-response, but goes further as it focuses more on the sustained elimination of exacerbations and symptoms, rather than the reduction of asthma attacks at a given time point.(20) As our definition of super-response incorporates a long time period and required no disease manifestations over a sustained period, our strict outcome measure might resemble remission, rather than super-response. Consensus on the criteria for response or remission is consolidating. Long-term, real-world observations as presented in **chapter 2** are a crucial addition to this process, as the RCTs usually have limited follow-up. Also, the patients treated in the RCTs differ from patients treated in the real-world.(14,21) Therefore, what outcome can be considered 'response' cannot be established without studying the patients that are actually treated in the real-world.

We strive to achieve super-response (or remission), as super-response currently is the best achievable outcome for patients with severe asthma. Therefore, predicting what patients have a high chance of achieving this outcome is important. Due to our small number of super-responders, multivariable regression analysis was not feasible in our study. Other studies defined super-response in different ways and found different predictors of response. The mechanism behind these differences in super- partial- and non-responders is currently unknown, but there are several suggestions of the underlying mechanism. As monoclonal antibodies are large proteins, immunogenicity can be induced, which is observed for biologics used in for example Crohn's disease and rheumatoid arthritis.(22-24) The development of anti-drug antibodies can (in theory) neutralize the efficacy of biologics and lead to loss of response. Underlying factors, for example comorbidities such as obesity, bronchiectasis or dysfunctional breathing might also contribute to different types of response, though these are typically optimized before biological treatment is initiated. It is also possible that patients with a suboptimal response had other inflammatory pathways driving the disease, for example the anti-IL-4/IL-13 pathway, leading to the residual disease manifestations. Remarkably, we found in **chapter 3** that switching patients with a suboptimal response to a biologic with the same mechanism of action led to beneficiary results.

In this study, we evaluated the real-world effectiveness of reslizumab treatment using data from the Dutch Registry of Adult Patients with Severe Asthma for Optimal DIsease management (RAPSODI), both in biologic naive patients (initiators) as in patients that received previous biological treatment (switchers). We found that reslizumab add-on treatment significantly reduced the rate of asthma exacerbations (OR (95%CI) 0.10 (0.05-0.21), p<0.001). The proportion of patients on maintenance OCS decreased from 57.9% to 39.7% (OR (95%CI) 0.20 (0.08-0.48), p<0.001), as well as the dose of maintenance OCS, which decreased from 5.0 (0.0-10.0) to 0 (0.0-5.0) mg/day, p<0.001. These beneficial effects were not only evident in patients receiving reslizumab as their first add-on biologic therapy, but also in those who previously failed on another type 2 biologic and switched to reslizumab. We found that the real-world effectiveness of reslizumab was comparable as observed in phase 3 trials and in other real-world studies.(7,25-27) In contrast to other real-world studies, our study included a large proportion of patients that switched to reslizumab due to insufficient response to other type 2 biologics. Reslizumab, while targeting the same cytokine in the vast majority of switchers, showed additional benefit, further reducing the use of OCS and exacerbations. Importantly, this additional value was also recognized by asthma experts. This poses the questions what underlying reason may explain this additional benefit. Is it the result of greater drug potency, better dosing, pharmacodynamics or pharmacokinetics, the type of antibody or target, is it merely a consequence of a longer-term inhibition of the inflammatory process in the airways with equally effective agents or a combination of the above? In the end, only a head-to-head trial will give the definitive answer as to which biologic is the most effective in which patient in the treatment of severe eosinophilic asthma.

The importance of data obtained from real-world evidence is emphasized in **chapter 3**. The included patients in this study were at the extreme end of asthma severity and complexity, given that the majority (58%) was OCS dependent, almost all (92%) suffered from co-morbidities and a large proportion (58%) had previous treatment with another biologic. These comorbidities would have precluded participation in the RCTs. However, the beneficial effects from reslizumab were comparable to the effects seen in RCTs, suggesting that reslizumab is effective, even if the strict inclusion criteria from the phase 3 trials are not met.

A major goal of the biologics for severe asthma, especially the anti-IL-5 biologics, is to reduce the use of oral corticosteroids, as these are known to be associated with a multitude of serious adverse effects including diabetes, cardiovascular disease, psychiatric complications and adrenal insufficiency.(28) These side effects are associated with the cumulative exposure to OCS.(29,30) However, RCTs and real-

world studies studied the effect of anti-IL-5 biologics on the *maintenance* OCS dose. Insight in the effect of the anti-IL-5 biologics on the *cumulative* OCS exposure over a longer period before and after anti-IL-5 initiation is lacking. To gain this insight, we performed the study in **chapter 4**, in which we mapped the use of OCS two years before and two years after anti-IL-5 initiation in a nationwide population from the Dutch RAPSODI registry.

We were able to include a large number of patients and we were able to get a complete overview of the OCS exposure due to the fact that patients consented to have their pharmacy-data collected when included in the registry. By providing insight in a long period before initiating anti-IL-5, we found that patients with lower and shorter exposure to OCS were more likely to completely cease the use of OCS over a sustained period. This suggests that early intervention with anti-IL-5 biologics may be preferable, guiding physicians in the clinical decision-making. Population-based registries offer an opportunity to study long-term data. This is in contrast to RCTs, as RCTs generally have a short follow-up and do not study the period before intervention due the high costs of a RCT. Population-based registries are therefore a crucial complement to modern-day healthcare. However, real-world evidence is limited to generating new hypotheses. Subsequently, new prospective studies are warranted to study whether early treatment intervention indeed gives the better outcome.

The outcome measure in **chapter 4** was long-term response, defined as completely ceasing the use of OCS in the 18 to 24 months after initiating anti-IL-5. We found that 52% of our population was able to completely cease OCS. We discussed the different methods of defining response and the need for consensus on what response is. In our study we only had reliable long-term data on the use of OCS and therefore chose this pragmatic outcome measure. We discussed the concept of asthma remission, being a sustained suppression of the disease. As our outcome measure incorporated a sustained, complete lack of OCS prescriptions, this might resemble remission. Future policy makers may want to introduce the sustained cessation of OCS based on pharmacy data to the definition of remission, as either exacerbations or maintenance OCS use result in the dispensing of OCS. We do recognize the logistical challenge that this poses, as different healthcare professionals can prescribe OCS. However, the community pharmacists might claim a role in the OCS stewardship by providing a signal to the clinicians as soon as the sustained period of not using OCS is achieved or lost.

