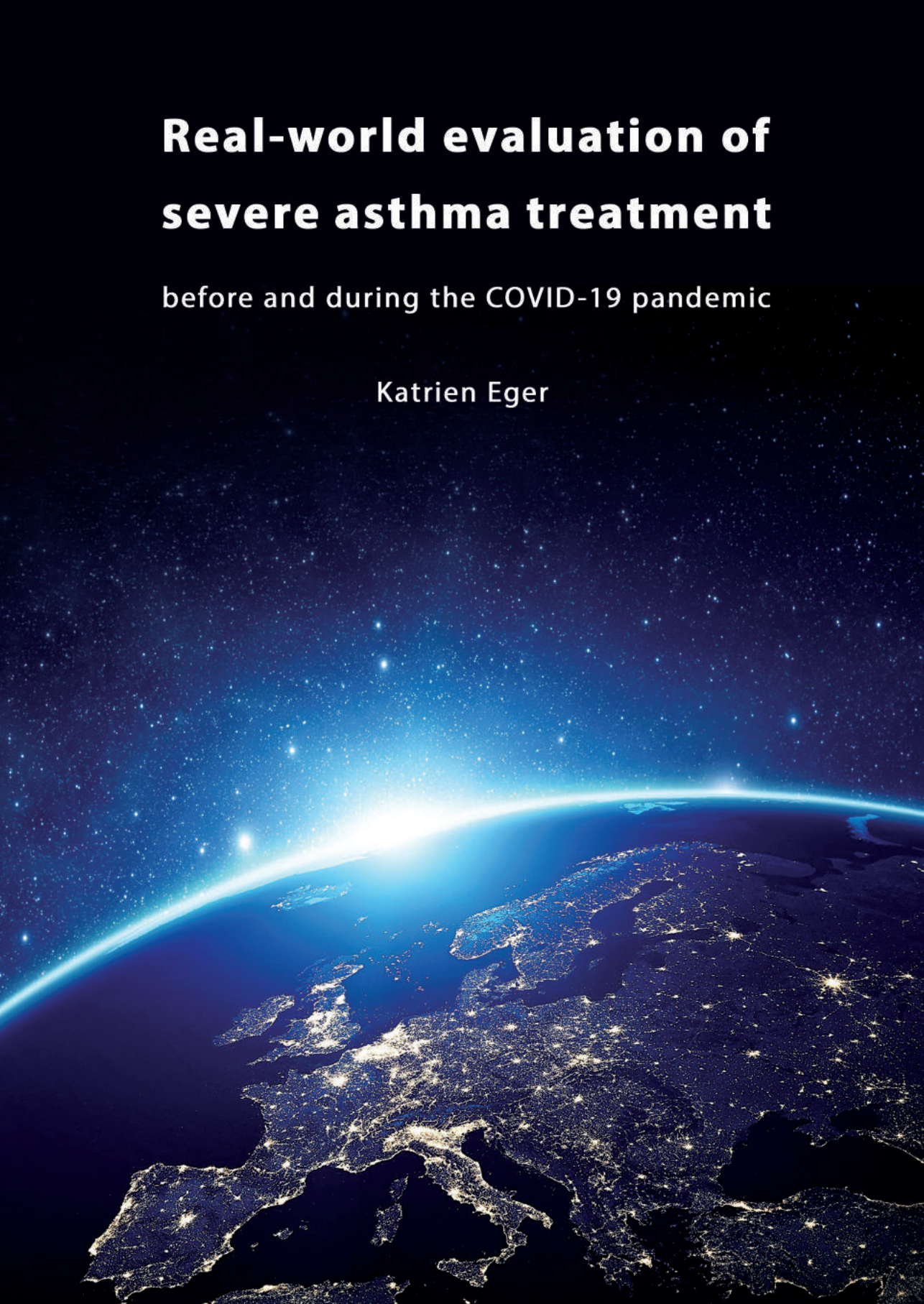
Real-world evaluation of severe asthma treatment

before and during the COVID-19 pandemic

Katrien Eger



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Chapter 1

General introduction and research questions

Introduction of severe asthma

Asthma is a chronic airway disease defined by a history of variable respiratory symptoms such as dyspnea, wheeze, chest tightness or cough, combined with confirmed variable expiratory airflow limitation, and often characterized by chronic airway inflammation [1]. The cornerstone of asthma treatment is inhaled corticosteroids (ICS). The majority of the approximately 300 million asthma patients worldwide have mild or moderate asthma, which can be controlled with low to moderate doses of ICS [2]. However, about 5% of the asthma population has severe asthma [3]. These patients have uncontrolled asthma despite high-dose inhaler therapy, or become uncontrolled when this therapy is tapered. Uncontrolled asthma is characterized by debilitating respiratory symptoms, recurrent or severe exacerbations and/or fixed airflow limitation [4, 5]. As a consequence, patients with severe asthma suffer from a high burden of disease and a reduced quality of life, while causing high health-care costs [6–8]. Previously, many patients with severe asthma were dependent on frequent or chronic use of oral corticosteroids (OCS), but this number has been greatly reduced as an increasing number of new OCS-sparing drugs have come onto the market in recent years.

Oral corticosteroids for asthma

History and indications of oral corticosteroids in asthma

The use of corticosteroids for asthma dates back to 1950, when several historical case series of patients with asthma reported positive effects of intramuscularly injected and, in later studies, orally administered cortisone [9–11]. The first placebo-controlled study with cortisone in patients with status asthmaticus showed impressive clinical improvements from a 9-day course of cortisone tablets compared to placebo [12]. However, in chronic asthma cortisone tablets had far less beneficial effects, as shown by the first placebo-controlled study for this indication in the same issue of the Lancet in 1956 [13]. This latter finding may have been due to methodological issues, but may also have been the first signal that not all chronic asthma patients are equally responsive to steroids. Nevertheless, for many years prednisolone and cortisone tablets were the only chronic anti-inflammatory treatment options available to asthma patients, alongside treatment with short-acting bronchodilators that have been available as metered-dose inhaler therapy since the mid-1950s [14]. Although the first reports of inhaled applications of cortisone were published in the 1950s, it was not until the early 1970s that ICS became available for daily clinical practice, allowing OCS to be tapered in many patients [15–17]. Since then, there have been two major indications for OCS in asthma patients. OCS are either prescribed as short rescue courses to treat exacerbations, or as chronic therapy in a subset of severe asthma patients to maintain acceptable levels

of disease control [18]. However, in low-income countries, OCS may be prescribed in mild/moderate asthma as well, since OCS tablets are much more affordable than the relatively expensive ICS [19].

Positive and negative effects of oral corticosteroids

The biological effect of OCS in asthma is multifaceted, and includes suppression of airway inflammation, reduction of endothelial barrier leakage, upregulation of beta-adrenergic receptors and reduction of mucus production (Figure 1) [20, 21]. Next to these as yet unsurpassed positive treatment effects, it soon became apparent that the use of OCS unfortunately also had several downsides. Regular OCS use can lead to multiple serious complications in the short and long term, which are associated with the cumulative dose of both intermittent and chronic OCS prescriptions.

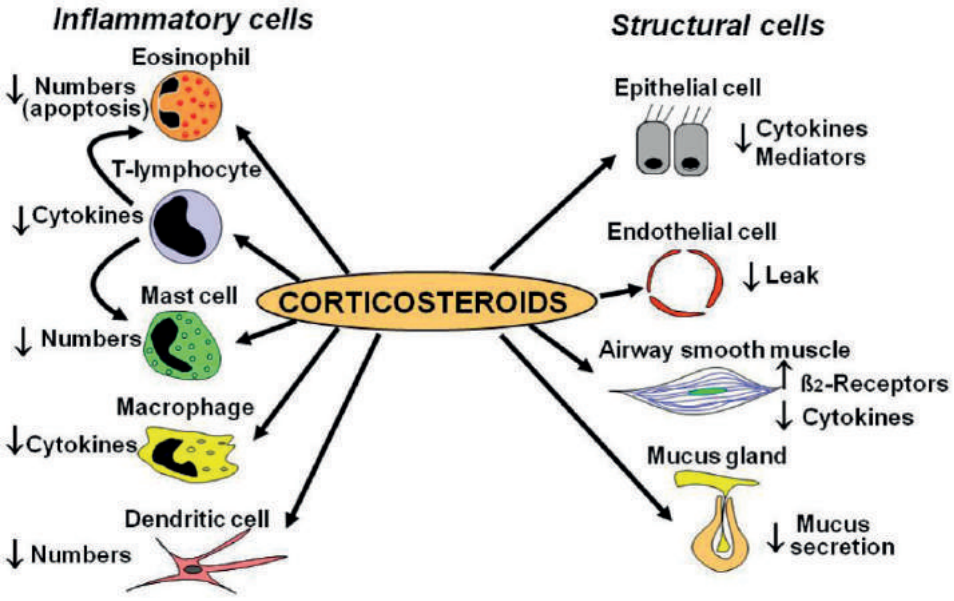

Figure 1. The multifaceted biological effect of corticosteroids in asthma. The biological effect of corticosteroids in asthma includes suppression of inflammatory cells, reduction of endothelial leakage, upregulation of beta-adrenergic receptors and reduction of mucus production. From Barnes [20].

These complications include infection/sepsis, venous thromboembolic events, osteoporosis, hypertension, obesity, type 2 diabetes, dyspeptic disorders, psychiatric disorders, ocular diseases and adrenal insufficiency [22–26]. In addition, OCS-induced morbidity in severe asthma patients further contributes to high health-care utilization and costs, reduced quality of life and even increased mortality [27–34]. For these reasons, it is crucial to prevent any inappropriate OCS use (i.e. OCS overuse) [35].

Minimizing OCS overuse starts with addressing conservative treatment strategies to improve asthma control, such as asthma education, optimization of inhaler therapy, avoidance of triggers and treatment of co-morbidities. A systematic assessment by dedicated asthma physicians involving these interventions has been shown to reduce oral corticosteroid maintenance dose and exacerbation frequency [36, 37]. Such assessment is also essential in the diagnostic work-up of severe asthma, and allows to distinguish patients with difficult-to-control asthma from truly severe asthma patients [4, 38]. Only those patients who still require regular OCS treatment despite optimization of all modifiable factors qualify as "severe asthma patients", and could be potential candidates for one of the new, expensive OCS-sparing targeted therapies for severe asthma [39].

Targeted therapies for severe asthma

History of asthma phenotypes and first signals of its relevance for therapy

The recognition of heterogeneity between asthma patients is almost a century old. The first paper suggesting the existence of different asthma phenotypes dates from 1940, written by dr. Francis Rackemann, who was a pioneer in this area. In the first sentence of this paper, "All is not allergy that wheezes", he referred to the observed distinction between so-called "extrinsic" (allergic) and "intrinsic" (non-allergic) asthma [40]. Additionally, he described distinct patterns of disease course in patients with "intrinsic asthma" which can still be recognized in daily practice. In this same paper, Rackemann also suggested a role for eosinophils in both "extrinsic" and "intrinsic" asthma, further building upon the initial histopathological findings of eosinophils in airways of deceased asthma patients in the early 20th century [41].

It was nearly 20 years after Rackemann's paper that a relationship between asthma phenotype and treatment response was first noted. In 1958, dr. Harry Morrow Brown published results from a follow-up trial of OCS in asthma in The Lancet, and described "striking improvement in the eosinophilic cases and poor results in the other patients" [42]. These pivotal early observations of different types of asthma,

the role for eosinophils and differential responses to OCS associated with eosinophilic inflammation, represent the basis of current research on asthma phenotypes and targeted therapies.

From a 'one treatment fits all' strategy to targeted therapies in severe asthma

Interestingly, the first decades following these early observations of different asthma phenotypes and its association with treatment response, asthma was nonetheless regarded as a single disease, with bronchial spasms and hyperreactivity being the most important aspects of asthma pathophysiology [43, 44]. As a consequence, asthma treatment was largely based on a 'one treatment fits all' strategy. Up to this day, international guidance reports including the Global Initiative for Asthma (GINA) recommend asthma management with "step-up" or "step-down" in treatment intensity (e.g. ICS dose) based on asthma control, ranging from as needed inhaler therapy in "step 1" up to chronic OCS therapy in "step 5" [1]. Consequently, treatment escalation to GINA step 5 (i.e. chronic OCS therapy) has occurred in many patients with severe asthma, irrespective of their underlying phenotype. Because of the harmful side effects of OCS, there has been a huge need for OCS-sparing therapies in these patients. Over the years, several potentially OCS-sparing agents have been investigated in clinical trials. Unfortunately, all these therapies, including methotrexate, azathioprine, colchicine and oral gold therapy, failed to show a clinically relevant OCS reducing effect [45–48]. Since these drugs known to have OCS-sparing effects in other diseases had failed to reduce OCS use in severe asthma, newly developed therapies were eagerly awaited.

In the early 2000s, the landscape of severe asthma treatment underwent its first drastic change. Omalizumab, a monoclonal antibody targeting immunoglobulin E (IgE) showed to significantly reduce exacerbation rate in patients with severe allergic asthma in a phase 3 trial. These results led to the approval of omalizumab for the treatment of severe allergic asthma in 2003, being the first biologic therapy for patients with severe asthma, and the first treatment for a specific phenotype. Although very promising at first, only about 50-60% of patients showed a favorable response, with signals for suboptimal responses particularly in the most severe patients [49–51]. In the same period, the first trials with antibodies targeting interleukin (IL)-5 were performed. IL-5 was recognized as a major driver of eosinophilic inflammation, and at the time, eosinophils were considered the most important effector cells in every patient with asthma [52, 53]. However, these trials in unselected mild-moderate asthma patients failed to show improvements in the primary outcomes, which were asthma symptoms and lung function parameters, although there were signals for positive effects on exacerbation reduction in some patients [54, 55]. These findings of differential

responses to omalizumab and anti-IL-5 biologics represented another important signal that asthma was more than just a single disease, questioning the 'one treatment fits all' approach.

Over the last two decades, asthma research on pathophysiology and phenotypes made huge progress. It is now well-established that asthma is a complex heterogeneous disease consisting of distinct phenotypes with different underlying mechanistic pathways. An important distinction in asthma phenotypes is based on the presence or absence of type 2 inflammation, previously called Th2 inflammation, which is characterized by cytokines such as interleukin (IL-)4, IL-5 and IL-13 and inflammatory cells such as T helper (Th)-2 cells, type 2 innate lymphoid cells, and eosinophils [49, 56]. Important phenotypes with a type 2 inflammatory profile are eosinophilic and allergic asthma, as shown in Figure 2. Besides deeper insight into phenotypes and related biomarkers, the better understanding of type 2 inflammatory pathways has revealed many potential targets for therapy. This has led to a true revolution in asthma research with the development of numerous "targeted therapies".

In 2009, the New England Journal of Medicine published the next landmark studies in the field of severe asthma. These follow-up phase 2 studies of the previously failed mepolizumab trials, specifically included patients with severe eosinophilic asthma, and had exacerbation frequency and chronic OCS dose as the primary outcomes. In these studies by Haldar *et al*. and Nair *et al*., mepolizumab significantly reduced exacerbations and chronic OCS dose, respectively [57, 58]. Shortly thereafter, in 2012 and 2014, large-scale phase 3 trials (DREAM, MENSA and SIRIUS) confirmed the positive results observed in the phase 2 trials [59–61]. These key studies led to the approval of mepolizumab as the second biologic agent for the treatment of severe asthma in 2015. And more was to yet come. In recent years three other biologics have been approved for the treatment of severe asthma patients with evidence of type 2 inflammation [58, 62–66]. These include two other biologics targeting the IL-5 pathway, namely reslizumab which also blocks IL-5, and benralizumab which targets the IL-5 receptor. The most recent new monoclonal that came to the market in 2018 (in the United States) and in 2019 (in Europe) is dupilumab, which targets the alpha subunit of the IL-4 receptor, thus blocking the IL-4 and IL-13 pathway simultaneously.