Chapter 2 to 4 all included data from the Dutch nationwide RAPSODI registry and show examples of the potential of population-based registries. Several European countries established their own nationwide registries to collect real-world data from patients with severe asthma. However, the conclusions that can be drawn from nationwide registries are limited. The relatively small number of included patients restricts the ability to deliver generalizable evidence and answer important research questions. Therefore, combining data from multiple nationwide registries is required in order to generate more robust and meaningful outcomes by increasing sample size and statistical power.

To this end, the European Respiratory Society founded the clinical research collaboration SHARP, which has the ambition to connect all European severe asthma registries. In **chapter 5** we described the process of connecting these registries and provided a guide for other clinical research networks that wish to undertake the ambitious journey of connecting multiple registries.

Connecting registries is bound to strict privacy regulation and faces several logistical challenges, for example differences in language and methods of capturing data. To overcome these challenges, SHARP harmonized the individual registries to a common data model and leveraged a federated analysis platform in order to generate summary statistics. Meta-analysis then enables researchers to draw conclusions from the data. **Chapter 6** is the first study using the SHARP federated analysis platform and serves as a proof-of-concept. This study assessed the real-world effectiveness of mepolizumab in patients with severe asthma in Europe. We anticipated that data on mepolizumab would be widely available and complete, due to the fact that mepolizumab was the first anti-IL-5 biologic available in most European countries.

We succeeded in linking data from 10 different nationwide registries, harmonized data for almost six thousand patients and demonstrated the real-world effectiveness of mepolizumab in almost a thousand patients, which is an important complement to RCTs and other real-world studies. The harmonization process has been completed and we demonstrated the feasibility of the SHARP federated analysis platform. This platform can now be further used to obtain real-world evidence to help guide better treatment and care to the many thousands of patients with severe asthma in Europe. However, there still are some challenges regarding studies using the SHARP federated analysis platform, as well as studies from the RAPSODI registry.

Future perspectives to Part I

The studies described in **chapters 2 to 6** have several things in common. There are the clear similarities like the focus on the biologics used for severe asthma that target the anti-IL-5 pathway, and the fact that we provided examples of generating real-world evidence using population-based registries. Other, less obvious, themes were missing data and the difficulty of performing analyses on large databases. Due to the lack of strict monitoring and retrospective collection of the data, real-world studies are prone to missing data. Enrichment of the databases was required in all studies, ranging from -relatively simply- opening the patients' files in our local hospital to coordinating doctors and nurses across Europe. This was very time-consuming, but a necessary effort in order to adequately perform our studies.

Moreover, not all data were captured in a similar fashion or on standardized time points, limiting the effects of manual data collection and ultimately the conclusions that can be drawn from real-world studies. Standardization of the hospital-, nation-, or Europe-wide healthcare processes would greatly improve real-world evidence, but we recognize the tremendous effort that this would take. Initiatives like SHARP strive towards this standardization, but this still has a long way to go, as **chapters 5 and 6** revealed the heterogeneity of both the data being captured as well as the patients being included in the registries. Also, not all patients gave informed consent for international studies. It would be beneficiary if healthcare professionals have high ambitions, like international studies, in mind when setting up a population-based registry.

Population-based registries are often designed from the perspective of the persons collecting the data. This introduces difficulties when analyzing datasets, as a simple export of a dataset is seldom directly usable for data analysis. Refinement of the data, selection of the patients and variables of interest either requires manual labor or advanced statistical skills. Both have disadvantages, as manual labor is sensitive to errors while automatic selection using statistics is rigid and might exclude patients that could be included otherwise. Standardization and automation of the data collection would greatly enhance the potential of automatically selecting patients, as this would force the data to align with analysis scripts.

In the current age of digitalization, the automatic capture of data from electronic health records into a population-based registry is a possibility. The application of standardized discrete fields in the doctors' assessments and connecting those fields to a population-based registry would greatly reduce the effort of completing and analyzing a dataset. Challenges that need to be overcome are the guaranteeing

of patients' privacy and choice of variables of interest, as it is not always known beforehand what variables would be interesting in future studies. Furthermore, it is important to prevent an enormous administrative effort for doctors when seeing their patients. This might be achieved by automatically gathering information like pulmonary function tests or having patients fill in electronic questionnaires that are captured in the electronic health records. These solutions are within reach, as modern electronic health records are designed with these objectives in mind. Lastly, we should ensure that this proposed standardization leaves room for exceptions, as each patient is different.

PART II: PREDICTION OF RESPONSE

The costs of healthcare in The Netherlands 2021 were €124.77 billion (14.5% of the GDP) and these costs are expected to increase in the following years.(31) We as healthcare professionals have a social responsibility to use our resources as effective as possible. This also applies to the biological treatment for severe asthma, as the treatment at the end of 2022 costs around €15.000,- per patient per year. Therefore, precision medicine is applied, in which the appropriate biologic is given based on the clinical profile of the patient. However, despite this initial selection of patients, there still are some patients that do not respond to the biological treatment. We therefore strive to treat the patients that have the best chance of benefit from the biological treatment. Prediction of response –or non-response– is therefore a major knowledge-to-care gap in current clinical practice.

In **chapter 7** we provided a literature overview on the current state of response prediction. We found that predictive variables varied per study and were derived from post-hoc analyses of large RCTs or real-world studies with limited numbers of patients. Assessing response based on data from RCTs creates difficulty, as the highly selected populations in RCTs differ from the patients treated in the real-world.(32) Therefore there is a need for large real-world studies focusing on long-term outcomes. Adequate response prediction, especially for the novel biologics, was not feasible based on current knowledge. More evidence has been generated for the older biologic omalizumab, which led to the incorporation of an evaluation moment at 16 weeks in order to predict long-term response.(33,34)

To this date, the Summaries of Product Characteristics of the novel biologics mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab state that the treatment should be evaluated after 12 months.(35-39) This implicates that a non-responder is treated for at least a year without adequate control of the disease,

at the cost of quality of life for the patient and resources for society. Fortunately, the GINA guidelines state that the treatment should be evaluated after 4-6 months, similarly to omalizumab.(40) However, evidence for this evaluation moment is lacking. Furthermore, it can be debated whether 4-6 months after initiating the treatment is 'early'.

To explore whether treatment could be evaluated even sooner, we studied early changes in asthma-related parameters and long-term response after initiating mepolizumab treatment in **chapter 8**. The difficulty of defining long-term response has been discussed in this thesis. In order to overcome this difficulty, a pragmatic outcome measure was chosen in this study: continuing mepolizumab treatment after 12 months. The doctors apply current guidelines and decide, based on the observed clinical response, whether the patients are allowed to continue the treatment or whether the patients need the stop the treatment due to insufficient efficacy. This outcome measure therefore gives a reflection of response in clinical practice, without the difficulty of heterogeneity in types of response.

At baseline, there was no statistically significant difference in ACQ and AQLQ for the long-term responders and non-responders (p=0.204 and p=0.168, respectively) while at 8 weeks a statistically significant difference between responders and non-responders was found for both parameters (p=0.018 and p=0.009, respectively). In addition, all patients with an ACQ-score ≤0.75 at 8 weeks, which indicates well-controlled asthma, were responders on the long-term. This study included a limited number of patients, restricting the conclusions that can be drawn based on this study. However, the signal that response to biological treatment might be evaluated after a very short period, is an interesting finding.

Based on this study, we evaluated the added value of outcomes at 3 months in the prediction of long-term benralizumab response in **chapter 9** using the Dutch RAPSODI registry. We again demonstrated the value of a population-based registry, as we were able to include a far larger number of real-world patients than in **chapter 8** to test our hypothesis. We again pragmatically assessed response based on whether a patient continued benralizumab after 12 months. We showed the added value of outcomes at 3 months in predicting benralizumab response and proposed a tool to predict long-term response based on baseline characteristics combined with outcomes at 3 months.

Future perspectives to Part II

By not only focusing on a single moment in time but also incorporating variables at an evaluation moment, we found that response could be predicted better. Policymakers recognized that annual evaluation of the biological treatment is undesirable and propose to evaluate treatment response after 4-6 months.(40) Our findings suggest that this evaluation may occur even sooner, as we saw added value by incorporating outcomes at 3 months in the prediction of response.

While we attempted to predict response to benralizumab, we realize that adequate response prediction is still far away. A major limitation that we encountered was the lack of a validation dataset, mainly due to the lack of patients. By connecting population-based registries as demonstrated by SHARP, we could greatly increase the number of patients available for data analyses. Furthermore, in order to predict response, we need a clear consensus on what the definition of response is. Future studies including more patients, focusing on the other biologics for severe asthma and prospectively testing prediction tools such as the one proposed in this thesis might continue our initial steps towards the prediction of response based on real-world evidence.

PART III: PATIENT-TAILORED OUTCOMES

Based on the RCTs, it has been widely recognized that treatment with the biologics for severe asthma requires an individualized approach.(41) The different mechanisms of action warrant that the biologics are prescribed in patients with the appropriate phenotype. In addition, real-world findings, such as those described in this thesis, identified the different types of response and the discrepancies between findings from RCTs and clinical practice regarding response.

The different types of response beg the question whether the one-size-fits-all dosing interval that is used in the majority of biologics for severe asthma is appropriate and whether an even more patient-tailored approach could be beneficial for some patients. In clinical practice, the different degree of response sometimes lead to adjustment of the dosing intervals. For example, there are patients with an excellent response in whom prolongation of the dosing interval is possible without loss of asthma control.(42) On the other hand, some patients feel that their asthma symptoms worsen towards the end of their dosing interval, sometimes leading to dose escalation by shortening dosing intervals.(43)

In other diseases, for example in rheumatoid arthritis and inflammatory bowel disease (IBD), biological serum levels and the relation with (non-)response was assessed. This led to the application of therapeutic drug monitoring (TDM) to personalize the costly biological treatment in some patients.(44) TDM is currently not applied in the treatment with the biologics for severe asthma, as a serum level-effect relationship was not studied and assays to determine biological serum levels are not commercially available for the novel biologics. In **chapter 10**, we studied the variability in omalizumab serum levels and assessed whether long-term responders to omalizumab treatment experienced a need for the next administration. In this explorative study, we found that lower serum levels were associated with a higher patient-reported need for the next administration.

Almost half of the patients reported a moderate to extreme need for the next administration, or ≥3 on a scale of 0-10. While clinicians recognize that some patients experience a need for the next administration, studies that focus on this phenomenon are lacking. To this end we performed the study in **chapter 11**. In this study, we used a two-sided approach, both qualitatively and quantitatively. After interviewing a sample of our population, we constructed a questionnaire that focused on the perceived waning of effect and distributed this questionnaire to the rest of the population.

We found that two-thirds of patients with severe asthma perceive a waning of biological effect at the end of the dosing interval. Several of these patients indicated a wish to shorten their dosing interval, whereas, on the other hand, a subset of the patients with no perceived waning effect were willing to increase their dosing interval.

Chapter 12 demonstrates another example of real-world data. In this case report we described a patient receiving benralizumab treatment during ICU admission for a COVID-19 pneumonia, which did not yield apparent detrimental consequences. Such findings from clinical practice further contribute to knowledge about the biologics that would never be derived from RCTs, as comorbidities like ICU admission would lead to the exclusion of these patients.

Future perspectives to Part III

The findings in **chapters 10 and 11** show that by asking a relatively simple question, real-world findings can be an important addition to evidence generated by RCTs, expose previously unknown issues and provide input for future studies. Real-world data are hypothesis generating. This is also the case for the studies in this thesis

and our implications warrant prospective studies, for example focusing on the mechanism behind the perceived waning of effect. Variability in biologic serum levels might be an explanation and, if confirmed, therapeutic drug monitoring might be an addition to current clinical practice, providing an objective tool on which dosing interval adjustments can be made.

New knowledge-to-care gaps based on this thesis are whether dose escalation by increasing the dose or shortening the dosing interval could resolve the perceived waning of effect, whether dose de-escalation by decreasing the dose of prolonging the dosing interval while maintaining asthma control could be appropriate and cost-effective, and in which patients these are feasible. This approach could help to optimize treatment with the costly biologics and improve patient-satisfaction, further pursuing shared decision-making and personalized medicine. The new, seemingly relevant, patient-reported outcome measure that we introduced in this thesis is an important addition to this process. The psychological aspect of this waning of effect cannot be ignored. It is possible that this perception from the patient is just that, a perception. In that case, policy-makers should discuss whether solving this waning of effect with dose escalation would be worth the increased healthcare costs and possible loss of asthma control in the case of dose de-escalation.