Although all these biologics met their primary outcomes in phase 3 trials by showing significant reductions in exacerbation rate and chronic OCS dose in patients with severe type 2 asthma, some subtle differences in the results of other outcomes could be observed, for instance regarding biomarker levels. Blocking the IL-5 pathway induced a profound reduction in blood eosinophil levels, which was expected, given its role in eosinophil differentiation, maturation and survival [59, 63, 64]. In contrast to the anti-

IL-5 biologics, dupilumab induced a (transient) increase in blood eosinophil levels. Whereas dupilumab caused a significant reduction in IgE levels and exhaled nitric oxide (FeNO), the anti-IL-5's did not seem to affect FeNO levels to the same extent. In addition, dupilumab seemed to induce larger improvements in FEV_1 than the anti-IL-5 biologics [65, 66]. However, it is important to notice that head-to-head trials have not been performed, limiting the possibility to make comparisons between the biologics for severe asthma.

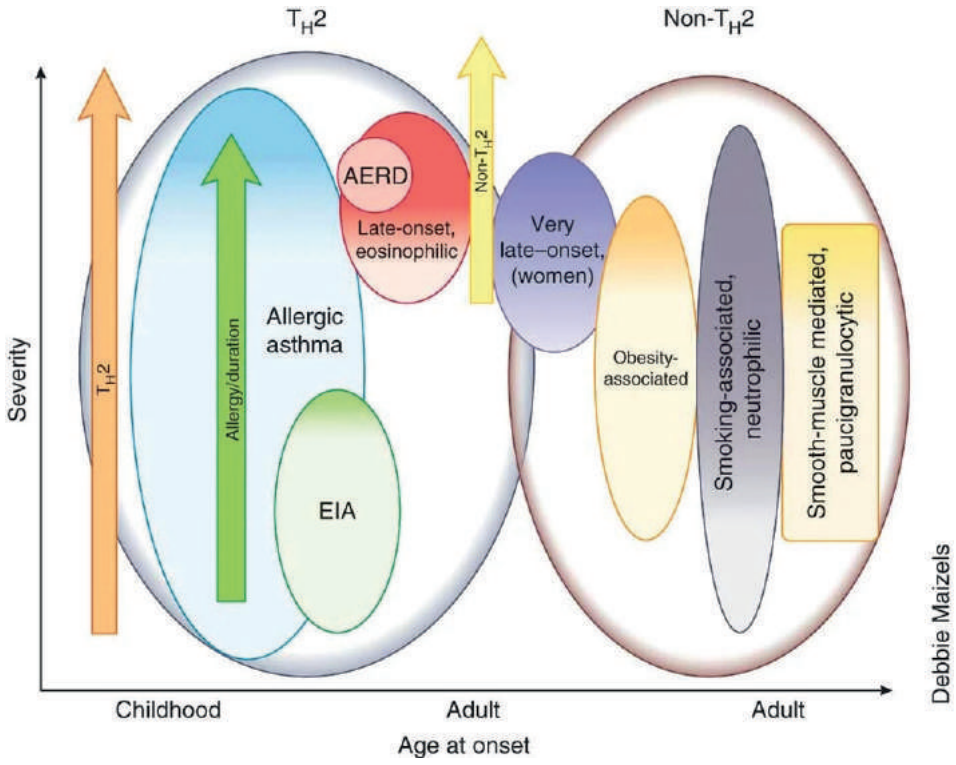

Figure 2. Asthma phenotypes with and without type 2 inflammation. An important distinction in asthma phenotypes is based on the presence of type 2 inflammation (Th2) or absence of type 2 inflammation (non-Th2). Age of onset and severity of disease are other important distinctive factors. Abbreviations: *EIA*; exercise induced asthma, *AERD*; aspirin exacerbated respiratory disease. From Wenzel [49].

Another important distinction between the currently available asthma biologics is the applicability of these drugs in other diseases. Besides having positive effects on type 2 asthma, some of these biologics have shown to be effective in other diseases driven by type 2 inflammation, which resulted in the approval for other indications as well [67–72]. Dupilumab, for instance, is approved for the treatment of atopic dermatitis

and nasal polyposis, omalizumab for the treatment of nasal polyposis and chronic idiopathic urticaria, and mepolizumab is FDA (Food and Drug Administration) approved for the treatment of eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome and nasal polyposis.

Thus, with the emergence of these type 2 biologics, OCS exposure could finally be reduced in numerous patients with severe asthma, resulting in improvements in quality of life for many [73, 74]. Furthermore, the GINA guidance report has recently been adjusted, and now recommends adding an asthma biologic in "step 5" first, in case of severe type 2 asthma, and adding OCS only as a last resort treatment option (Figure 3) [1].

Real-world studies

Clinical trials vs. real-world studies

The phase 3 studies investigating biologics for severe asthma and other type 2 diseases have been pivotal in proving efficacy of these therapies. Phase 3 studies are randomized controlled trials (RCTs), conducted in homogenous well-selected patient populations and in highly controlled clinical settings, and are preferably placebo controlled [75]. The process of randomization is a critical step in RCTs to reduce the potential of bias, and to enable identification of causal relations between interventions and outcomes [76]. RCTs and subsequent meta-analyses, which combine results from several RCTs, provide the highest level of scientific evidence and remain the gold standard for proving therapy efficacy [77]. Therefore, RCTs are the primary source for acquiring approval labels and for reimbursement decisions.

However, because of their tightly controlled setting, RCTs do not adequately reflect routine clinical practice [76]. For instance, patient populations at the (respiratory) outpatient clinic are very heterogeneous, and many patients would not meet inclusion criteria for RCTs, for example because of age, smoking history, co-morbidities or co-medication [78]. In addition, follow-up in daily clinical practice will differ between patients as a result of differences in local protocols, physicians' routines, and individual patients' needs. Furthermore, adherence to therapy in routine practice may be much less than observed in clinical trials due to the Hawthorne effect (i.e. patients tend to change their behavior, e.g. increase therapy adherence, when they are aware of participating in an experimental study) [79]. This heterogeneity in patient population and follow-up in daily practice, in contrast to the homogeneous and tightly controlled conditions in clinical studies, raises the question whether results from RCTs are generalizable to everyday clinical practice (i.e. the external validity) [80].

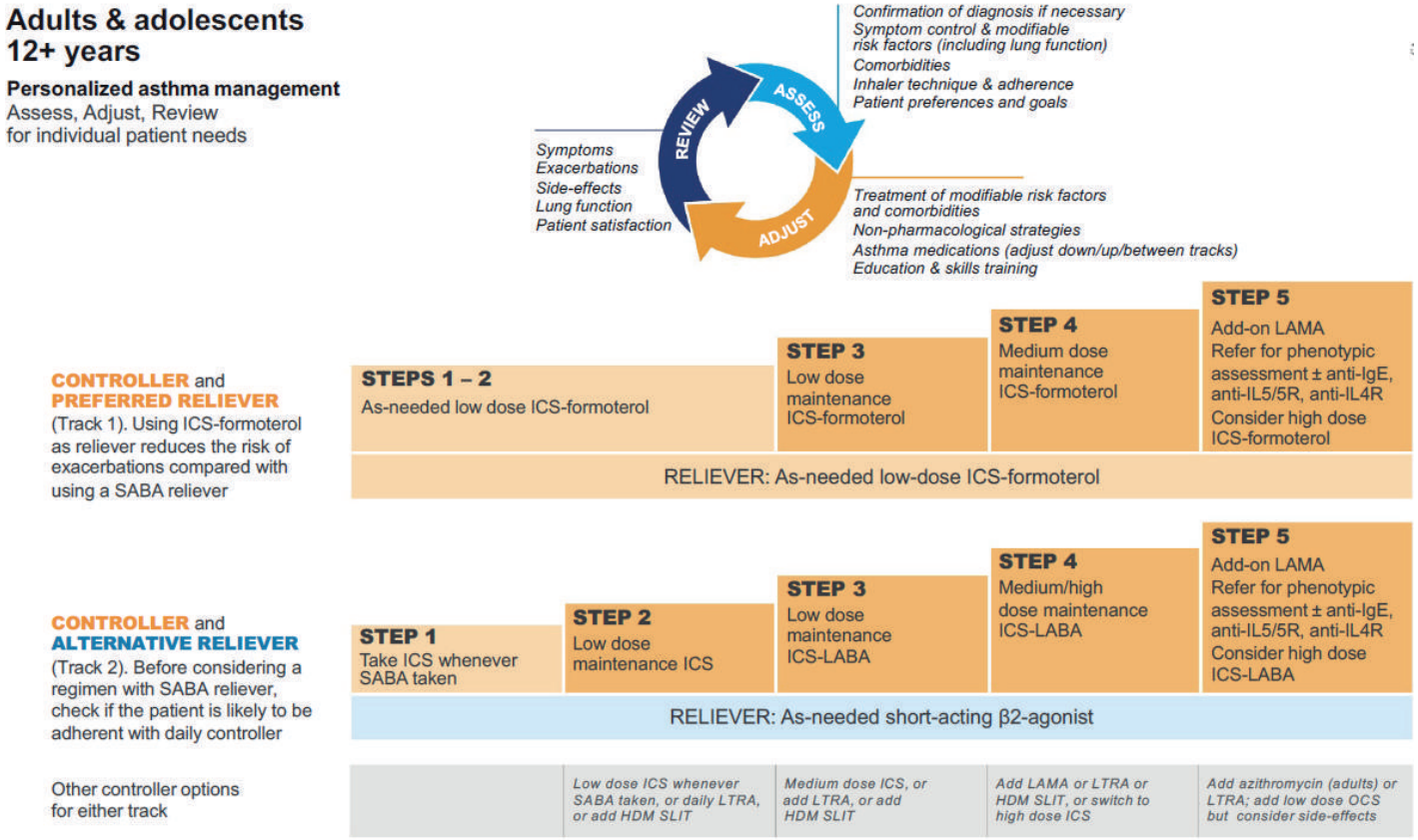

Figure 3. The step-wise approach to asthma treatment as recommended by GINA. The GINA report recommends to adjust intensity of asthma treatment based on asthma control. In the most recent version, add-on of low dose OCS should only be considered as a last treatment option in step 5. From GINA [1].

This is exactly why real-world studies, whose setting involves the diverse routine practice, play an increasingly important role in providing essential information complementary to RCTs [81–83]. While the aim of traditional clinical trials is to investigate mechanisms and "efficacy" (i.e. does the treatment work and is it safe?), real-world studies investigate "effectiveness" (i.e. what are the benefits and risks in the intended patient population in routine practice?) [84]. In addition to treatment "effectiveness", real-world data can also provide valuable information for reflection regarding quality of care (e.g. are patients treated according to the current guidelines?) or uniformity of care (e.g. do treatment regimens differ between centers or countries?) [85]. Another important difference between clinical trials and real-world studies, is that real-world data can be collected without having predefined research questions, end points or subgroup analyses [77].

A major advantage of real-world studies over RCTs is their relatively low costs, allowing them to run for many years and recruit large patient numbers. Also, monitoring by expensive Contract Research Organizations is not mandatory. In addition, it is not necessary for participating staff or nurses to have significant experience in research activities, in contrast to RCTs which are mostly conducted in experienced expertise or academic centers. Lastly, real-world studies may address clinical questions that are not feasible or ethical to perform in RCT setting [76]. However, also real-world studies have their limitations, mostly related to data quality and possibility of biases, which, however, could be controlled for with advanced statistical methods [86].

Real-world studies generate real-world data. The FDA defined real-world data as 'data relating to patient health status and/or delivery of health-care that are routinely collected from a variety of sources' [87]. These sources include for example electronic health records, claims databases, patient-generated data (e.g. surveys), or data derived from other sources such as mobile devices. In addition to observational real-world studies, interventional studies can also contain real-world elements. Such trials are called 'pragmatic trials'. The relationship between pragmatic trials vs. traditional trials is not dichotomous, and trials may contain elements of both [88]. This heterogeneity in methods specifically for asthma-related studies is depicted in Figure 4, in which traditional RCTs, pragmatic trials and real-world observational studies are distinguished based on the extent of control of 'ecology of care' (e.g. follow-up) and of 'patient selection' [75].

In summary, real-world studies are becoming increasingly recognized as complementary to phase 3 clinical trials, and the role of real-world evidence in clinical and regulatory decision-making is expected to continue to grow in the future.

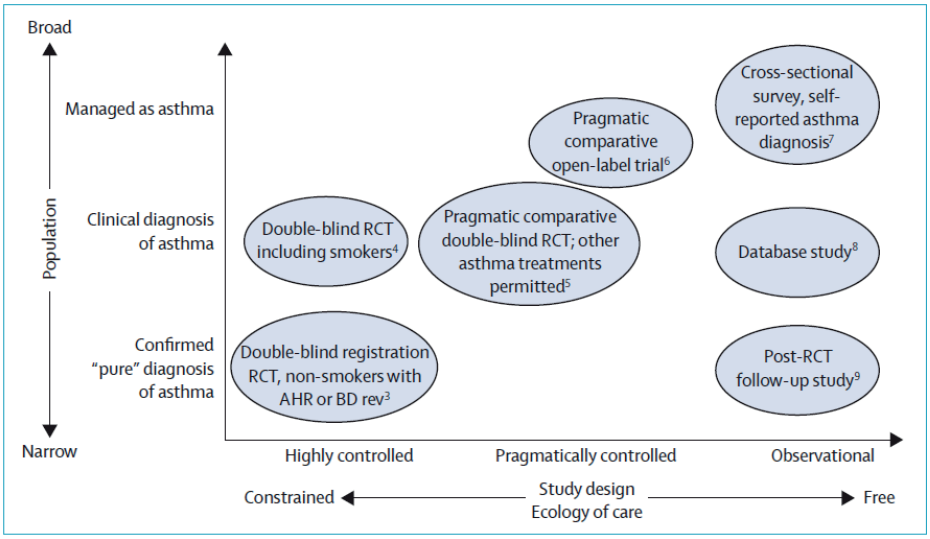

Figure 4. Schematic representation of differences in methodology of asthma-related studies. Methods of asthma-related studies may differ based on the extent of control of 'ecology of care' and 'patient selection', which determines their degree of 'pragmatism'. From Roche *et al.* [75].

Severe asthma registries

Collecting data from patients about disease course, treatment response, side effects, etc., has been done by physicians for many years, probably using paper lists in the early times, and spreadsheets in later times. However, the emergence of electronic data collection systems and the implementation of electronic health records in the last decades have boosted the development of large-scale registries worldwide. The first registries were mostly pharmacovigilance databases, which performed safety monitoring of patients on novel therapies, such as biologics for rheumatoid arthritis, to identify any long-term or rare adverse events [89]. It was soon recognized that these large-scale electronic databases could be applied to answer clinical research questions beyond safety, and the number of patient, drug and device-related registries increased exponentially in recent years.

Thus, several severe asthma registries emerged worldwide in the last couple of years, including the Dutch severe asthma registry 'Registry of Adult Patients with Severe asthma for Optimal DIsease management' (RAPSODI). Patients are included in the RAPSODI registry after having provided informed consent. Subsequently, baseline characteristics and yearly follow-up data are recorded by using real-world data extracted from the patient's electronic health record. Collected data include demographics, exacerbation frequency, lung function and inflammatory biomarkers. As a result, RAPSODI represents

a large-scale database with prospectively collected, observational, real-world data. In addition to national databases, there is a growing number of international collaborations between individual registries, such as the European collaboration 'Severe Heterogeneous Asthma Registry Patient-Centred' (SHARP) and the more global collaboration 'International Severe Asthma Registry' (ISAR) [90, 91].

Although severe asthma registries are relatively new, their scientific output is already expanding. For instance, publications addressed phenotypes, use of co-medications, co-morbidities, and differences in patient characteristics between countries or between registry and RCT populations [78, 92–94]. However, numerous research questions regarding real-world treatment of severe asthma remain unanswered, and registry-databases represent an important data source for addressing many of these questions.