As pharmacists generally have a broad view of the patient and his or her medication, there might be a role for the (hospital) pharmacist when striving for patient-tailored approaches. For example, if the application of therapeutic drug monitoring becomes part of the clinical process, the interpretation of biological serum levels and consequently adaptation of dose or dosing interval could be facilitated by the hospital pharmacy, as this is already daily practice for other drugs. Ultimately, the hospital pharmacist could become a more important contributor to the shared decision-making and optimization of the treatment.

FINAL REMARKS

In this thesis we studied real-world outcomes to biological treatment for severe asthma. We showed examples of the potential of population-based registries and formulated new objectives for future studies. By focusing on a new patient-reported outcome measure, we also demonstrated the importance of involving the patient in the healthcare process. This continuous involvement of the patient, resulting in shared decision-making between patient, doctor and pharmacist, based on evidence-based medicine complemented by medicine-based evidence, show a bright future of a healthcare process in which patients with severe asthma are treated optimally.

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Chapter 14

Summary
Samenvatting

ENGLISH SUMMARY

Asthma is a heterogeneous, inflammatory airway disease, characterized by symptoms of coughing, wheezing and shortness of breath. The symptoms are caused by variable airway obstruction, airway hyperresponsiveness and mucus hypersecretion. Around 339 million people worldwide suffer from asthma. Most patients with asthma are adequately treated with inhaled medication, focusing on inflammation reduction and airway smooth muscle relaxation.

However, 3% to 10% of the patients with asthma has severe asthma. Many of these patients with severe asthma experience asthma exacerbations and rely on high dose systemic corticosteroids to reduce asthma symptoms. Despite being very effective in reducing asthma symptoms, there are severe side effects associated with the use of (long-term) systemic corticosteroids. Due to these side effects, there is a major interest in oral corticosteroid-sparing treatment options to maintain or achieve asthma control.

The identification of different asthma phenotypes based on clinical, functional or inflammatory parameters led to the development of new targeted treatment options in the form of monoclonal antibodies. These novel biologics have shown to markedly reduce asthma exacerbations and oral corticosteroid (OCS) use, as well as to improve asthma symptoms, lung function and quality of life. There are currently six biologics approved in Europe for the treatment of severe asthma.

Randomized controlled trials (RCTs) are the gold standard of evidence-based medicine. Despite the evident advantages of RCTs, the strict inclusion and exclusion criteria limit the applicability of RCTs in the real-world. Therefore, real-world evidence, or medicine-based evidence, is an important addition to knowledge derived from RCTs. This is also applicable to the biologics for severe asthma. In the current age of digitalization, data from large real-world populations are often collected in population-based registries.

The Dutch RAPSODI registry strives to include patients with severe asthma and collects follow-up annually. Furthermore, multiple countries in Europe founded their own registries, leading to several populations with similar data. One of the ambitious goals of the SHARP Clinical Research Collaboration is to combine pan-European data of patients treated with the biologics. In order to connect and harmonize registries in a privacy-proof manner, SHARP seeks to develop a federated analysis platform, paving the way for real-world studies involving thousands of patients across Europe.

In this thesis, we describe several studies with a variety of study designs in order to gain insight in real-world outcomes of biological treatment for severe asthma.

PART I: POPULATION-BASED REGISTRIES

In **chapter 2**, we utilized the Dutch RAPSODI registry to study the effectiveness of anti-interleukin(IL)-5 biologics after 2 years of treatment. A subset (14%) of patients was completely free of any disease manifestations after 2 years. We labeled these patients "super-responders". Partial responders (69%) experienced residual disease manifestations even after 2 years of treatment, including inadequately controlled symptoms of asthma or rhinosinusitis, persistent airflow limitation, or OCS dependency. Only 11% of patients discontinued anti-IL-5 treatment and were labeled non-responders. Switches between anti-IL-5 biologics occurred frequently (41%), mostly because of an incomplete treatment response. An important clinical implication of our study is that although the anti-IL-5 biologics lead to an impressive clinical response in the majority of patients, physicians should realize that many patients are still left with unresolved disease manifestations. It seems therefore advisable to evaluate the therapeutic response in a systematic way and to strive for optimization of residual disease manifestations.

We found in **chapter 3** that reslizumab add-on treatment significantly reduced the rate of asthma exacerbations, the proportion of patients on maintenance OCS, as well as the dose of maintenance OCS. This effect was seen both in patients receiving reslizumab as their first biologic for severe asthma, as well as in patients who previously failed on another type 2 biologic and switched to reslizumab. This additional value of reslizumab was recognized by clinical severe asthma experts in an anonymous survey. The results in this study imply that it may be worthwhile to switch patients who do not respond to one specific type 2 biologic to a second add-on biologic, even if this has a similar mechanism of action.

Studies have shown that OCS-related adverse effects are dose dependent and associated with the *cumulative* OCS exposure rather than the mean *daily* dose of OCS. To gain insight in the effectiveness of anti-IL-5 treatment on the cumulative OCS exposure, we performed the study in **chapter 4**. In this study, we mapped the complete use of OCS based on pharmacy dispensing data, two years before and two years after anti-IL-5 initiation, in a nationwide population from the Dutch RAPSODI registry. We found a significant reduction in cumulative oral corticosteroid exposure over a 2-year period after patients initiated anti-IL-5 therapy. By providing insight in a long period before initiating anti-IL-5, we found that patients with lower and

shorter exposure to OCS were more likely to completely cease the use of OCS over a sustained period. This suggests that early intervention with anti-IL-5 biologics may be preferable, guiding physicians in the clinical decision-making.

In **chapter 5** we described the process of connecting several European severe asthma registries within the SHARP Clinical Research Collaboration. Connecting registries is bound to strict privacy regulation and faces several logistical challenges, for example differences in language and methods of capturing data. To overcome these challenges, SHARP harmonized the individual registries to a common data model and leveraged a federated analysis platform in order to generate summary statistics. **Chapter 6** is the first study using the SHARP federated analysis platform and serves as a proof-of-concept. We succeeded in linking data from 10 different nationwide registries, harmonized data for almost six thousand patients and demonstrated the real-world effectiveness of mepolizumab in almost a thousand patients, which is an important complement to RCTs and other real-world studies. This study paves the way for future pan-European real-world severe asthma studies using patient-level data in a privacy-proof manner.

Working with large population-based registries in **chapters 2 to 6** faced several difficulties. Missing data was a recurrent theme, as is the case in most real-world studies. Furthermore, different methods of capturing data limit the effects of manual data collection and ultimately the conclusions that can be drawn from real-world studies. Initiatives like SHARP strive towards a standardization of data collection, but this still has a long way to go. In the current age of digitalization, the automatic and standardized capture of data from electronic health records into a population-based registry is a possibility that might provide a solution for these challenges.

PART II: PREDICTION OF RESPONSE

Despite the initial selection of treatment-eligible patients, there still are some patients that do not respond to the biological treatment. Due to the high costs of the treatment, we strive to treat the patients that have the best chance of benefit from the biological treatment. Prediction of response –or non-response– is therefore a major knowledge-to-care gap in current clinical practice.

In **chapter 7** we provided a literature overview on the current state of response prediction. We found that predictive variables varied per study and were derived from post-hoc analyses of large RCTs or real-world studies with limited numbers

of patients. Assessing response based on data from RCTs creates difficulty, as the highly selected populations in RCTs differ from the patients treated in the real-world. Therefore there is a need for large real-world studies focusing on long-term outcomes. Furthermore, the best timing to assess biologic response needs to be elucidated.

To explore whether treatment could be evaluated even sooner than stated in current guidelines, we studied early changes in asthma-related parameters and long-term response after initiating mepolizumab treatment in **chapter 8**. All patients with an ACQ-score ≤0.75 at 8 weeks, which indicates well-controlled asthma, were responders on the long-term. This study, however, included a limited number of patients, restricting the conclusions that can be drawn based on these results. Based on this study, we evaluated the added value of outcomes at 3 months in the prediction of long-term benralizumab response in **chapter 9** using the Dutch RAPSODI registry and included a larger population. We showed the added value of outcomes at 3 months in predicting benralizumab response and proposed a tool to predict long-term response based on baseline characteristics combined with outcomes at 3 months. Prediction tools incorporating outcomes at 3 months and baseline characteristics, as proposed in this study, may help physicians to optimize the use of the costly biologics.

PART III: PATIENT-TAILORED APPROACHES

The different types of response beg the question whether the one-size-fits-all dosing interval that is used in the majority of biologics for severe asthma is appropriate and whether an even more patient-tailored approach could be beneficial for some patients. In other diseases, for example in rheumatoid arthritis and inflammatory bowel disease (IBD), biological serum levels and the relation with (non-)response was assessed. This led to the application of therapeutic drug monitoring (TDM) to personalize the costly biological treatment in some patients.

In **chapter 10**, we studied the variability in omalizumab serum levels and assessed whether long-term responders to omalizumab treatment experienced a need for the next administration. In this explorative study, we found that lower serum levels were associated with a higher patient-reported need for the next administration. Almost half of the patients reported a moderate to extreme need for the next administration, or ≥3 on a scale of 0-10. While clinicians recognize that some patients experience a need for the next administration, studies that focus on this phenomenon are lacking.

To this end we performed the study in **chapter 11**. In this study, we used a two-sided approach, both qualitatively and quantitatively. After interviewing a sample of our population, we constructed a questionnaire that focused on the perceived waning of effect and distributed this questionnaire to the rest of the population. We found that two-thirds of patients with severe asthma perceive a waning of biological effect at the end of the dosing interval. Several of these patients indicated a wish to shorten their dosing interval, whereas, on the other hand, a subset of the patients with no perceived waning effect was willing to increase their dosing interval. **Chapter 12** demonstrates a case report of a patient receiving benralizumab treatment during ICU admission for a COVID-19 pneumonia, which did not yield apparent detrimental consequences.

The findings in **chapters 10 and 11** show that by asking a relatively simple question, real-world findings can be an important addition to evidence generated by RCTs, expose previously unknown issues and provide input for future studies. New knowledge-to-care gaps based on this thesis are whether dose escalation could resolve the perceived waning of effect, whether dose de-escalation while maintaining asthma control could be appropriate and cost-effective, and in which patients these are feasible. This approach could help to optimize treatment with the costly biologics and improve patient-satisfaction, further pursuing shared decision-making and personalized medicine.

FINAL REMARKS

In this thesis we studied real-world outcomes to biological treatment for severe asthma. We showed examples of the potential of population-based registries and formulated new objectives for future studies. By focusing on a new patient-reported outcome measure, we also demonstrated the importance of involving the patient in the healthcare process. This continuous involvement of the patient, resulting in shared decision-making between patient, doctor and pharmacist, based on evidence-based medicine complemented by medicine-based evidence, show a bright future of a healthcare process in which patients with severe asthma are treated optimally.

NEDERLANDSE SAMENVATTING

Astma is een heterogene, inflammatoire luchtwegaandoening, gekenmerkt door symptomen van hoesten, piepende ademhaling en kortademigheid. De symptomen worden veroorzaakt door variabele luchtwegobstructie, hyperreactiviteit van de luchtwegen en hypersecretie van slijm in de luchtwegen. Wereldwijd lijden ongeveer 339 miljoen mensen aan astma. De meeste patiënten met astma worden adequaat behandeld met inhalatiemedicatie, waarbij de nadruk ligt op het verminderen van ontsteking in de luchtwegen en het ontspannen van de gladde spieren van de luchtwegen.

Drie tot tien procent van de patiënten met astma heeft ernstig astma. Veel van deze patiënten met ernstig astma hebben last van astma exacerbaties. Daarnaast zijn vaak hoge doses systemische corticosteroïden nodig om de astmasymptomen te verminderen. Systemische corticosteroïden zijn erg effectief in het verminderen van astmasymptomen. Er zijn echter ernstige bijwerkingen verbonden aan het (langdurig) gebruik van systemische corticosteroïden. Vanwege deze bijwerkingen is er grote belangstelling voor behandelopties waarmee de astma onder controle kan worden gehouden of gebracht, terwijl het gebruik van orale corticosteroïden wordt teruggedrongen.