Unanswered questions regarding real-world treatment of severe asthma

At present, biologic treatment for severe asthma is relatively new. An increasing number of targeted therapies are under investigation in clinical trials, and an increasing number of biologics have now been approved for the treatment of severe asthma. Although phase 3 studies have provided much information about the efficacy of asthma biologics, many questions remain to be explored. The lack of head-to-head trials between the different asthma biologics, is an important caveat. One of the major challenges for respiratory physicians and allergologists in daily practice, for instance, is the large overlap in indications of the available asthma biologics [95]. The choice for a biologic may therefore be based on aspects other than asthma, for example co-morbidities or logistical reasons. After dupilumab received FDA approval for use in patients with nasal polyposis in 2019, the co-existence of asthma and nasal polyposis favored dupilumab over the other biologics. However, omalizumab and mepolizumab have recently also been approved for the treatment of severe nasal polyposis. Therefore, uncontrolled type 2 co-morbidities have become less suitable for selecting a biologic. However, logistical considerations can still have a role in preference for a biologic, for instance because not all biologics are available in all countries. In addition, the mode (subcutaneous vs intravenous), site (home vs in-hospital administration) and interval of administration (varying from 2 to 8 weeks), or type of health-care insurance may guide the selection of a biologic.

Currently, there is only sparse, mostly expert-based literature about the selection of biologics, and there are many other unresolved issues related to severe asthma treatment [96, 97]. For instance, it is unknown what proportion of patients using high doses of OCS would qualify for biologic therapy; how and when to evaluate response to biologic therapy; what criteria should be used for a super-response to biologics;

what the criteria should be for the discontinuation of the biologic therapy in the event of a less favorable response; when to switch to another biologic in case of incomplete response and to which biologic; whether switching between biologics is safe; whether measurement of plasma drug levels may be useful in dosing biologic therapy; whether the dosing interval could be extended after a period of excellent response, or medication could be discontinued in a subgroup of patients with complete response; whether asthma biologics have disease-modifying capacity (e.g. what is the effect on airway remodeling?); whether biologics are cost-effective, whether there are any safety concerns on the long-term (e.g. ≥10yr), etc. Real-world evidence could make an important contribution to answering many of these questions.

The COVID-19 pandemic

During the preparation of this thesis, a very unusual circumstance suddenly emerged, namely a viral pandemic. In December 2019 a cluster of patients with pneumonia of unknown cause was reported in Wuhan, China. Shortly thereafter a novel coronavirus, called "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), was identified as the causative pathogen [98]. The virus spread around the world very rapidly in the first weeks after its identification. In February 2020, the World Health Organization named the illness caused by the novel virus "corona virus disease 2019" (COVID-19), and declared the outbreak a pandemic in March 2020, when over 100.000 infections were reported in 114 countries [99, 100]. The first large study on the clinical spectrum of COVID-19 reported mild disease (asymptomatic, upper respiratory symptoms or mild pneumonia) in about 80% of cases, severe pneumonia in 15% of cases (hypoxemia or infiltrates covering ≥50% of the lungs), and critical disease (respiratory or multi-organ failure) in 5% of patients [101]. Health-care systems worldwide were suddenly put under heavy pressure, and abrupt adaptations in organization of care were required in order to create capacity for the high numbers of critically ill COVID-19 patients, while preserving regular health-care as much as possible.

From the beginning of the pandemic real-world evidence played an important role for rapid sharing of observations and experiences from clinical practice. In a short period of time huge numbers of studies on COVID-19 were published, reaching nearly 26.000 by June 2020 to over 179.000 in September 2021 [102, 103]. Many of the early publications were real-world cohort studies investigating for instance routes of transmission, diagnostic procedures, patient populations at risk, clinical presentation, dynamics in laboratory values, imaging and viral clearance, or disease management. These studies not only contributed to knowledge about for instance risk factors for severe COVID-19, but also revealed potential targets for therapy, such as immunosuppressant therapy

for the hyper-inflammatory state observed in critically ill patients, or prophylactic anticoagulation therapy because of the observed high prevalence of thromboembolic events in hospitalized COVID-19 patients [104].

Risk factors for severe COVID-19 disease course that were identified early in the pandemic included older age, male sex, diabetes, cardiovascular disease and obesity [101, 105, 106]. The earliest studies, however, also identified patients with chronic respiratory diseases, including asthma and COPD patients, at risk for severe COVID-19, although there was no distinction between the different types of chronic respiratory diseases [101, 107]. The World Health Organization subsequently classified patients with any chronic lung disease as a COVID-19 risk group for whom strict shielding advices were recommended [108].

In the context of limited evidence available at the time, this advice was appropriate, not least because viral infections are known to trigger exacerbations in many pulmonary diseases. Since then, many studies specifically focusing on patients with (severe) asthma have been published. Given the subject matter of this thesis, we were able to instantly focus on new research questions raised by the COVID-19 pandemic, thus contributing to some of the real-world issues related to COVID-19 and severe asthma.

Unanswered questions of real-world severe asthma treatment during the COVID-19 pandemic

Initially, three main issues emerged regarding COVID-19 and (severe) asthma patients, related to the susceptibility of SARS-CoV-2 infection and the risk of severe COVID-19 disease course in (severe) asthma patients; the safety of asthma biologics during SARS-CoV-2 infection; and the adequate continuation of severe asthma care in pandemic conditions. Real-world data from registries and surveys were again important resources for exploring these new issues.

Research questions of the thesis

As outlined above, many research questions regarding the real-world use of severe asthma treatment remain unanswered. This thesis will focus on several key questions regarding real-world severe asthma therapy, namely the prevalence of OCS overusing asthma patients and potential biologic candidates, response to anti-IL-5 biologics, safety of switching between biologics, COVID-19 risks for severe asthma patients and reorganization of severe asthma care during the COVID-19 pandemic. The thesis is divided into two parts. In part I real-world severe asthma treatment will be evaluated

under normal conditions, i.e. "before the COVID-19 pandemic", while in part II aspects of real-world severe asthma management will be evaluated "during the COVID-19 pandemic".

The following research questions were formulated:

Part I

1. What is the prevalence of asthma patients using high doses of OCS in addition to high-dose inhaler therapy, and what could be the role of improved therapy adherence, optimization of inhaler technique, or biologic therapy in reducing OCS use in these patients?

2. What is the prevalence of super, partial and non-responders to long-term anti-IL-5 therapy, can predictors for super- and non-response be identified, how often do switches between anti-IL-5 biologics occur, and what is the nature of residual disease manifestations in partial responders?

3. What are possible complications after switching from anti-IL-5 biologics to dupilumab, and how could these be managed?

Part II

4. Are (severe) asthma patients, and particularly severe asthma patients on biologic therapy, at increased risk of severe COVID-19?

5. How was severe asthma care in Europe reorganized during the COVID-19 pandemic, how did this impact patient satisfaction with care and asthma control, and what aspects of reorganized care may be adopted in future care?

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Part I

Evaluation of severe asthma treatment before the COVID-19 pandemic

Chapter 2

The emergence of new biologics for severe asthma

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Abstract

Patients with severe asthma experience severe symptoms and frequent exacerbations despite intensive treatment with inhaled and oral glucocorticoids. Biologics for severe asthma aim to reduce asthma-related and glucocorticoid-induced morbidity. Recently, new biologics targeting interleukin (IL)-5, IL-5 receptor and IL-4/IL-13, which are all cytokines involved in so-called type 2 airway inflammation, were approved for severe asthma. They show a reduction in exacerbation rate and an oral glucocorticoid-sparing effect. Studies with upstream biologics targeting alarmin cytokines such as thymic stromal lymphopoietin (TSLP) and IL-33 are underway, and newly designed bispecific antibodies targeting more than one pathway are in early phases of development. Such pathway-targeted add-on treatments will soon become standard of care for all patients with severe asthma.

Introduction

Severe asthma is a debilitating disease, associated with frequent severe exacerbations and poor quality of life [1]. Until recently, patients with this condition were dependent on the chronic use of high-dose inhaled and oral glucocorticoids. Long-term maintenance therapy with oral glucocorticoids can increase the risk of serious and life-threatening adverse events [2,3]. Moreover, recurrent short courses of glucocorticoids for treatment of exacerbations as well as high doses of inhaled corticosteroids contribute to the systemic adverse effects of glucocorticoid therapy [3,4]. Fortunately, the recent introduction of biologics for severe asthma has led to improvements with respect to treatment diversity for patients with severe asthma. In 2003, omalizumab, a monoclonal antibody that binds immunoglobulin (Ig)E, was the first FDA approved biologic for treatment of severe allergic asthma [5]. More than a decade later the development of biologics came in a fast track. Several biologics targeting key cytokines of so called "type 2" airway inflammation (interleukin (IL)-4, IL-5, IL-13) [6] were tested in phase 3 studies and 4 of these are now FDA approved. These include therapies targeting IL-5 (mepolizumab [7–9], reslizumab [10–12]), the IL-5 receptor (benralizumab [13–15]) and the alpha subunit of the IL-4 receptor (IL-4Rα, dupilumab [16,17]), and have resulted in impressive reductions in asthma morbidity. Other biologics, unfortunately, failed in phase 2 (anti-IL-4R [18]) and phase 3 studies (anti-IL-13 [19,20]). Promising upcoming treatments interfering with more upstream molecules, such as alarmins, transcription factors and receptors expressed on immune cells, are entering phase 3 trials [21–23].

So fortunately, there is a growing number of treatment options for patients with severe asthma who remain uncontrolled despite high-dose inhaled or oral glucocorticoids and experience recurrent exacerbations. This review will give an update on the most recent developments in the fast moving field of biologic treatment for severe asthma.

Current concepts on asthma pathophysiology

Asthma is a heterogeneous, inflammatory airway disorder with complex pathophysiologic mechanisms [24]. Knowledge on the different asthma phenotypes and their differential pathophysiology is exponentially increasing. However, exact mechanisms and pathways of asthma pathogenesis are not yet clear. In 1940, Rackemann suggested that eosinophils played an important role in 'extrinsic' or allergic and 'intrinsic' or non-allergic asthma [25]. In the following decades, the focus moved towards airway smooth muscle spasm and airway hyperresponsiveness as the most important underlying mechanisms, but in the 90s, eosinophils were again considered key cells in all patients with asthma [26]. Initially, asthma associated with eosinophilic airway inflammation

was known as "Th2-high" asthma because of the orchestrating role of T-helper (Th)2 cells and its cytokines (Figure 1) [27], with IL-4 driving the production of immunoglobulin E (IgE) by B-cells, IL-5 recruiting and activating eosinophils and IL-13 stimulating airway smooth muscle and mucus glands [1]. In 2011, another key immune cell was identified, the type 2 innate lymphoid cell (ILC2) [28], which is capable of releasing large amounts of IL-5 and IL-13 after exposure of the epithelium to non-specific stimuli such as microbes and pollutants [29]. Since then, "Th2 asthma" was renamed as "type 2 asthma". The mechanism of non-type 2 asthma is much less understood, although IL-17-induced neutrophilic inflammation might play an important role [30].

Interestingly, the variable effects of biologic therapy in patients with type 2 asthma provide additional insight into pathophysiologic mechanisms. Some patients are good responders to one biologic, but not to another, while others have less exacerbations but show no improvements in lung function [7,8,10,15–17,31]. In addition, several pathways may be activated within the same patient, dominant pathways may change over time, depending for instance on therapy or triggers, or the blockage of one pathway could stimulate another [32–35]. This illustrates that the network of inflammatory pathways in asthma is complex and dynamic, and interacts with environmental factors. Given this complexity, there is an urgent need to identify pathway-related biomarkers to target the right pathways in each individual patient.

Currently approved and failed biologics targeting type 2 inflammation

Nearly fifteen years after omalizumab became available for patients with severe allergic asthma in 2003, biologics targeting the eosinophil were introduced, including antibodies against IL-5 or IL-5 receptor [7,8,10,11,13,14]. Mepolizumab, reslizumab and benralizumab were approved by the FDA in 2015, 2016 and 2017, respectively, for severe eosinophilic asthma in adults and children ≥12 years (except for reslizumab that was approved for adults only and mepolizumab that was approved by the EMA for children ≥6 years) [36]. They all showed a significant reduction in exacerbation rates in phase 3 studies [7,9–14]. More importantly, mepolizumab and benralizumab showed an impressive oral glucocorticoid-sparing effect [8,15]. Post hoc analyses of phase 2 and 3 studies with these biologics showed that patients with late-onset asthma (>40 years), frequent exacerbations, impaired lung function, or chronic rhinosinusitis with nasal polyposis benefited most from anti-IL-5 treatment with greater reductions in exacerbation rates and larger improvements in forced expiratory volume in 1 second (FEV_1) compared to placebo [31,37,38]. These clinical characteristics are now considered typical of the severe eosinophilic asthma phenotype [39]. Currently, there

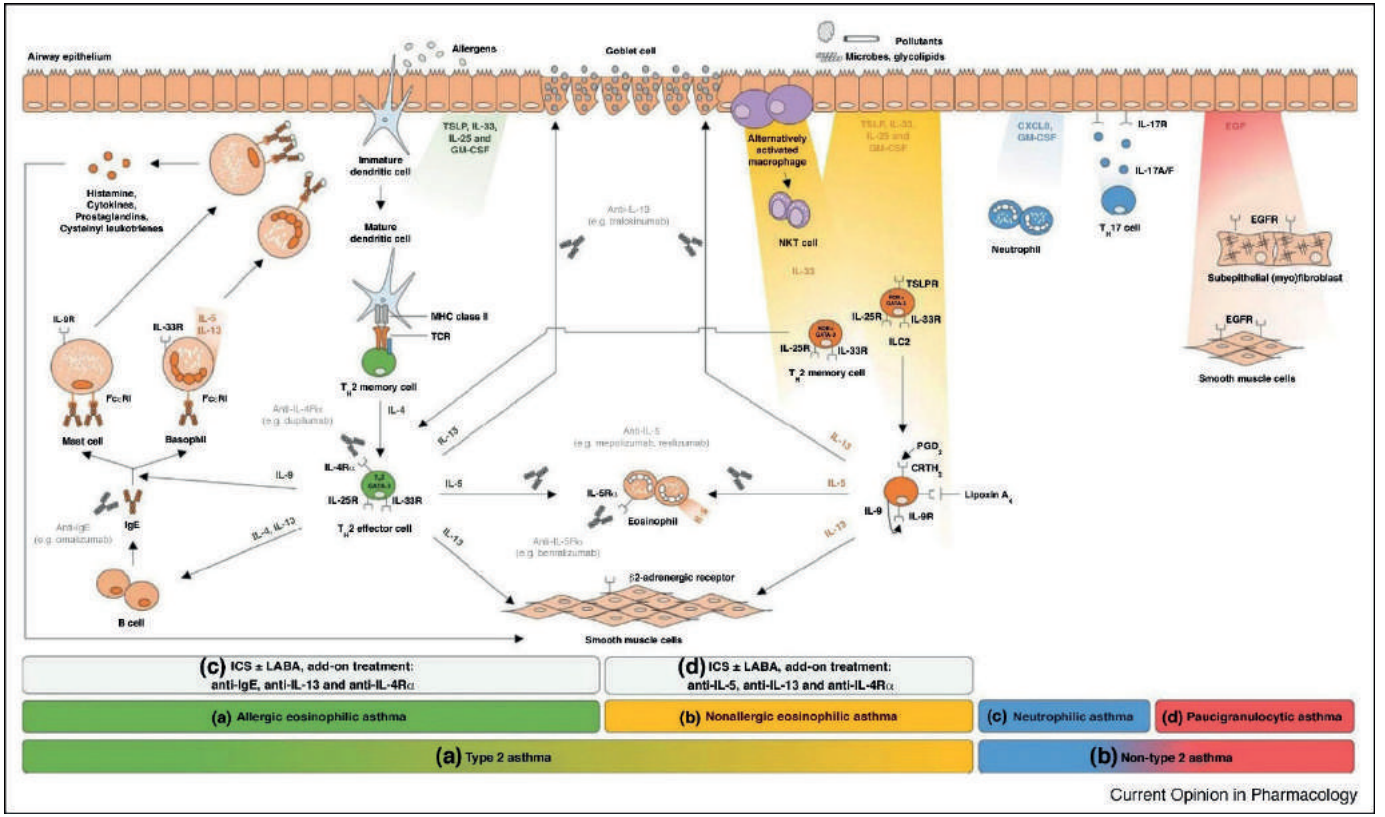

Figure 1. Currently known pathways of airway inflammation in asthma. Simplified schematic representation of 4 different types of airway inflammation in asthmatic patients: allergic eosinophilic asthma, non-allergic eosinophilic asthma, neutrophilic asthma and paucigranulocytic asthma. From Godar *et al.* [29].

are no head-to-head studies comparing the efficacy of the 3 anti-IL-5 biologics yet, but one trial comparing omalizumab with mepolizumab in severe combined allergic and eosinophilic asthma is underway (PREDICTUMAB) [40]. Nonetheless, there are some differences between these biologics which may be relevant to clinicians. For example, mepolizumab showed efficacy in patients with severe asthma and blood eosinophils >150 cells/L, whereas this was >400 cells/L for reslizumab and >300 cells/L for benralizumab; mepolizumab and benralizumab are given subcutaneously, whereas reslizumab is only approved for intravenous use; the approved doses of mepolizumab and benralizumab for severe asthma are fixed, whereas the dose of reslizumab is weight-adjusted; and importantly, the dosing interval of benralizumab is 8 weeks, whereas both mepolizumab and reslizumab are to be given every 4 weeks. These practical issues may be quite important for patients and physicians when choosing between different anti-IL-5 treatments (Table 1).

In addition to the anti-IL-5 therapies, another interesting biologic has become available, namely dupilumab, which targets IL-4 and IL-13 by blocking the shared IL-4Rα. Two phase 3 trials investigating the effect of dupilumab in patients with moderate-to-severe asthma showed significant reductions in exacerbation rates and oral glucocorticoid-sparing effects [16,17]. Dupilumab appeared to be ineffective in patients with non-eosinophilic asthma (blood eosinophil counts <150 cells/µl) and was therefore FDA approved in October 2018 for moderate-to-severe asthma patients aged 12 years and older with the eosinophilic phenotype or with oral glucocorticoid-dependent asthma.

As a consequence of its mode of action, dupilumab differs from the anti-IL-5 biologics in several aspects. First, in contrast to the anti-IL-5's, dupilumab does not decrease blood eosinophils [7,9,10,12–14,16]. Instead, it lowers levels of IgE and exhaled nitric oxide (FeNO), which is not the case with anti-IL-5 treatment [41]. Dupilumab has to be administered subcutaneously every two weeks, which is more frequent compared to anti-IL-5 biologics. Finally, dupilumab appears to be very effective against atopic co-morbidities like atopic dermatitis and nasal polyposis [42,43], which suggests that dupilumab could be particularly beneficial for atopic patients with combined eosinophilic asthma, dermatitis and nasal polyposis.

Unfortunately, two initially promising biologics failed to reach the market. In phase 2 studies, tralokinumab and lebrikizumab, both neutralizing antibodies against IL-13, showed positive effects on FEV_1 and exacerbation rates in subgroups of patients with increased type 2 biomarkers, in particular periostin [44,45]. However, in phase 3 studies, these effects could not be reproduced [19,20]. In line with these results, tralokinumab failed to decrease airway eosinophils in a phase 2 trial and showed no oral glucocorticoid-sparing effect in another phase 3 trial [46,47]. These failures could

Table 1. Features of the currently FDA approved biologics

Biologic	Target	FDA approved (yr)	Patient population with clinical benefit in phase 3 studies	Route of administration	Dosing	Interval of administration	Main effect on asthma	Effect on biomarkers
Omalizumab (Xolair)	IgE	2003	Uncontrolled moderate-to-severe allergic asthma with total IgE serum level ≥30 IU/ml and specific IgE or positive skin prick test to a perennial allergen and FEV ≤80% [5,69,70]	Subcutaneous	75-600 mg, depending on weight and baseline total IgE level	2-4 weeks, depending on weight and baseline total IgE level	Reduction exacerbation rate [5,69]	Minimal reduction in FeNO [70] Reduction in free circulating IgE [5]
Mepolizumab (Nucala)	IL-5	2015	Severe eosinophilic asthma with blood eosinophils ≥150-300 cell/μL, and ≥2 exacerbations previous year or dependent on oral glucocorticoids [7–9]	Subcutaneous	100 mg	4 weeks	Reduction exacerbation rate [7–9] Glucocorticoid-sparing effect [8]	Reduction blood and sputum eosinophils [7,9,41]
Reslizumab (Cinqaero)	IL-5	2016	Uncontrolled (ACQ ≥1,5) severe eosinophilic asthma with blood eosinophils ≥400 cell/μL [10–12]	Intravenous	3 mg/kg	4 weeks	Reduction exacerbation rate [10–12]	Reduction blood and sputum eosinophils [10–12,71]
Benralizumab (Fasenra)	IL-5Rα	2017	Severe eosinophilic asthma with blood eosinophils ≥300 cell/μL, and ≥2 exacerbations previous year or dependent on oral glucocorticoids [13–15]	Subcutaneous	30mg	First 3 doses interval of 4 weeks, thereafter 8 weeks	Reduction exacerbation rate [13–15] Glucocorticoid-sparing effect [15]	Reduction blood and sputum eosinophils [13,14,72]
Dupilumab (Dupixent)	IL-4Rα	2018	Severe eosinophilic asthma, FEV_1 ≤80%, and with either blood eosinophils >150 cell/μL and episode of worsening asthma previous year, or glucocorticoid dependent asthma [16,17]	Subcutaneous	300 mg	2 weeks	Reduction exacerbation rate [16,17] Increase FEV_1 [16] Glucocorticoid-sparing effect [17]	Reduction FeNO and total IgE level [16,17] Transient increase blood eosinophils [16,17]

Abbreviations: *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced exhaled volume in 1 second; *IgE*, immunoglobulin E; *IL*, interleukin; *Rα*, receptor alpha.

be possibly a result of solely inhibiting IL-13, which may not be sufficient to reduce eosinophilic airway inflammation or to prevent exacerbations in patients with severe asthma. Further development of these anti-IL-13 antibodies for asthma has been discontinued.

Promising new developments

The next generation of biologics targeting upstream cytokines may be very promising as they interfere early in the type 2 inflammatory cascade [48]. Tezepelumab is a human monoclonal antibody against TSLP, an "alarmin" cytokine produced by the bronchial epithelium in response to several inflammatory triggers that activates both innate and adaptive immune cells [48]. In a large phase 2 trial, tezepelumab reduced annualized asthma exacerbation rates in both patients with low and high Th2 inflammatory status (based on total IgE level and blood eosinophil count) and, in accordance to the upstream mode of action, it reduced both blood eosinophils, FeNO and total IgE serum levels [21]. Two phase 3 trials with tezepelumab are currently recruiting patients and results are eagerly awaited. IL-33 and IL-25 are two other alarmins. IL-33 is currently being investigated as potential drug target in phase 2 studies, while there are no ongoing clinical trials with anti-IL-25 [49]. Theoretically, the downside effect of upstream biologics could be immune dysregulation or suppression of host defense [50]. Therefore, patients treated with these biologics should be closely monitored. However, current evidence suggests that these drugs are safe.

Bispecific antibodies, which are in early phases of development, are another interesting class of biologics for the treatment of severe asthma. These molecules recognize two different epitopes [51] and can thereby tackle different pathways simultaneously. A neutralizing antibody targeting IL-4Rα/IL-5 has been recently investigated in preclinical studies [52]. Another antibody against IL-13/TSLP has just been developed [53]. An anti-IL-13/IL-17 antibody, which might be a potential treatment option for patients with combined eosinophilic and neutrophilic inflammation (mixed granulocytic asthma [54]) or in patients with counter-regulated non-type 2 inflammation after targeted treatment of type 2 inflammation [33], has recently been tested in a phase 1 trial [55]. Further developments on bispecific antibodies will likely occur in the near future. As with upstream biologics, safety profiles should also be closely monitored with bispecific antibodies.

Two other classes of drugs, which are formally not considered to be biologics (i.e. drugs produced by living cells [29]), also have promising potential as treatment strategies for asthma. One strategy involves the modulation of receptors of key inflammatory cells

[56]. Fevipripant is an example of a small molecule inhibiting the prostaglandin DP_2 receptor, also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [56,57]. Orally administered fevipiprant showed efficacy in phase 2 trials by improving lung function in asthma patients with moderate or severe airflow limitation [58,59], and in asthma patients with sputum eosinophilia [23]. Another new treatment strategy involves the inhibition of transcription factors by catalytically active antisense oligonucleotides. SB010, an inhaled DNAzyme, targets GATA-3, a key transcription factor in the type 2 inflammatory pathway [60]. This DNAzyme showed effective inhibition of the early and late asthmatic response to inhaled allergens in patients with mild asthma, which was associated with a decrease in type 2 inflammatory markers [22].

Biologics for non-type 2 inflammation

No effective biologics for non-type 2 related asthma are available yet. The group of patients with non-type 2 inflammation is heterogeneous [61], which makes this group challenging to investigate [29]. Targeting neutrophilic inflammation with biologics such as anti-CXCR2, anti-TNF-α, and anti-IL-17R failed to show efficacy in patients with asthma [62–65]. However, one trial with an anti-IL-17 antibody in patients with low type 2 status is ongoing with other biomarker targets under investigation [66]. Although there is growing attention for non-type 2 asthma, there is currently a notable unmet need for effective therapy for these patients.

Remaining issues

With the emergence of biologic therapies for severe asthma, a significant number of patients can now be treated with a remarkable positive impact on their lives. However, there are still many unresolved issues. For instance, there are currently no adequate biomarkers to assess the dominant inflammatory pathway in an individual patient. As a consequence, biologic treatment is now given on a trial-and-error base. In addition, there is no clear definition of response to biologic therapy in patients with severe asthma nor is there consensus on the timing for evaluation of this response. Furthermore, it could be questioned whether a fixed dose of biologic therapy is suitable for all patients. Those with very severe inflammation might be under-treated, whereas others may be over-treated. Finally, it is currently not known how to manage patients who do not respond, or only partially respond to anti-IL-5 (receptor) or anti-IL-4/IL-13 biologics, who may also have residual inflammation through other non-targeted pathways [6]. Thus, many questions about biologic therapy for severe asthma remain unanswered.

Summary

Important clinical studies with biologics targeting key cytokines of the type 2 inflammatory pathways have been conducted over the last few years. These studies showed significant decreases in exacerbation rates and reductions in chronic oral glucocorticoids use, which resulted in the approval of anti-IL-5 (receptor) and anti-IL-4/IL-13 biologics. In the next few years, research will be focused on drugs interfering with upstream targets (e.g. TSLP, IL-33, GATA-3) or drugs that simultaneously inhibit different key inflammatory cells (e.g. CRTH2). Now that it is increasingly recognized that different pathways can be (reciprocally) activated in one single patient [6,67], future research directions may focus on combined therapies [29] or biologic therapy with bispecific antibodies. Inactivating different pathways simultaneously seems like an important research avenue, but safety will need to be carefully considered. Thus, we are getting increasingly closer to the ultimate treatment for patients with severe asthma, which is to identify accurate biomarkers of activated type 2 or non-type 2 pathways in an individual patient, and to optimize and develop (combinations of) treatments that adequately target all these different activated pathways in a single patient. That would represent real precision medicine! [68]

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Chapter 3

Overuse of oral corticosteroids, underuse of inhaled corticosteroids, and implications for biologic therapy in asthma

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Abstract

Background

Asthma patients using high cumulative doses of oral corticosteroids are at risk of serious adverse events and are increasingly being treated with steroid-sparing asthma biologics. However, it is unknown whether prescribing these expensive biologics is always justified.

Objectives

This study aimed to (1) assess the prevalence of asthma patients using high cumulative doses of oral corticosteroids, (2) explore the role of suboptimal inhaler therapy, and (3) estimate the proportion of patients to whom asthma biologics might be prescribed unnecessarily.

Methods

All adults (n=5002) with at least one prescription of high-dose inhaled corticosteroids (≥500-1000 mcg/day fluticasone-equivalent) and/or oral corticosteroids (GINA step 4-5) in 2010 were selected from a pharmacy database including 500,500 Dutch inhabitants, and sent questionnaires. Of 2312 patients who returned questionnaires, 929 had asthma. We calculated the annual cumulative oral corticosteroid dose and prescription fillings, and checked inhaler technique in a sample of 60 patients. Patients estimated to have good adherence and inhaler proficiency who still required high doses of oral corticosteroids (≥420 mg/year) were considered candidates for initiating biologic treatment.

Results

29.5% of asthma patients on GINA 4-5 therapy used high doses of oral corticosteroids, of which 78.1% were likely to have poor therapy adherence or inadequate inhaler technique. Only 21.9% were considered definitive candidates for biologic therapy.

Conclusion

High oral corticosteroid use in Dutch GINA 4-5 asthma patients was common. However, in 4 out of 5 patients adherence to inhaled corticosteroid therapy and/or inhaler technique was considered suboptimal. Since optimizing inhaler therapy may reduce the need for oral corticosteroids, this should be mandatory before prescribing expensive steroid-sparing drugs.

Introduction

Many patients with severe or uncontrolled asthma use oral corticosteroids (OCS) in addition to treatment with inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA), either intermittently to treat exacerbations or chronically to maintain acceptable levels of asthma control [1,2]. Chronic or frequent use of OCS for asthma is known to be associated with a variety of serious and debilitating acute and chronic adverse effects [3], the incidence, type and severity of which depend on the cumulative OCS dose used by the patient [4-6]. Even cumulative exposures as low as 0.5 to 1 g prednisolone equivalent have been reported to be associated with adverse outcomes [5].

Over the past five years, new biologics for severe asthma have become increasingly popular after studies had shown that these treatments can significantly reduce OCS courses in patients experiencing frequent asthma exacerbations and lower the OCS maintenance dose in OCS-dependent patients.

A major drawback of these biologic treatments however, is the high cost compared to OCS tablets. It is therefore of the utmost importance that these expensive treatments are only prescribed to patients in whom all measures have been taken to reduce or prevent the use of OCS. In particular, it is important to ascertain whether patients have been prescribed sufficiently high doses of inhaled corticosteroids (ICS), whether they demonstrate optimal adherence to ICS and whether their inhaler technique is adequate. There is good reason for uncertainty in this respect, given the large "placebo" effect in the various phase 3 OCS tapering studies [7-9].

Therefore, the aim of the present study was to investigate whether asthma patients with high cumulative OCS use were adherent to ICS therapy and used their inhalers correctly, and to estimate the proportion of patients to whom asthma biologics might be prescribed unnecessarily.

Material and Methods

Design and Study Population

This is a cross-sectional study using data from a pharmacy database with prescription data from 65 community pharmacies in the Netherlands, including 500,500 patients from the general population. This database was also used in a previous study on the prevalence of severe asthma by Hekking *et al* [10]. First, patients with at least one ICS prescription between January 1st 2011 and January 1st 2012 (study period) were identified.

From these patients, patients with severe or uncontrolled asthma were identified. This included subjects with at least one prescription of high-dose ICS (≥1000mcg fluticasone-equivalent) or medium-high dose (500-1000mcg/day fluticasone-equivalent) combined with maintenance OCS therapy (≥5mg/day prednisone-equivalent for ≥6 months in the previous year). All these patients (n=5002) were sent questionnaires, which included questions on demographics, medical history, medication consumption, smoking history, and asthma control. A total of 2312 patients completed and returned the questionnaires (response rate of 46.2%). Table 1 shows characteristics of responders and non-responders: mean age, ICS and OCS dose were similar between responders and non-responders; however, non-responders were slightly younger and less often adherent to ICS than responders. Based on the data from the questionnaires we selected adult patients (≥18 years) with a diagnosis of asthma (i.e. self-reported diagnosis of "asthma" or self-reported diagnosis of "COPD" with a smoking history of less than 10 pack-years). Patients with other self-reported pulmonary diagnoses, such as sarcoidosis, cystic fibrosis, or bronchiectasis, were excluded.

Table 1. Patient characteristics of responders and non-responders to the questionnaires

	Responders n=2312	**Non-responders n=2690**	***p-value***
Age (yr) – med. IQR	64 (55-74)	61 (49-73)*	0.000
Male sex – %	44%	43.5%	0.720
Prescribed inhaled corticosteroids per day (mcg)† – med. IQR	1000 (600-1000)	1000 (600-1000)	0.059
Adherence to inhaled corticosteroids (%)# – med. IQR	82 (49-107)	67 (39-99)*	0.000
Total oral corticosteroid dose per year (mg)‡ – med. IQR	400 (210-826)	360 (210-840)	0.329

†Inhaled corticosteroid dose is provided as fluticasone-equivalent; #Proportion of prescriptions that were filled; ‡Oral corticosteroid dose is provided as prednisone-equivalent; *p-value <0.05.