De identificatie van verschillende astma fenotypen op basis van klinische, functionele of inflammatoire parameters leidde tot de ontwikkeling van nieuwe, gerichte behandelingsopties in de vorm van monoklonale antilichamen, ook wel biologics genaamd. Van deze nieuwe biologics is aangetoond dat ze astma exacerbaties en het gebruik van orale corticosteroïden (OCS) aanzienlijk verminderen, terwijl astmasymptomen, longfunctie en kwaliteit van leven verbeteren. Er zijn momenteel zes biologics goedgekeurd in Europa voor de behandeling van ernstig astma.

Gerandomiseerde gecontroleerde onderzoeken (RCT's) zijn de gouden standaard van 'evidence-based medicine'. Ondanks de duidelijke voordelen van RCT's is de toepasbaarheid in de klinische praktijk beperkt door de strikte in- en exclusiecriteria. Daarom zijn bevindingen op basis van real-world data een belangrijke aanvulling op de kennis uit de RCT's. Dit geldt ook voor de nieuwe biologics tegen ernstig astma. In het huidige tijdperk van digitalisering worden gegevens van grote real-world populaties vaak verzameld in registers.

Het Nederlandse RAPSODI-register streeft ernaar om patiënten met ernstig astma te includeren en verzamelt jaarlijks follow-up van deze patiënten. Verschillende landen

in Europa hebben hun eigen registers opgericht, wat heeft geleid tot meerdere onderzoeksgroepen met vergelijkbare gegevens. Een van de ambitieuze doelen van de SHARP Clinical Research Collaboration is het combineren van pan-Europese gegevens van patiënten die met de biologics zijn behandeld. Om registers op een privacy-bestendige manier met elkaar te verbinden en te harmoniseren, probeert SHARP een 'federated analysis platform' te ontwikkelen, dat de weg vrijmaakt voor real-world studies waarbij duizenden patiënten in heel Europa kunnen worden onderzocht.

In dit proefschrift beschrijven we verschillende studies met verschillende onderzoeksopzetten om inzicht te krijgen in real-world uitkomsten van de behandeling van ernstig astma met biologics.

DEEL I: REGISTERS GEBASEERD OP POPULATIES

In **hoofdstuk 2** hebben we het Nederlandse RAPSODI-register gebruikt om de effectiviteit van anti-interleukine(IL)-5 biologics na 2 jaar behandeling te bestuderen. Een subgroep (14%) van de patiënten was na 2 jaar volledig vrij van ziekteverschijnselen. We bestempelden deze patiënten als "super-responders". Gedeeltelijke responders (69%) ervoeren zelfs na 2 jaar behandeling resterende ziektemanifestaties, waaronder astmasymptomen, rhinosinusitis, aanhoudende beperking van de longfunctie of afhankelijkheid van orale corticosteroïden. Slechts 11% van de patiënten staakte de anti-IL-5 behandeling en werd als non-responder bestempeld. Er werd vaak gewisseld tussen anti-IL-5 biologics (41%), voornamelijk als gevolg van een onvolledige respons op de behandeling. Een belangrijke klinische implicatie van onze studie is dat, hoewel de anti-IL-5 biologics bij het merendeel van de patiënten tot een indrukwekkende klinische respons leiden, artsen zich moeten realiseren dat veel patiënten nog steeds met onopgeloste ziekteverschijnselen zitten. Het lijkt daarom raadzaam om de therapeutische respons op een systematische manier te evalueren en te streven naar optimalisatie van resterende ziekteverschijnselen.

We vonden in **hoofdstuk 3** dat behandeling met reslizumab het aantal astma exacerbaties, het aantal patiënten met dagelijks gebruik van OCS en de dosis van OCS significant verlaagde. Dit effect werd zowel waargenomen bij patiënten die reslizumab kregen als hun eerste biologic tegen ernstig astma, als bij patiënten die eerder faalden op een ander type 2 biologic en overstapten op reslizumab. Deze toegevoegde waarde van reslizumab werd erkend door experts op het gebied van ernstig astma in een anoniem onderzoek. De resultaten van deze studie impliceren

dat het de moeite waard kan zijn om patiënten die niet reageren op één specifiek type 2 biologic, over te zetten op een tweede biologic, zelfs als dit een vergelijkbaar werkingsmechanisme heeft.

Studies hebben aangetoond dat OCS-gerelateerde bijwerkingen dosisafhankelijk zijn en meer verband houden met de *cumulatieve* blootstelling aan OCS dan met de gemiddelde *dagelijkse* dosis OCS. Om inzicht te krijgen in de effectiviteit van anti-IL-5 behandeling op de cumulatieve OCS blootstelling, hebben we de studie in **hoofdstuk 4** uitgevoerd. In deze studie hebben we het volledige gebruik van OCS in kaart gebracht op basis van apotheekuitgiftegegevens, twee jaar voor en twee jaar na het starten van anti-IL-5 therapie in een landelijke populatie uit het Nederlandse RAPSODI-register. We vonden een significante vermindering van de cumulatieve blootstelling aan orale corticosteroïden in de periode van 2 jaar nadat patiënten met anti-IL-5 therapie waren begonnen. Door inzicht te geven in een lange periode vóórdat anti-IL-5 therapie werd gestart, ontdekten we dat patiënten met een lagere en kortere blootstelling aan OCS meer kans hadden om het gebruik van OCS gedurende een langere periode volledig te staken. Dit suggereert dat vroege interventie met anti-IL-5 biologics de voorkeur kan hebben. De resultaten uit dit onderzoek kunnen dienen als leidraad voor artsen bij de klinische besluitvorming.

In **hoofdstuk 5** hebben we het proces beschreven van het koppelen van verschillende Europese ernstig astma registers binnen de SHARP Clinical Research Collaboration. Het koppelen van registers is gebonden aan strikte privacyregelgeving en kampt met verschillende logistieke uitdagingen, bijvoorbeeld verschillen in taal en methoden voor het vastleggen van data. Om deze uitdagingen het hoofd te bieden heeft SHARP de individuele registers geharmoniseerd naar een 'common data model' en werd een federated analysis platform gebruikt om summary statistics te genereren. **Hoofdstuk 6** is de eerste studie die gebruik maakt van het SHARP federated analysis platform en dient als een proof-of-concept. We zijn erin geslaagd om gegevens uit 10 verschillende landelijke registers te koppelen, gegevens van bijna zesduizend patiënten te harmoniseren en de real-world effectiviteit van mepolizumab bij bijna duizend patiënten aan te tonen, hetgeen een belangrijke aanvulling is op RCT's en andere real-world studies. Deze studie maakt de weg vrij voor toekomstige pan-Europese real-world onderzoeken naar patiënten met ernstig astma waarbij gegevens op patiëntniveau op een privacy-bestendige manier worden gebruikt.

Het werken met grote bevolkingsregisters in de **hoofdstukken 2 tot en met 6** ging gepaard met verschillende uitdagingen. Ontbrekende gegevens waren een terugkerend thema, zoals het geval is in de meeste real-world studies. Bovendien

worden de effecten van handmatige dataverzameling beperkt door verschillende methoden voor het vastleggen van data en dit beperkt uiteindelijk de conclusies die kunnen worden getrokken uit real-world studies. Initiatieven als SHARP streven naar standaardisatie van dataverzameling, maar hebben nog een lange weg te gaan. In het huidige tijdperk van digitalisering is het automatisch en gestandaardiseerd vastleggen van gegevens uit elektronische medische dossiers in een bevolkingsregister een mogelijkheid die een oplossing zou kunnen bieden voor deze uitdagingen.

DEEL II: VOORSPELLEN VAN RESPONS

Ondanks de aanvankelijke selectie van patiënten die in aanmerking komen voor behandeling, zijn er patiënten die niet reageren op de biologics. We streven ernaar, gezien de hoge kosten van de biologics, om de patiënten te behandelen die de grootste kans hebben om baat te hebben bij de biologics. Voorspellen van respons –of non-respons– is daarom een belangrijk kennishiaat in de huidige klinische praktijk.

In **hoofdstuk 7** hebben we een literatuuroverzicht gemaakt van de huidige status van het voorspellen van respons. We vonden dat voorspellende variabelen per studie verschilden en vooral afkomstig waren uit post-hoc analyses van grote RCT's of real-world studies met een beperkt aantal patiënten. Het beoordelen van de respons op basis van gegevens uit RCT's levert problemen op omdat de patiënten in RCT's verschillen van de patiënten die in de echte wereld worden behandeld. Er is daarom behoefte aan grote, real-world studies die zich richten op respons op de lange termijn. Bovendien moet de beste timing om de respons op de biologics te beoordelen worden opgehelderd.

Om te onderzoeken of de behandeling met biologics sneller kan worden geëvalueerd dan in de huidige richtlijnen wordt vermeld, hebben we in **hoofdstuk 8** vroege veranderingen in astma gerelateerde parameters en lange termijn respons na het starten van de behandeling met mepolizumab bestudeerd. Alle patiënten met een ACQ-score ≤0.75 na 8 weken, wat duidt op goede astmacontrole, waren responders op de lange termijn. Deze studie omvatte echter een beperkt aantal patiënten, waardoor de conclusies die op basis van deze resultaten kunnen worden getrokken, beperkt zijn. Op basis van deze studie hebben we de studie in **hoofdstuk 9** opgezet binnen het Nederlandse RAPSODI-register, waarbij een grotere populatie kon worden geïncludeerd. We evalueerden de toegevoegde waarde van uitkomsten na 3 maanden bij het voorspellen van benralizumab-respons op lange termijn. We

toonden aan dat het toevoegen van uitkomsten na 3 maanden meerwaarde heeft bij het voorspellen van benralizumab-respons en stelden een tool voor om lange termijn respons te voorspellen op basis van baseline karakteristieken gecombineerd met uitkomsten na 3 maanden. Voorspellingsmodellen die uitkomsten na 3 maanden bevatten, zoals het model dat is voorgesteld in deze studie, kunnen artsen helpen om het gebruik van de kostbare biologics te optimaliseren.

DEEL III: PATIËNTGERICHTE BENADERINGEN

De variatie in mate van respons roept de vraag op of het one-size-fits-all doseerregime dat wordt gebruikt bij de meeste biologics bij ernstig astma geschikt is en of een nog meer op de patiënt afgestemde benadering gunstig zou kunnen zijn voor sommige patiënten. Bij andere aandoeningen, bijvoorbeeld bij reumatoïde artritis en inflammatoire darmaandoeningen, werden biological serumspiegels en de relatie met (non-)respons onderzocht. Dit heeft geleid tot het toepassen van therapeutic drug monitoring (TDM) om de kostbare behandeling met biologics bij sommige patiënten te personaliseren.

In **hoofdstuk 10** onderzochten we de variabiliteit in omalizumab serumspiegels en beoordeelden we of langdurige responders op omalizumab behandeling behoefte voelden aan de volgende toediening van omalizumab. In deze verkennende studie ontdekten we dat lagere serumspiegels geassocieerd waren met een hogere door de patiënt gerapporteerde behoefte aan de volgende toediening. Bijna de helft van de patiënten rapporteerde een matige tot extreme behoefte aan de volgende toediening, of ≥3 op een schaal van 0-10. Hoewel clinici erkennen dat sommige patiënten behoefte hebben aan de volgende toediening, ontbreken studies die dit fenomeen onderzoeken.

Hiertoe hebben we het onderzoek in **hoofdstuk 11** uitgevoerd. In dit onderzoek hebben we een tweeledige benadering gebruikt, zowel kwalitatief als kwantitatief. Na een steekproef van de patiënten met astma in het Medisch Centrum Leeuwarden te hebben geïnterviewd, hebben we een vragenlijst opgesteld die zich richtte op de waargenomen afname van het effect van het biologic tegen het einde van het doseerinterval. Deze vragenlijst werd vervolgens verspreid onder de rest van de patiënten met astma. We ontdekten dat twee derde van de patiënten met ernstig astma een afname van het effect van het biologic waarneemt aan het einde van het doseringsinterval. Verschillende van deze patiënten gaven aan hun doseringsinterval te willen verkorten, terwijl een subgroep van de patiënten zonder afnemend effect van hun biologic bereid was hun doseringsinterval te verlengen. **Hoofdstuk 12**

beschrijft een case report van een patiënt die benralizumab kreeg tijdens een IC-opname voor een COVID-19 pneumonie. Toediening van benralizumab leverde geen duidelijke nadelige gevolgen op.