Outcomes

"High cumulative OCS consumption" was defined as a cumulative dose of ≥420 mg prednisone-equivalent during the 1-year study period. We chose this cumulative cut-off dose because it corresponds to two OCS rescue courses per year (30 mg/day prednisone-equivalent for 7 consecutive days), which is a criterion for the diagnosis of severe asthma by GINA and has shown to be associated with OCS-induced adverse effects [5, 11].

Good therapy adherence was defined as ≥80% fillings of ICS prescriptions during the study period. Inhaler technique was verified by pharmacists in a representative subsample of adherent patients, and adequate inhaler technique was defined as correct use (i.e. without making critical errors that would lead to insufficient drug reaching the airway) of all prescribed inhaler devices [11].

Statistical Analysis

We calculated the cumulative dose of prescribed OCS in our asthma patients and selected those who had used ≥420 mg prednisone equivalent during the one-year study period. Then, we assessed the percentage of filled ICS prescriptions, and classified patients into 'adherent' and 'non-adherent'. Among the adherent patients who used high cumulative OCS doses, we computed the proportion of patients using their inhaler devices correctly. Standard errors and 95% confidence intervals for proportions were computed for single proportions and were adjusted using the delta method for products of proportions. Approval for this study was obtained from the medical ethical committee (MEC W11-064; NTR no.3546).

Results

Prevalence of asthma patients on high cumulative doses of oral corticosteroids

Of the patients with severe or uncontrolled asthma in the pharmacy database who returned questionnaires (n=2312), asthma was diagnosed in 929 (40.2%). Of these, 274 (29.5%) patients were treated with high cumulative doses of OCS (shown in Figure 1). These patients were mostly elderly females, with late-onset asthma, allergies, and recurrent exacerbations, taking median prednisone-equivalent doses of 750mg per year (Table 2).

Adherence and inhaler technique

Of the 274 asthma patients using high dose OCS, 130 patients (47.4%) were not adherent to ICS (prescription filling <80%). Amongst a random sample of 60 adherent patients only 41.6% showed adequate inhaler technique (shown in Figure 2). Thus, only 21.9% of patients were adherent to ICS therapy and used their inhalers correctly, implying that 78.1% of patients with severe or uncontrolled asthma could be falsely labeled as candidates for biologic therapy.

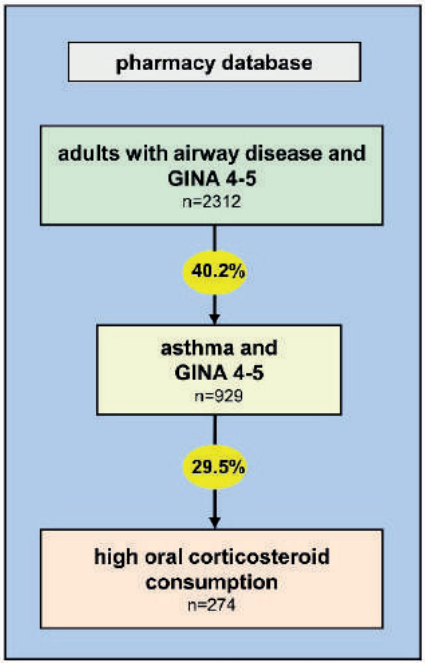

Figure 1. Calculation of the prevalence of asthma patients on step 4-5 who use high doses of oral corticosteroids. Results from clinical questionnaires were combined with data on medication use to calculate prevalences of patients with severe or uncontrolled asthma, and the subset of patients using ≥420mg prednisone-equivalent per year. Abbreviations: *GINA*, Global Initiative for Asthma.

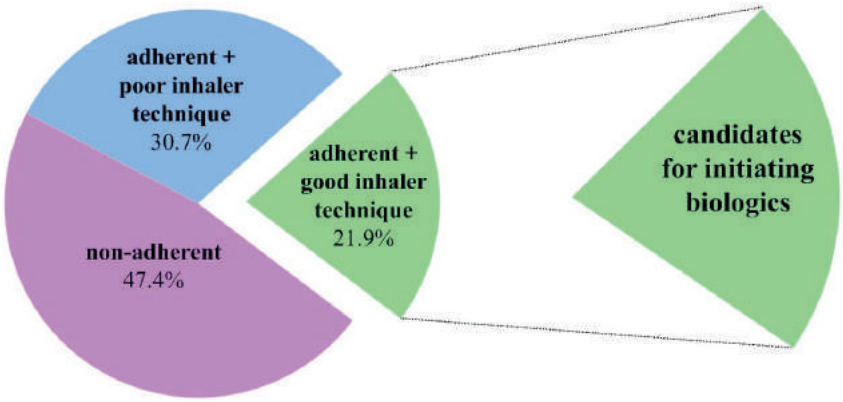

Figure 2. Therapy adherence and inhaler technique in GINA 4-5 asthma patients who use high doses of oral corticosteroids. From a large pharmacy database, 274 patients were identified with severe or uncontrolled asthma using high doses of oral corticosteroids. Of these 78.1% were considered non-adherent or having poor inhalator technique, only 21.9% were truly refractory to inhaled asthma therapy. Adherence rates were derived from prescription refills; inhaler technique was verified by pharmacists in a sample of 60 adherent patients.

Table 2. Characteristics of patients with severe or uncontrolled asthma using high cumulative doses of oral corticosteroids

Demographics	**n=274**[†]	
Age (yr) – med. IQR	67	59-78
Male sex – no.%	84	30.7%
BMI (kg/m^2) – med. IQR *(n=171)*	25	23-30
Current smoker – no.% *(n=267)*	13	4.9%
Pack years (PY)[‡] – med. IQR *(n=271)*	0	0-1
Asthma features		
Allergy symptoms[§] – no.% *(n=260)*	156	60%
Nasal polyps – no.% *(n=262)*	74	28.2%
Treating physician *(n=267)*		
General practitioner – no.%	66	24.7%
Pulmonologist – no.%	201	75.3%
Asthma control		
ACQ-6 score[¶] - med. IQR	1.67	0.83-2.52
Rescue OCS courses in past year		
None – no.%	59	21.5%
1-2 courses – no.%	106	38.7%
3 or more – no.%	109	39.8%
Hospital admission for asthma in past year		
None – no.%	197	71.9%
1-2 admissions – no.%	57	20.8%
3 or more – no.%	20	7.3%
Medication		
Prescribed inhaled corticosteroids per day (mcg)[††] – med. IQR	750	600-1000
Total prescribed oral corticosteroid dose per year (mg)[‡‡] – med. IQR	750	510-1650

[†]Unless otherwise stated; [‡]One packyear equals smoking of 20 cigarettes per day during one year; [§]Self-reported allergy to common inhaled allergens; [¶]ACQ-6 is the 6-item Asthma Control Questionnaire; [††]Inhaled corticosteroid dose is provided as fluticasone-equivalent; [‡‡]Oral corticosteroid dose is provided as prednisone-equivalent.

Discussion

This study shows that in 2010-2011 about 30% of asthma patients with severe or uncontrolled asthma (7% of the total asthma population) used high cumulative doses of OCS. Given the median prednisone-equivalent dose of 750 mg/year these patients were at risk of serious adverse effects in the short and long term [5,11]. However, 78% of these patients were considered to have either poor therapy adherence or inadequate inhaler technique, or both, which may have contributed significantly to OCS overuse. Therefore only 22% of the patients with high OCS use were regarded definite candidates for initiating therapy with biologics.

In our study, 30% of patients with severe or uncontrolled asthma were exposed to high cumulative doses of OCS. Other studies found slightly different prevalences. A recent systematic review on the use and health-related adverse effects of systemic corticosteroids in asthma elegantly summarized the findings of 129 studies addressing this topic [1]. For patients with difficult-to-treat or severe asthma, short-term OCS was used in 46–93% of patients over a 1-year period, while chronic OCS use ranged from 33–65% in five studies in patients with moderate-to-severe or severe asthma. A study from Germany in asthma patients treated with high-dose ICS/LABA showed that 22% used ≥1 OCS prescription in 1 year [12]. Another study from the U.S. found that 23% of GINA 4-5 asthma patients could be classified as high OCS users at some point during an average follow-up of 40.8 months, with high OCS use defined as ≥450mg prednisone-equivalent in a 90 days-period [13]. An Australian study reported high OCS use defined as ≥1 g prednisone-equivalent/yr in 10% of asthma patients on high- dose ICS/LABA [14]. Such differences in reported prevalences of OCS using asthma patients are not surprising, and may relate to differences in population, definitions of OCS use or management strategies.

Our study shows that 47% of high OCS users were non-adherent to inhaler therapy, which is in line with previous reports showing similar disappointing rates, ranging from 43% to 65% [14-18]. Still, when checking inhaler proficiency in a representative sample of 60 adherent patients, more than half (60%) were not able to use their inhaler correctly. Our finding of poor inhaler technique is slightly lower than that from another recent study, in which critical inhaler technique mistakes were made in 70% to 87% of patients, depending on the inhaler device [11]. Lastly, our findings of 22% of patients being adherent and showing good inhaler technique are consistent with the findings of another study showing that after an educational program of adherence and inhaler technique assessment, 27% of patients were truly refractory to therapy [19]. Overall, the observations in this study are important and clinically relevant, since it shows that

in the majority of patients with severe asthma and high OCS use, at least one major modifiable factor can be identified that is likely to contribute to overuse of OCS which should be addressed before biologic therapy is considered in these patients.

The present study may have some limitations. First, the prevalence of high OCS users may have been underestimated for several reasons such as differences between responders and non-responders to the questionnaires in adherence rates (lower in non-responders) or other factors such as ongoing allergen exposure or uncontrolled co-morbidities that were not taken into account. Second, our study was confined to the Dutch population, which may limit generalizability to other countries. And lastly, it is likely that OCS overuse is not restricted to patients with severe or uncontrolled asthma and also occurs in patients with less severe disease (e.g. GINA step 2-3) [1].

The strengths of this study are the large number of representative patients in the pharmacy database, the availability of clinical data derived from questionnaires, the availability of therapy adherence data, as well as the assessment of inhaler technique in a representative sample. Further, we were able to compute the cumulative dose of OCS therapy, which increased the accuracy of assessing the prevalence of patients excessively exposed to OCS and thus the population at risk for adverse side effects.

The possible reasons for OCS overuse in asthma patients are numerous. However, the most obvious and common reason is that many patients are under-treated with ICS/LABA, due to non-adherence to treatment or inadequate inhaler technique [18, 20]. These patients are likely to require much less OCS, if these factors were addressed. This is also illustrated by the large placebo effect observed in many controlled trials with oral steroid-sparing biologics [7-9]. Another reason of OCS overuse may be that these drugs are prescribed inappropriately for non-steroid responsive conditions, including non-type 2 asthma, remodeled airways without active inflammation, or symptoms of co-morbidities such as obesity, dysfunctional breathing, or bronchiectasis [21,22]. Finally, some asthma patients may still use high cumulative doses of OCS because they are not recognized as high OCS users and are not referred to an asthma specialist. This is illustrated by the present study in which 1 in 4 patients with high OCS use were not monitored by a pulmonologist.

This study has important clinical implications. Patients who require high doses of OCS, either recurrent short courses or maintenance treatment, should always undergo a thorough clinical assessment, including an evaluation of adherence, inhaler technique, exposures to asthma triggers and comorbidities [23-25]. If not done before, they should also undergo trial therapy with long-acting muscarinic antagonist or macrolides. Patients that are still refractory to therapy despite all these measures and who show

clear signs of type 2 airway inflammation should be eligible for biologic therapy. This also includes chronically poor adherent patients who carry a very large burden of the disease (e.g. patients admitted in ICU, frequently admitted to the ward, or already suffering from very severe OCS-induced side effects) to whom all efforts available have been provided.

In summary, our study shows that almost one third of GINA step 4-5 asthma patients in the Netherlands were exposed to high and potentially harmful cumulative doses of OCS in the pre-biologic era. Eighty percent of these patients were considered to be non-adherent to inhaled asthma treatment or to have inadequate inhaler proficiency, two major factors that are known to contribute to poor asthma control and could be improved. OCS use could probably have been reduced in a proportion of patients if these issues had been addressed. Physicians should therefore not prescribe expensive biologics to patients with high OCS use until they have thoroughly verified that inhaled ICS therapy is being used in an adequate and appropriate manner.

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Chapter 4

Long-term therapy response to anti-IL-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, severe asthma patients 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 severe asthma patients, 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 is limited data about long-term effects of anti-IL-5 treatment in severe asthma patients 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 ≥3 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 <50 ppb, 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/m²	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 >50 ppb - %	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%
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.

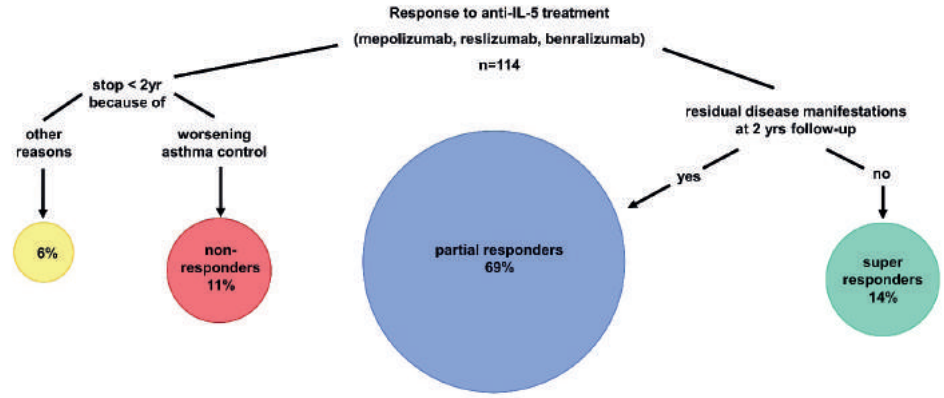

Figure 1. Prevalence of super-responders, partial responders and non-responders after 2 years of treatment with anti-IL-5 biologics for severe eosinophilic asthma. In this observational cohort study 11% of patients could be labelled as non-responders, 69% as partial responders and 14% as super-responder 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 year	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 patients switched because of adverse effects (5%).

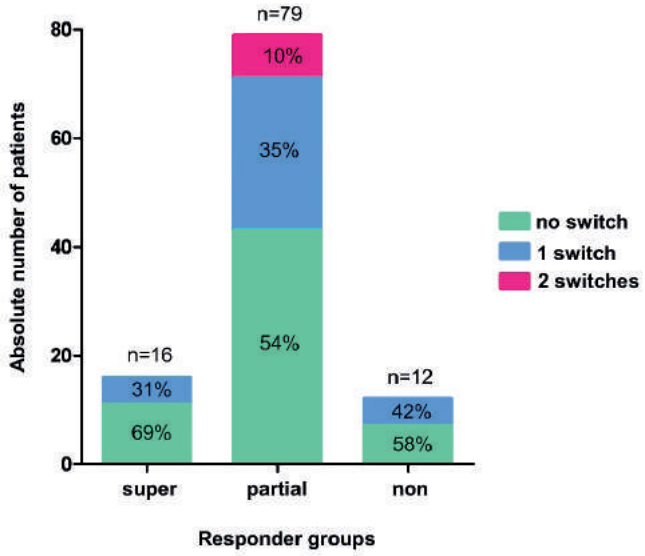

Figure 2. Frequency of switches between anti-IL-5 treatments in the different response groups. Figure 2 shows the number of switches between anti-IL-5 treatments in super-responders, partial responders and non-responders. There was no significant difference in the number of switches between the different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

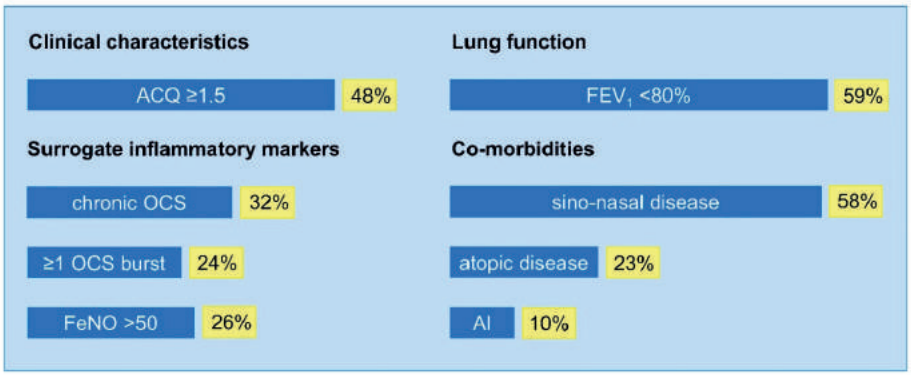

Figure 3. Residual disease manifestations in partial responders after 2 years anti-IL-5 treatment. OCS bursts were recorded <3 months before 2-years follow-up. Sino-nasal disease is uncontrolled chronic rhinosinusitis, or presence of nasal polyps or chronic otitis. Atopic disease is uncontrolled allergic 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 5

Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma

Eger K, Pet L, Weersink EJM, Bel EH
Journal of Allergy and Clinical Immunology: In Practice
2021 Jul; 9(7):2913-2915

Currently, five biologic therapies have been approved for the add-on treatment of severe asthma. They all block type 2 inflammatory pathways, either by targeting immunoglobulin E (IgE) (omalizumab), the interleukin (IL)-5 pathway (mepolizumab, reslizumab, benralizumab) or the IL-4/13 pathway (dupilumab) [1]. If asthma control to one biologic is incomplete, patients often switch between treatments [2]. This can be done safely from anti-IgE to anti-IL-5's, but only limited data exist about switching from anti-IL-5 to anti-IL-4/13 biologics [3-5]. One important difference between these two classes of biologics, is that anti-IL-5's induce a profound decrease in blood eosinophil counts, whereas anti-IL-4/13 biologics induce a transient increase in blood eosinophils as shown by the phase 3 studies in which 4-14% of patients developed predominantly asymptomatic blood eosinophilia [1,6,7]. In this case series, we describe four patients who developed unexpected eosinophilic complications after initiation of dupilumab. All were previously treated with an anti-IL-5 biologic for oral corticosteroid (OCS)-dependent asthma. While most of them had been able to reduce or discontinue prednisone use during anti-IL-5 treatment, three were still OCS-dependent, while all suffered from refractory sino-nasal disease and/or poor lung function with high levels of exhaled nitric oxide, prompting a trial with dupilumab on the assumption of an activated IL-4/13 pathway.

The first patient (female, 59yr) switched from benralizumab to dupilumab, and soon developed worsening of chronic sinusitis symptoms. Despite intensifying her maintenance prednisone treatment from 10 to 20 mg/day, symptoms worsened and she developed dyspnea and fever. Blood eosinophil counts had increased from 108 to 5080 cells/μL and chest CT revealed diffuse bilateral consolidations (Figure 1). Bronchoalveolar lavage showed 6% eosinophils (despite prednisone), a negative Galactomannan assay and fungal culture, and a few Haemophilus influenzae colonies. Serologic tests for common parasitic infections were negative. We diagnosed her with eosinophilic pneumonia, increased prednisone to 60 mg/day and discontinued dupilumab (Table I). Shortly after, she developed an acute coronary syndrome followed by cardiac arrest with return of spontaneous circulation after twenty minutes of cardiopulmonary resuscitation. A coronary angiogram showed multiple distal occlusions and anticoagulation therapy was initiated. One week after discharge from the ICU, she developed focal unilateral neurologic deficits due to multiple ischemic cerebrovascular events. Antiphospholipid and anti-nuclear cytoplasmic antibodies (ANCA) were negative, and cardiac MRI did not show myocarditis or intracardiac thrombus formation. Fortunately, she gradually recovered, prednisone dose was tapered to 10 mg/day and benralizumab was restarted later. Currently, she still suffers from dyspnea on exertion.

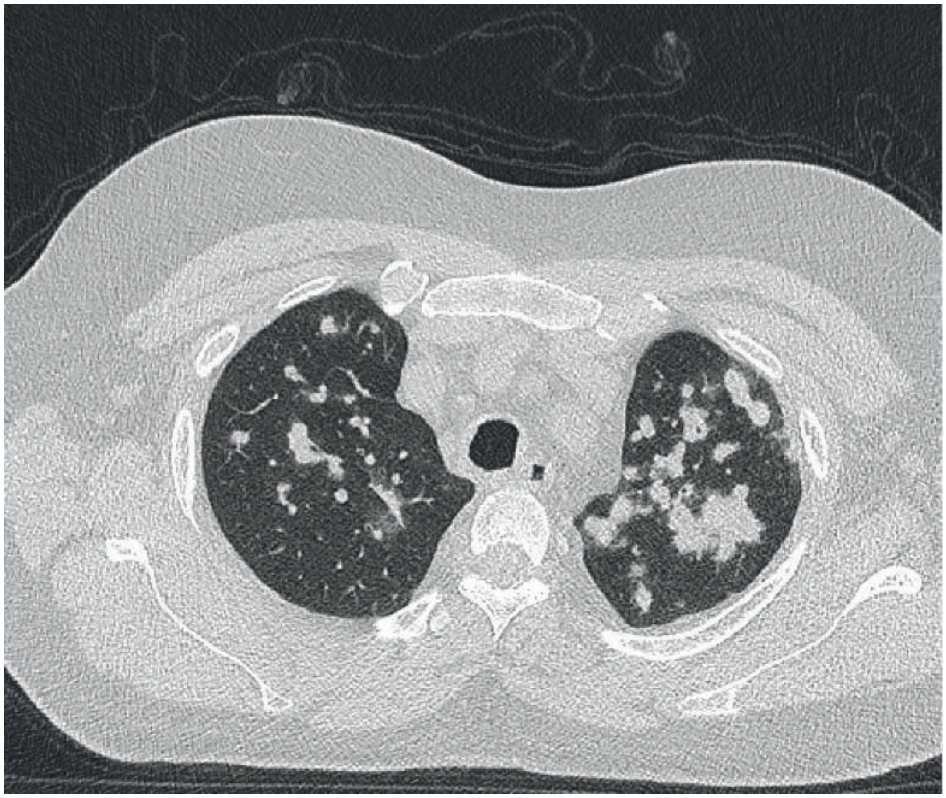

Figure 1. Eosinophilic pneumonia after switching from anti-IL-5 treatment to dupilumab. Chest CT-scan showing bilateral pulmonary consolidations in the first patient with severe asthma who developed hypereosinophilia after switching from an anti-IL-5 biologic to dupilumab.

The second patient (male, 35yr) switched from reslizumab to dupilumab. He had eliminated prednisone six months earlier. Based on our previous experience we closely monitored eosinophil counts. Although he initially reported excellent improvement of sino-nasal symptoms, his asthma relapsed in full force after the third administration of dupilumab, with eosinophil counts up to 1020 cells/µL. Immediately, prednisone 30 mg/day was restarted, but his clinical condition worsened and blood eosinophils continued to raise to nearly 5000 cells/µL. We then decided to restart reslizumab treatment and only then his asthma stabilized. Prednisone dose could be tapered but sino-nasal blockage recurred.

The third patient (female, 47yr) switched from reslizumab to dupilumab as well, and also showed substantial improvement of sino-nasal symptoms initially. However, when tapering maintenance prednisone dose from 7.5 to 5mg/day she experienced serious worsening of her asthma and her blood eosinophils counts increased from 90 to 1100

cells/μL. Having learned from the two earlier cases, we swiftly increased her prednisone dose, discontinued dupilumab and initiated benralizumab. Soon thereafter her asthma improved, but sino-nasal symptoms recurred.

The fourth patient (female, 63yr) switched from benralizumab to dupilumab after a washout period of one year. Her asthma had not improved on anti-IL-5 therapy, but showed good response to dupilumab. Eosinophil counts stayed low and she cautiously tapered her prednisone (30 to 22,5 mg/day). After eight administrations of dupilumab she suddenly developed dysarthria and left sided neurologic deficit as a result of a minor stroke. She did not report any asthma symptoms, but eosinophils had abruptly risen to 3940 cell/μL and a CT scan showed new bilateral pulmonary consolidations. We immediately increased her prednisone dose, discontinued dupilumab, and started high-dose (300 mg) mepolizumab on the assumption of a flare of ANCA-negative eosinophilic granulomatosis with polyangiitis (EGPA). Currently, the patient's asthma is stable, but she still has minor neurological sequelae.

These cases illustrate that greatly elevated blood eosinophil levels after anti-IL-4/13 initiation are not always benign. Two of our patients developed life-threatening events and two others acute severe asthma worsening. Transient eosinophilia is commonly observed after initiation of dupilumab, but is mostly asymptomatic and probably due to inhibited trafficking of eosinophils to the tissues resulting from reduced chemotaxis [6,8]. Several cases have been reported about dupilumab-induced hypereosinophilia accompanied by respiratory symptoms or pulmonary infiltrates, and one case of a patient who clinically deteriorated and required high-dose prednisone after switching from anti-IL-5 to anti-IL-4/13 [3,6,9]. These cases recovered with OCS only, which was not the case in our patients.

The reason why our patients developed these severe events after switching from anti-IL-5 to anti-IL-4/13 is not completely understood. Although patients 2 and 3 did not strictly meet the criteria, we hypothesize that our patients may have originally suffered from a latent ANCA-negative EGPA, previously misdiagnosed as severe eosinophilic asthma with high levels of blood eosinophils masked by OCS maintenance therapy (Table I). By switching to anti-IL-4/13, anti-IL-5's were discontinued without supplementing OCS to original doses. Subsequently, the anti-IL-5-induced eosinopenia gradually wore off, while at the same time anti-IL-4/13 concomitantly had an eosinophil-elevating effect. These events may all have contributed to a very high eosinophil count with a subsequent flare of EGPA, including eosinophilic tissue infiltration and end-organ damage. Although no end-organ damage occurred in patients 2 and 3, we observed a similar pattern of rapid clinical deterioration with a concomitant sharp increase in eosinophils as in patient 1, so we acted quickly before organ damage would

occur. Clearly, treatment with dupilumab was not able to reverse this deterioration. The fourth patient had stopped anti-IL-5 one year before anti-IL-4/13 initiation. Although OCS were tapered very slowly, tapering below a certain dose may have triggered hypereosinophilia and associated complications.

What can we learn from these four cases? First, one should always keep in mind that patients with severe asthma who are OCS-dependent can have underlying (ANCA negative) EGPA. Second, on rare occasions anti-IL-4/13 biologics like dupilumab may induce hypereosinophilia, with sudden deterioration of asthma, tissue infiltration by eosinophils and EGPA-like symptoms such as thromboembolic events. Therefore, our current strategy is to stop dupilumab and (re)start anti-IL-5 therapy if eosinophils rise >1000 cells/L and asthma symptoms worsen. Finally, eosinophilic complications may occur after switching from an anti-IL-5 to an anti-IL-4/13 monoclonal despite an initial favorable response. This illustrates that activated IL-5 and IL-4/13 pathways can simultaneously contribute to airway inflammation in patients with severe asthma, implying that only combined blockage of the two pathways will result in optimal disease control in these patients. This could be achieved by treating patients with two biologics at the same time, but ideally the next generation of biologics for asthma will target both pathways so that serious complications as described in these cases will never occur again.

Table I. Asthma outcome parameters pre-anti-IL-5 treatment and pre- and post-initiation of dupilumab

	patient 1	patient 2	patient 3	patient 4
age (yr)	59	35	48	63
sex (F/M)	F	M	F	F
pre-anti-IL-5 treatment				
asthma exacerbations (n/yr)	"frequent"	>10	"frequent"	"frequent"
ACQ score	>4	>4	>2	>3
prednisolone (mg/day)	15	40	40	32,5
FEV_1 (% pred)	58%	38%	54%	68%
blood eosinophils (cells/μL)*	1190	1670	2200	760
FeNO (ppb) *	159	>300	221	n/a
total IgE (IU/L)	1663	753	366	96
specific IgE to aspergillus (IU/L)	<0.35	1.63	0.37	0.61
ANCA IFT screening	negative	negative	negative	negative
successive biologic treatments	mepolizumab benralizumab	mepolizumab reslizumab benralizumab	mepolizumab reslizumab	mepolizumab reslizumab benralizumab
pre-dupilumab†				
asthma exacerbations (n/yr)	1	2	3	2
ACQ score	2.00	4.17	2.83	1.17
prednisolone (mg/day)	5	0	7.5	32.5
FEV_1 (% pred)	84%	35%	30%	43%
blood eosinophils (cells/μL)	100	500	90	60
FeNO (ppb)	39	112	64	205
post-dupilumab‡				
asthma exacerbations (y/n)	no	no	no	no
ACQ score	2.50	1.33	0.17	0.00
prednisolone (mg/day)	10-20	0	5	22.5
FEV_1 (% pred)	n/a	n/a	n/a	71%
blood eosinophils (cells/ μL)	5080	4864	1010	3956
FeNO (ppb)	n/a	n/a	n/a	19
complications and acute therapies				
rapid asthma worsening (y/n)	yes	yes	yes	no
cardiovascular events (y/n)	yes	no	no	yes
pulmonary infiltrates (y/n)	yes	n/a	n/a	yes
prednisolone (mg/day)	60	30	20	30
anti-IL-5 therapy	no	reslizumab	benralizumab	mepolizumab¥

*highest historical eosinophil counts and FeNO levels before the initiation of anti-IL-5 biologics; †most recent values before initiation of dupilumab; ‡most recent values before acute therapy of adverse events; ¥mepolizumab 300 mg s.c. (high dosage). Abbreviations: *ACQ*, asthma control questionnaire; *ANCA IFT*, anti-neutrophilic cytoplasmic autoantibody immune fluorescence test; *FEV_1*, forced exhaled volume in 1 second; *IgE*, immunoglobulin-E; *IL-5*, interleukin-5; *FeNO*, fractional exhaled nitric oxide; *n/a*, not available; *OCS*, oral corticosteroids.

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Reply to "The immunology of switching biologics in severe eosinophilic asthma patients"

We appreciate the response from Spadaro *et al*. concerning our recent publication 'Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma' [1,2]. The authors list a number of possible immunological mechanisms that might have contributed to the eosinophilic complications we observed in our patients. Currently, we can only speculate about the underlying pathophysiology of these complications. The proposed mechanisms of the authors are plausible. However, we believe that the lack of sufficient immunosuppressive treatment (oral glucocorticoids or other) in an active underlying eosinophilic disease (e.g. eosinophilic granulomatosis with polyangiitis) may be sufficiently explanatory for the events in our patients. This hypothesis is supported by the observation that in all our patients symptoms could be readily suppressed after resuming the treatment with (the same dose) of anti-IL-5. Nonetheless, the letter from Spadaro *et al*. is of great value for generating hypotheses. It is clear that we still have much to learn about the immunology of switching between biologics for severe asthma. More insight into the pathogenesis as well as additional real-world data may assist in identification of patients at risk for severe eosinophilic complications. Until then, close monitoring of patients switching from anti-IL-5(R) biologics to dupilumab remains essential.

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Part II

Evaluation of severe asthma treatment during the COVID-19 pandemic

Chapter 6

Asthma and COVID-19: do we finally have answers?

Eger K, Bel EH
European Respiratory Journal
2021 Mar 4; 57(3):2004451

The 2019 coronavirus disease (COVID-19) pandemic has already claimed the lives of nearly 1.5 million people and the virus is continuing to spread across the world [1]. The disease can affect anyone, and although SARS-CoV-2 infection leads to mild COVID-19 in the majority of cases, the proportion of patients developing severe pneumonia is of great concern.

It is now well-recognized that older age, obesity, cardiovascular disease and diabetes are risk factors of poor COVID-19 outcome [2–4]. What is not yet clear is whether chronic respiratory diseases like asthma are amongst the risk factors as well. The many studies that have addressed this question show discrepant results and point towards numerous factors that may play a role in the susceptibility and severity of COVID-19 in asthma patients [5–10]. These include the severity of asthma itself, the asthma phenotype (allergic or non-allergic), asthma medication (corticosteroids or no corticosteroids), and co-morbidities [11–15]. Because of this complex interplay between numerous factors involved, there is a need for large-scale studies that allow adjustment for confounders, making it possible to evaluate the true impact of asthma on the susceptibility and outcome of COVID-19.