De bevindingen in **hoofdstukken 10 en 11** laten zien dat door een relatief eenvoudige vraag te stellen, real-world bevindingen een belangrijke aanvulling kunnen zijn op bevindingen uit RCT's en voorheen onbekende kwesties aan het licht kunnen brengen die input kunnen leveren voor toekomstig onderzoek. Nieuwe kennishiaten op basis van dit proefschrift zijn of dosisescalatie de waargenomen afname van het effect zou kunnen oplossen, of dosisde-escalatie met behoud van astmacontrole passend en kosteneffectief zou kunnen zijn en bij welke patiënten dit toepasselijk is. Deze aanpak zou kunnen helpen om de behandeling met de kostbare biologics te optimaliseren en de patiënttevredenheid te verbeteren, waarbij besluitvorming tussen arts en patiënt en personalized medicine verder worden nagestreefd.

LAATSTE OPMERKINGEN

In dit proefschrift hebben we de real-world uitkomsten van behandeling met biologics bij ernstig astma bestudeerd. We lieten voorbeelden zien van het potentieel van grote registers en formuleerden nieuwe doelstellingen voor toekomstig onderzoek. Door in te zetten op een nieuwe, patiënt-gerapporteerde uitkomstmaat hebben we ook laten zien hoe belangrijk het is om de patiënt te betrekken bij het zorgproces. Deze continue betrokkenheid van de patiënt, resulterend in gedeelde besluitvorming tussen patiënt, arts en apotheker, gebaseerd op evidence-based medicine aangevuld met medicine-based evidence, laten een toekomst zien van een zorgproces waarin patiënten met ernstig astma optimaal worden behandeld.

Appendices

List of publications

Author affiliations

Curriculum vitae

De bloemen

Dankwoord

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CURRICULUM VITAE

Hans Kroes werd geboren op 7 november 1992 te Groningen. Hij groeide op in Westervelde en behaalde zijn vwo-diploma in 2012 aan het Augustinus College in Groningen. Aansluitend begon hij met de studie farmacie in Groningen. Zijn masteronderzoek heeft hij uitgevoerd in het Medisch Centrum Leeuwarden onder begeleiding van Berdien Oortgiesen. Daarnaast heeft hij in het Medisch Centrum Leeuwarden een keuzevak gevolgd waarin onderzoek werd gedaan naar patiënten met ernstig astma die werden behandeld met mepolizumab. In 2018 behaalde hij zijn masterdiploma farmacie met het predicaat cum laude.

Vanaf september 2018 kon Hans zijn keuzevak vervolgen met een promotieonderzoek onder begeleiding van prof. dr. Eric van Roon, dr. Anneke ten Brinke en dr. Sander Zielhuis. Bij dit onderzoek is hij betrokken geraakt bij het Nederlandse RAPSODI register en het Europese samenwerkingsverband SHARP. Naast het uitvoeren van onderzoek deed Hans klinische dagdiensten in de ziekenhuisapotheek. In januari 2023 is Hans gestart met de vierjarige opleiding tot ziekenhuisapotheker in het Medisch Centrum Leeuwarden en het Universitair Medisch Centrum Groningen. Deze opleiding combineert Hans met het uitvoeren van verder onderzoek naar patiënten met ernstig astma.

Hans woont samen met Berdien Oortgiesen in Leeuwarden.

DE BLOEMEN

We naderen het einde van dit proefschrift. Ik ben u, de lezer, een uitleg verschuldigd aangaande de bloemen die u terugvindt in dit proefschrift.

De omslag van dit proefschrift bestaat uit 11 verschillende bloemen, één voor elk onderzoek in dit proefschrift. Deze bloemen laat ik vervolgens per respectievelijke sectie en respectievelijk hoofdstuk terugkomen. Dit idee is ontstaan bij het bedenken van het acroniem van hoofdstuk 10 (PHarmacokinetic evaluation of LOng-term Xolair treatment, de vlambloem PHLOX) en vervolgens heb ik dit als overkoepelend thema gebruikt voor mijn acroniemen en de vormgeving van dit proefschrift.

In chronologische volgorde:

Hoofdstuk 2: **LO**ng-term therapy response to anti–IL-5 **B**iologics in sever**E** asthma—a real-**LI**fe ev**A**luation. (LOBELIA)
Hoofdstuk 3: Werktitel: Real-world evidence of **C**linical **O**utcomes with **R**eslizumab in adults with severe eosinophilic **A**sthma in the Netherlands. (CORA)
Hoofdstuk 4: Werktitel: The **R**eal-world **O**ral cortico**S**teroid burden in patients starting **A**nti-interleukin-5 therapy. (ROSA)
Hoofdstuk 5: **BLUE**print for harmonizing non-**S**t**A**ndardized disease re**G**istries to allow f**E**derated data analysis – prepare for the future. (BLUE SAGE)
Hoofdstuk 6: Werktitel: Use of Nucala in Severe Asthma, maar ik stemde voor **M**epol**I**zu**M**ab **O**utcomes in **S**evere **A**sthma. (MIMOSA)
Hoofdstuk 7: **P**rediction of response to b**I**ological treatment with monoclonal antibodies i**N** sever**E** asthma. (PINE)
Hoofdstuk 8: **P**atient-**R**eported outcome measures after 8 weeks of mepol**I**zu**M**ab t**R**eatment and long-term **O**utcomes in patients with **S**ever**E** asthma: an observational study. (PRIMROSE)
Hoofdstuk 9: Werktitel: **PR**ediction of benraliz**U**mab respo**N**se in severe asthma **US**ing clinical parameters and early treatment response: a national, real-life study. (PRUNUS)
Hoofdstuk 10: Werktitel: **PH**armacokinetic evaluation of **LO**ng-term **X**olair treatment. (PHLOX)
Hoofdstuk 11: Werktitel: **CR**aving to bi**O**logi**C**s **U**sed in **S**evere asthma. (CROCUS)
Hoofdstuk 12: Admini**STRA**tion of benralizumab i**N** a patient with severe as**T**hma admitted to the **I**ntensive care unit with COVID-19 pneumoni**A**: case report. (ASTRANTIA)

DANKWOORD

Tijdens de opleiding tot apotheker heb ik een college van Eric van Roon bijgewoond. Hierin werd de mogelijkheid tot het uitvoeren van een masteronderzoek in het Medisch Centrum Leeuwarden uitgelegd en deze mogelijkheid greep ik graag aan. Na dit masterproject heb ik een keuzevak gevolgd dat zich richtte op patiënten met ernstig astma. Dit keuzevak leidde tot een promotietraject en bijbehorend proefschrift dat ik graag af wil sluiten met dit dankwoord. De opsomming hieronder geeft mij het besef dat ik een gezegend mens ben.

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