This is exactly the approach taken by Choi *et al*. and Izquierdo *et al*. in the two real-world studies in this issue of the European Respiratory Journal [16,17]. While Choi *et al*. included all COVID-19 cases in Korea (n=7,590) by using a national claims database, Izquierdo *et al*. analyzed medical record data from 71,182 patients with asthma who attended medical services from a region in Spain. Choi *et al*. found a higher frequency of asthma in the COVID-19 population compared to the general population (2.9 vs 1.6-2.2%), while Izquierdo *et al*. found a higher frequency of COVID-19 amongst asthma patients compared to the general population (1.41 vs 0.86%). In addition, Izquierdo *et al*. showed an even higher incidence of COVID-19 in patients on biologic therapy (2.31%). Thus, both studies suggest that the susceptibility for contracting COVID-19 in asthma patients is higher than in the general population, especially in those with severe asthma on biologic therapy.

Regarding the severity of COVID-19, Izquierdo *et al*. reported equal hospitalization rates in asthma and non-asthma patients with COVID-19 (in both cases 26%). Likewise, Choi *et al*. found that COVID-19 severity as illustrated by ICU admission rate and duration were similar between COVID-19 patients with and without asthma. Although mortality rates were higher in patients with asthma, asthma and asthma severity did not show to be significant predictors of COVID-19 related mortality after adjustment for age, sex and co-morbidities. A higher prevalence of ICS users in patients who were hospitalized for COVID-19 was found by Izquierdo *et al*., but Choi *et al*. did not find any association between asthma medications and COVID-19 outcome.

The studies by Choi *et al*. and Izquierdo *et al*. are both unique and important because of their impressive sample size and innovative approach (big data analytics and artificial intelligence in the study by Izquierdo *et al*.). But have these large-scale studies provided us with definitive answers as to whether asthma, the severity of asthma and asthma medications affect COVID-19 susceptibility and severity? The higher incidence of COVID-19 among asthma patients reported in both studies is more or less consistent with other large (but smaller) studies [8,18–20]. However, there are still some outstanding issues that may have influenced the results. First, the method by which asthma was diagnosed was very strict in the study by Choi *et al*. and rather vague in the study by Izquierdo *et al*., possibly leading to under- or over-diagnosis, respectively. This may also explain differences in proportions of patients not using ICS between the two studies (23% vs 41%). Another bias factor may have been the methods by which COVID-19 was diagnosed. Choi *et al*. exclusively included PCR confirmed COVID-19 cases, while Izquierdo *et al*. also included patients with suspected COVID-19 based on clinical parameters. In addition, infection rates may also have been affected by testing policies or shielding advices, for example, if older patients, patients with co-morbidities like asthma, or patients with more severe symptoms tested more frequently or better protected themselves. Thus, with such inaccuracies in case definition and variations in local conditions, it remains difficult to determine with certainty whether asthma patients are more susceptible to getting COVID-19 or not.

How about the risk of poor outcome or death from COVID-19? Severity and outcome of COVID-19 are highly dependent on age, as children experience less severe COVID-19 than elderly people [22]. Age is therefore an important confounder in the assessment of risk of contracting severe COVID-19. Izquierdo *et al*. showed that asthma patients without COVID-19 were younger and more likely to have eczema and rhinitis, while those with COVID-19 were older and more likely to have co-morbidities like hypertension and diabetes. These results could very well be confounded by age. Choi *et al*. solved this issue by adjusting for age and co-morbidities in a multivariate analysis, which would have been of additive value in the study by Izquierdo *et al*.

What do the two studies teach us about safety of asthma medication, in particular inhaled corticosteroids with respect to COVID-19 susceptibility and outcome? There is much debate about the risk-increasing or protective effects of asthma medication in the course of COVID-19 disease [23]. In such risk-assessment, asthma severity and phenotype are important confounders. Choi *et al*. found higher health-care related costs in patients using oral short-acting beta agonists (SABA). However, less than 4% of patients used oral SABA in the 2 months before COVID-19 diagnosis, suggesting that not oral SABA itself, but other factors, such as the type of patient that is prescribed oral SABA, played a role in these increased costs. Not surprisingly, regression analysis

showed that asthma medications were not independently associated with poor outcome of COVID-19. Choi *et al*. also found a longer hospital stay in patients on Step 5 treatment (defined as ≥ 90 days oral corticosteroids in the previous year), but firm conclusions cannot be drawn as only 4 patients were on Step 5 treatment. Izquierdo *et al*. conclude that ICS use is "safe", because ICS users in their study were less frequently hospitalized for COVID-19 than non-ICS-users. This finding is however in contrast with a recent observational study in the UK showing an association between higher ICS doses and risk of COVID-19 related death in asthma patients [13]. The studies by Choi *et al*. and Izquierdo *et al*. did not take dosage of ICS into account, which may partly explain the discrepancy between the three studies regarding the influence of ICS use on COVID-19 outcome.

How about the use of asthma biologics and the risk of COVID-19? Currently available asthma biologics block pathways of type 2 inflammation. This type of inflammation, in particular allergic inflammation, has been suggested to have a protective effect through down-regulating the angiotensin converting enzyme (ACE)2 receptor used by the virus to enter host cells, or hypothetically, by counterbalancing the exaggerated anti-viral immune response observed in severe COVID-19 patients [24,25]. Izquierdo *et al*. analysed a large number of patients on biologic therapy (n=865), and found a relatively high incidence of COVID-19 of 2.3% in these patients, while this was 1.4% in the general asthma population. Only two out of 20 infected patients on asthma biologics (10%) were hospitalized. While these numbers are small, they are consistent with other reports suggesting that there is no increased risk of a poor outcome in asthma patients on biologics [21,26].

In summary, these large-scale studies have confirmed previous findings about the risk for asthma patients to develop (severe) COVID-19. Asthma patients appear to be slightly more susceptible to contracting COVID-19, but severe disease progression does not seem to be related to medication use, including asthma biologics, but rather to older age and co-morbidities. However, no definitive conclusions can be drawn yet as many factors can influence the reported incidences of (severe) COVID-19 (Figure 1). These potential bias factors have not been taken into account in the published studies so far and therefore many questions remain unanswered. Similar large-scale, preferably multinational real-life studies with detailed information on asthma phenotype and medication usage in patients with a confirmed diagnosis of COVID-19 would be an ideal next step to further build on this new evidence.

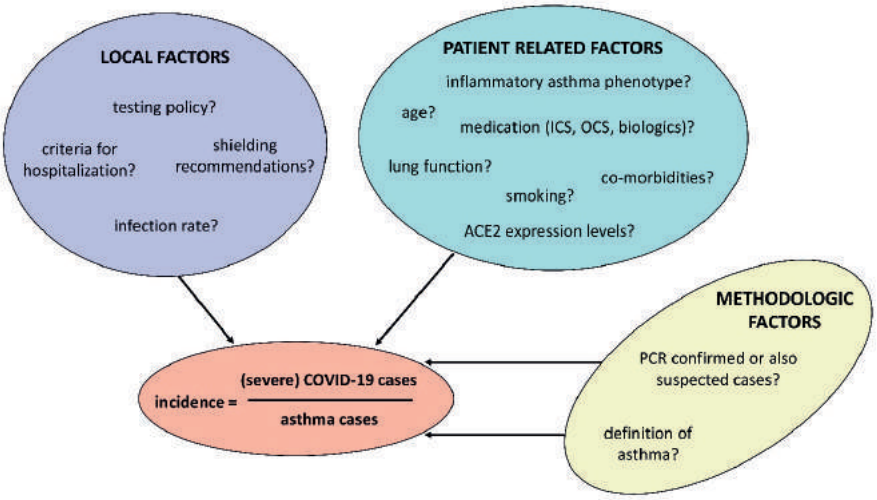

Figure 1. Factors that may influence reported incidences of (severe) COVID-19 in asthma patients The reported incidences of (severe) COVID-19 cases among asthma patients are not determined by patient-related factors alone. Also local factors and the applied methodologies can play an important role. Abbreviations: *ACE2*, angiotensin converting enzyme 2; *COVID-19*, coronavirus disease 2019; *ICS*, inhaled corticosteroids; *OCS*, oral corticosteroids.

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Chapter 7

Astma in de COVID-19 pandemie: risico of redding?

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Samenvatting

Vanaf het begin van de coronavirus disease-2019 (COVID-19) pandemie is er veel discussie geweest over de vraag of patiënten met astma al dan niet verhoogd vatbaar zijn voor infectie met het nieuwe coronavirus (SARS-CoV-2) of tot een risicogroep behoren voor een ernstig COVID-19 ziektebeloop. Op basis van de huidige literatuur lijken astmapatiënten geen verhoogd risico te hebben op een SARS-CoV-2-infectie. Daarnaast lijkt voor mild en matig astmapatiënten geen verhoogd risico te bestaan op een ernstig COVID-19 ziektebeloop. Ernstig astmapatiënten hebben daarentegen mogelijk wel een verhoogd risico op COVID-19 gerelateerde mortaliteit. Wereldwijd wordt een opvallende afname van (ernstige) astma exacerbaties gerapporteerd gedurende de pandemie, waarschijnlijk onder andere als gevolg van verminderde transmissie van andere virussen door de coronamaatregelen. Type 2 inflammatie en inhalatiecorticosteroïden hebben mogelijk een beschermend effect bij een SARS-CoV-2-infectie. Ook het gebruik van de astma biologicals lijkt veilig. Het wordt derhalve geadviseerd om ook tijdens de COVID-19 pandemie astmamedicatie (inclusief biologicals) voor te blijven schrijven volgens de geldende richtlijnen.

Introductie

Eind december 2019 wordt in de miljoenenstad Wuhan een cluster van patiënten gesignaleerd met symptomen van een longontsteking van onbekende oorzaak. Niet lang daarna wordt de verwekker geïdentificeerd: het nieuwe coronavirus *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). Op 11 maart 2020 stelt de World Health Organisation (WHO) dat er sprake is van een coronavirus disease (COVID-19) pandemie. Klinische manifestaties van SARS-CoV-2-infectie variëren van milde bovenste luchtwegklachten tot ernstig respiratoir falen met noodzaak tot invasieve beademing [1]. Inmiddels is een aantal risicofactoren voor een ernstig beloop van COVID-19 geïdentificeerd, waaronder het mannelijk geslacht, hogere leeftijd, obesitas, cardiovasculaire ziekte en diabetes [1,2]. Aan het begin van de pandemie stelt de WHO dat ook patiënten met een obstructieve longziekte tot deze risicogroep behoren [3]. Nu ruim een jaar later is er inderdaad toenemend bewijs dat COPD een risicofactor vormt voor een ernstig beloop van COVID-19 [4,5]. Het is echter de vraag of dit ook geldt voor astmapatiënten. Alhoewel patiënten met astma een verhoogde vatbaarheid hebben voor virusinfecties en daarnaast risico lopen op exacerbaties geluxeerd door virusinfecties, gaat dit wellicht niet op bij een SARS-CoV-2-infectie. Mogelijk hebben bepaalde vormen van luchtweginflammatie en gebruik van inhalatiecorticosteroïden zelfs een beschermend effect. In dit artikel zullen de meest recente inzichten worden besproken ten aanzien van de risico's van COVID-19 bij astmapatiënten, bijdragende factoren zoals fenotype en medicatie, als ook de neveneffecten van een lockdown op de astma populatie.

Vatbaarheid voor SARS-CoV-2-infectie

Aan het begin van de pandemie wezen de eerste Chinese onderzoeken richting een opvallende ondervertegenwoordiging van patiënten met astma onder COVID-19 patiënten [6]. In diezelfde periode publiceerde het Amerikaanse Center for Disease control (CDC) daarentegen bevindingen vanuit 14 staten, waarbij juist een hoge astma prevalentie (17%) werd gerapporteerd onder patiënten met COVID-19 [7]. Deze tegenstrijdige berichten markeerden het begin van een reeks van studies met wisselende uitkomsten over de prevalentie van astma onder COVID-19 patiënten, waarbij sprake bleek van grote geografische verschillen. Dit maakte het moeilijk om eenduidige conclusies te trekken [9].

Recentelijk boden twee grote meta-analyses van Sunjaya *et al*. en Terry *et al*. meer inzicht [10,11]. Sunjaya *et al*. includeerden 57 studies met in totaal bijna 600.000 patiënten, terwijl de analyse van Terry *et al*. ruim een miljoen patiënten omvatte, afkomstig uit 150 studies.

Vervolgens vergeleken de auteurs de astma prevalentie onder COVID-19 patiënten met de astma prevalentie onder de algemene regionale populatie. Ook in deze studies werd geconcludeerd dat de astma prevalentie in COVID-19 populaties fors verschilt tussen regio's en dat deze prevalenties in vergelijking met de astma prevalentie van de algemene bevolking in sommige delen van de wereld hoger uitviel (vooral in studies uit de Verenigde Staten), vergelijkbaar was of iets lager uitviel (vooral in Europese studies). Sunjaya *et al.* vonden een algehele astma prevalentie van 7.46% (95% betrouwbaarheidsinterval; 6.25–8.67%) in de totale COVID-19 populatie, wat min of meer overeenkomt met de globale prevalentie van zelf-gerapporteerde astmasymptomen van 8.6% [12]. Daarnaast vonden ze op basis van een subgroep analyse van ruim 300.000 patiënten zelfs een 14% lager risico op een COVID-19 besmetting bij patiënten met astma.

Hoe zijn de geobserveerde variaties tussen de geïncludeerde studies in beide meta-analyses nu te duiden? Waarschijnlijk heeft dit te maken met meerdere factoren, waaronder de gehanteerde definitie van astma (bijv. 'zelf-gerapporteerd', op basis van medicatie gebruik of declaratiegegevens), lokaal testbeleid (mogelijk laagdrempeliger bij astmapatiënten), lokale adviezen over zelf-isolatie voor astmapatiënten, en het vaak ontbreken van matching met de referentiepopulatie (geslacht/leeftijd/etc.) [8]. Verder moet worden opgemerkt dat enkele van de geïncludeerde studies preprints betroffen. Met inachtneming van deze limitaties, concluderen Terry *et al.* dat er geen trend is naar een hogere astma prevalentie in COVID-19 populaties, en Sunjaya *et al.* dat astmapatiënten mogelijk zelfs een lager risico hebben op SARS-CoV-2-infectie.

Risico op ernstig COVID-19

Wat is nu bekend over het risico op een ernstig beloop bij SARS-CoV-2-infectie bij astmapatiënten? Het eerste wat hierover opgemerkt kan worden, is dat SARS-CoV-2 opvallend genoeg geen belangrijke trigger is voor astma exacerbaties. Hoewel van andere coronavirussen bekend is dat ze verantwoordelijk zijn voor ca. 16% van de astma exacerbaties bij volwassenen, worden exacerbaties bij SARS-CoV-2-infectie vrijwel niet gezien [13,14,15]. Over de vraag of astmapatiënten een verhoogd risico lopen op ernstig COVID-19 is wederom een grote hoeveelheid artikelen gepubliceerd. In de tot dusver grootste gepubliceerde, prospectieve cohortstudie (Bloom *et al*, Verenigd Koninkrijk, VK) werden in totaal ruim 75.000 patiënten geïncludeerd die werden opgenomen in het ziekenhuis met (hoge verdenking op) COVID-19 [16]. De auteurs vonden onder andere een hogere astma prevalentie in de studiepopulatie dan in de algemene populatie; een grotere kans op kritische zorg of ventilatoire ondersteuning bij patiënten met astma in vergelijking met patiënten zonder astma, zelfs na correctie voor leeftijd, geslacht en comorbiditeit; maar geen verhoogd risico op mortaliteit bij astmapatiënten. Dit

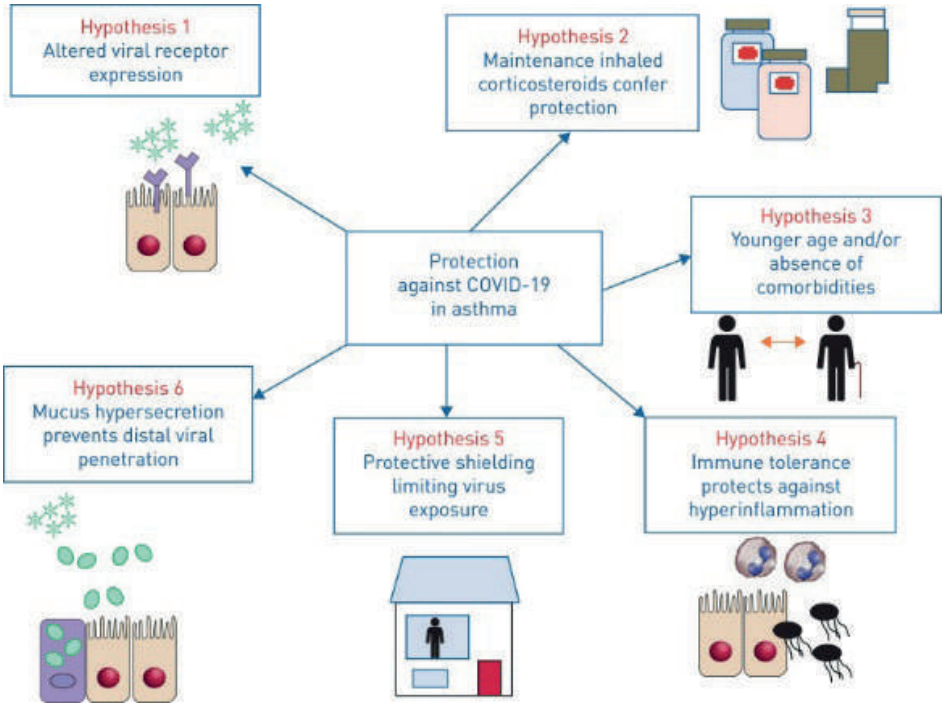
laatste is in lijn met de meta-analyse van Sunjaya *et al*. De resultaten van de reusachtige meta-analyse van Terry *et al.* en een eerder gepubliceerde meta-analyse van Liu *et al.* [17]. pleitten echter tegen een verhoogd risico op ernstig COVID-19 bij astmapatiënten en rapporteren zelfs een afname aan mortaliteit. Terry *et al*. vonden een 18% reductie aan risico op overlijden door COVID-19 bij astmapatiënten na correctie voor meerdere confounders [11,18]. Alhoewel de separate studies over astma en ernstig COVID-19 ook hier weer geen eenduidige resultaten laten zien, lijken astmapatiënten op basis van grote meta-analyses dus geen verhoogd risico te hebben op een ernstig verloop van COVID-19 en is er mogelijk zelfs sprake van een lager risico op COVID-gerelateerde mortaliteit.

Astma-fenotype

Wat zouden onderliggende mechanismen kunnen zijn van de mogelijk lagere kans op SARS-CoV-2-infectie en COVID-19-gerelateerde mortaliteit bij astmapatiënten? Verschillende hypothesen doen de ronde (Figuur 1). Ten eerste zou het kunnen dat astmapatiënten uit angst voor besmetting de regels rondom zelf-isolatie strikter naleven. Ten tweede zou type 2 inflammatie, zoals wordt gevonden bij patiënten met een allergisch of eosinofiel astma, mogelijk een beschermend effect hebben. Type 2 inflammatie wordt gekenmerkt door verhoogde inflammatiemarkers zoals interleukine (IL)-4, 5 en 13. Ook eosinofiele granulocyten zijn hierbij belangrijke spelers. Over de rol van eosinofielen bij virale afweer is nog veel onbekend, alhoewel in met name *in vitro* studies wel aanwijzingen zijn voor antivirale activiteit [19]. Een andere theorie over een mogelijk beschermend effect van type 2 inflammatie bij COVID-19 is dat een type 2 inflammatoire omgeving de antivirale interferon gemedieerde immuunrespons afremt, waardoor SARS-CoV-2 geïnduceerde hyperinflammatie wordt voorkomen [20]. Daarnaast hebben verschillende *in vitro* en *in vivo* studies aangetoond dat type 2 inflammatie invloed heeft op de expressie van de angiotensin-converting enzyme 2 (ACE2) receptor die door SARS-CoV-2 wordt gebruikt om gastheercellen binnen te dringen. Zowel allergeenexpositie, IL-13 en een type 2 genexpressie patroon zijn geassocieerd met een verlaagde ACE2-expressie in luchtwegepitheel [21,22]. Omgekeerd werd bij astmapatiënten met lage type 2 inflammatiemarkers (lage bloed eosinofielen) een verhoogde ACE2-expressie gevonden in bronchusepitheel [23]. Een derde hypothese omvat de mogelijk beschermende rol van inhalatiecorticosteroïden (ICS), waar in de volgende paragraaf dieper op zal worden ingegaan.

Zijn er ook aanwijzingen voor verschillende uitkomsten van COVID-19 tussen astma fenotypes op basis van epidemiologische studies? Alhoewel de meeste studies tot dusver geen onderscheid hebben gemaakt in astma fenotypes, is er een toenemend aantal publicaties waarbij dit wel gericht werd onderzocht. In een grote prospectieve

cohortstudie (UK Biobank) hadden patiënten met een niet-allergisch astma inderdaad een significant verhoogd risico op ernstig COVID-19 ten opzichte van patiënten zonder obstructief longlijden, in tegenstelling tot patiënten met allergisch astma [24]. Het verhoogde risico bij COVID-19 patiënten met een niet-allergisch astma werd bevestigd in een multivariate analyse op een groot Koreaans cohort, waarbij patiënten met niet-allergisch astma ook een significant langere opname duur hadden [25]. Recent zijn daarnaast twee studies verschenen die de relatie met bloed eosinofielen en het beloop van COVID-19 hebben onderzocht. In een studie van K.S. Ho *et al*. onder circa 5000 opgenomen COVID-19 patiënten in de regio New York was een maximaal gemeten eosinofielen getal van ≥200 cellen/µL tijdens opname in een multivariate analyse geassocieerd met een lager risico op mortaliteit, zowel bij patiënten met als zonder astma [26]. In lijn hiermee vonden Ferastraoaru *et al*. in astmapatiënten met COVID-19 dat een maximaal gemeten bloed eosinofielen waarde van ≥150 cellen/µL gedurende het ziektebeloop geassocieerd was met een lagere mortaliteit, evenals een pre-existent gemeten waarde van ≥150 cell/µL [27].



Figuur 1. Hypotheses gesuggereerd als verklaring voor de mogelijk lage prevalentie van astma in gehospitaliseerde COVID-19 patiënten en de relatief gunstige uitkomsten van astmapatiënten met COVID-19. Afkortingen: *COVID-19*, coronavirus disease 2019. Overgenomen van Farne *et al.* [49].

Concluderend kan gesteld worden dat er aanwijzingen zijn dat type 2 inflammatie een beschermende rol heeft bij SARS-CoV-2-infectie, en verder dat er enkele signalen zijn dat astmapatiënten met lage type 2 inflammatie mogelijk juist een hoger risico hebben op slechtere COVID-19 uitkomsten. Gezien de associatie tussen type 2-laag astma en obesitas/metabole dysfunctie, zou deze co-morbiditeit bij dit laatste ook een rol kunnen spelen [28]. Aanvullende mechanistische en epidemiologische studies zijn nodig om de invloed van astma fenotype op het COVID-19 ziektebeloop nader te onderzoeken.

Inhalatiecorticosteroïden

In het begin van de COVID-19 pandemie is er veel aandacht geweest voor de vraag of corticosteroïden, inclusief ICS, een schadelijk effect zouden hebben op het COVID-19 ziektebeloop. Inmiddels is bekend dat dexamethason bij hypoxemische COVID-19 patiënten resulteert in een lagere mortaliteit (RECOVERY trial) [29]. Wat is er nu bekend over het effect van ICS bij SARS-CoV-2-infectie? In meerdere studies is deze relatie onderzocht. Peters *et al*. analyseerden genexpressie levels van ACE2 in sputumcellen van astmapatiënten en vonden lagere ACE2 levels bij patiënten die ICS gebruikten [30]. Alhoewel nog veel onduidelijk is over de relatie tussen ACE2 expressie levels en vatbaarheid voor SARS-CoV-2, zou dit in theorie tot gevolg kunnen hebben dat astmapatiënten met ICS-onderhoudsbehandeling minder kans hebben op een SARS-CoV-2-infectie. Daarnaast zijn er aanwijzingen dat ICS de virusreplicatie kunnen remmen, met een enkele studie die daadwerkelijk een remmend effect heeft beschreven van ciclesonide op SARS-CoV-2-replicatie [31,32]. Mogelijk hebben ICS ook een remmend effect op virus-geïnduceerde cytokineproductie [33]. Deze mechanismen kunnen in theorie hyperinflammatie en progressie naar ernstig COVID-19 voorkomen.

Heeft ICS-gebruik dan ook daadwerkelijk een gunstig effect bij patiënten? De eerdergenoemde cohortstudie van Bloom *et al*. toonde een lagere mortaliteit bij astmapatiënten >50 jaar die ICS gebruikten in vergelijking met leeftijdgenoten. De meeste andere studies in astmapatiënten tonen echter geen voordelig, maar ook geen nadelig effect, van het gebruik van ICS tijdens COVID-19 [4,34].

Recent zijn de resultaten gepubliceerd van de eerste trial die hoge dosis ICS onderzocht bij patiënten met mild COVID-19. Obstructief longlijden was geen exclusiecriterium, maar recent ICS-gebruik was dat wel. Hoge dosis ICS bleek geassocieerd met een sneller herstel en minder bezoeken aan SEH of huisartsenpost. Op basis van deze studie was echter niet duidelijk of gebruik van hoge dosis ICS ook ziekenhuisopnames kan

voorkomen [35]. Grotere placebo gerandomiseerde studies zullen moeten uitwijzen of ICS progressie naar ernstig COVID-19 kan voorkomen en of ditzelfde ook geldt voor patiënten die al onderhoud ICS gebruiken.

Samenvattend kan men stellen dat geen eenduidig antwoord te geven is op de vraag of ICS-onderhoudsbehandeling bescherming biedt tegen COVID-19. Er is echter ook geen reden om aan te nemen dat ICS een negatieve invloed zouden hebben. Gezien de observatie dat recent en/of frequent prednison-gebruik bij astma geassocieerd is met ernstiger COVID-19 beloop met een hogere mortaliteit, is goede astma controle mogelijk wel van belang [2,36]. Het wordt daarom aanbevolen om ICS te blijven voorschrijven volgens de geldende richtlijnen [37].

Ernstig astma

Liggen de risico's anders voor patiënten met ernstig astma bij een SARS-CoV-2-infectie? En wat voor invloed hebben biologicals die de mogelijk beschermende type 2 inflammatie juist onderdrukken? In de meeste cohortstudies ontbreekt, net als over fenotype, ook gedetailleerde informatie over medicatiegebruik. Een aantal grote cohortstudies hebben echter wel gepoogd patiënten met ernstig astma te identificeren. Bijvoorbeeld, in hun cohort van opgenomen patiënten definieerden Bloom *et al*. ernstig astmapatiënten op basis van het gebruik van drie verschillende klassen aan astmamedicatie in de laatste twee weken voor opname (zoals langwerkende luchtwegverwijders, ICS, leukotriene-antagonisten, etc), en vonden een licht verhoogde mortaliteit ten opzichte van patiënten zonder ernstig astma. In lijn hiermee vond een eerdere grote cohortstudie met ruim 800.000 astmapatiënten een verhoogde mortaliteit bij de patiënten op hoge dosis ICS [4]. Meerdere grote, landelijke ernstig astma registers (Italiaans, Spaans, Belgisch, etc.) hebben inmiddels data gepubliceerd over SARS-CoV-2-infectie in hun ernstig astma populatie en vonden geen verhoogd risico op (ernstig) COVID-19 in patiënten behandeld met astma biologicals (omalizumab, mepolizumab, reslizumab, benralizumab of dupilumab) [36,38-40]. Opvallend genoeg hadden patiënten geïncludeerd in het Nederlands ernstig astma register (RAPSODI) die biologicals gebruiken wel een significant verhoogd risico op ernstig COVID-19 in vergelijking met de algemene Nederlandse populatie. In deze patiëntenpopulatie was echter ook sprake van frequent voorkomen van co-morbiditeiten, zoals obesitas en hart- en vaatziekten. Het is dan ook de vraag welke factoren bepalend zijn geweest voor het ernstige ziektebeloop in deze patiënten; de co-morbiditeit, het ernstig astma of de biologicals. Een andere nog onbeantwoorde vraag is wat te doen met de biological behandeling bij actieve SARS-CoV-2-infectie. Een Europese 'position paper' daterend van september 2020 stelt dat moet worden overwogen de biological tijdelijk te staken

of de volgende gift uit te stellen bij ernstige COVID-19, aangezien onbekend is wat voor invloed astma biologicals hebben op het beloop van een actieve SARS-CoV-2-infectie [41]. Dit moet echter afgewogen worden tegen het risico op een astma exacerbatie. Meer data zijn noodzakelijk om hier gefundeerd aanbevelingen over te doen. Het laatste wat nog opgemerkt kan worden over astma biologicals is dat, hoewel exacte getallen ontbreken, thuistoediening van biologicals tijdens de COVID-19 pandemie aan een opmars lijkt te zijn begonnen. Vermoedelijk zal thuistoediening ook na de COVID-19 pandemie steeds vaker toegepast gaan worden.

Al met al zijn er dus aanwijzingen dat astmapatiënten die volgens GINA stap 4 of 5 behandeld worden een verhoogd risico hebben op COVID-19 gerelateerde mortaliteit. Ten aanzien van astma biologicals zijn de bevindingen tot op heden echter voornamelijk geruststellend. Het wordt dan ook aanbevolen om biologicals te continueren gedurende de COVID-19 pandemie [37].

Astma controle gedurende de lockdown

De lockdown maatregelen hebben weliswaar een zwaar beslag gelegd op het collectieve welzijn, maar naast het terugdringen van het aantal SARS-CoV-2 besmettingen, zijn er specifiek bij de astma populatie ook andere positieve waarnemingen. Twee recent verschenen studies onderzochten de effecten van lockdown op de incidentie van astma exacerbaties. Shah *et al.* vonden in een cohort van ruim 100.000 astmapatiënten in Engeland gedurende de lockdown een significante afname van het aantal astma exacerbaties in de eerste lijn in vergelijking met de jaren voor de lockdown [42]. In aanvulling daarop vonden Davies *et al.* gedurende de eerste golf een reductie van 36% in astma-gerelateerde ziekenhuisopnames in Schotland en Wales [43]. Wat zijn mogelijke verklaringen voor deze observaties? Waarschijnlijk spelen meerdere factoren een rol. Afname aan luchtvervuiling door de reductie aan lucht- en wegverkeer, en afname aan transmissie van andere virale verwekkers door de coronamaatregelen spelen hierbij zeer waarschijnlijk een rol. Dit laatste werd bevestigd door twee studies uit Zuid-Korea en Singapore waarin gedurende de pandemie inderdaad sprake was van minder astma exacerbaties als gevolg van influenza en andere virusinfecties [44,45]. Daarnaast zijn er signalen dat patiënten meer aandacht hadden voor astma-zelfmanagement. Zo werd vaker online gezocht op 'asthma', werden video's met inhalatie-instructies frequenter bekeken en was sprake van een toename aan ICS-voorschriften vlak voor de lockdown [43,46,47].

Alhoewel er waarschijnlijk ook belangrijke nadelige effecten zijn zoals deconditionering en psychische klachten (bijv. angstklachten), hebben de coronamaatregelen wereldwijd netto een duidelijke afname aan astma exacerbaties tot gevolg gehad [48]. Het lijkt voor de hand te liggen om hier in toekomstige griepseizoenen van te leren. Verder onderzoek zal dan ook moeten uitwijzen welke preventieve maatregelen patiënten met astma en andere obstructieve longziekten na de COVID-19 pandemie kunnen nemen om virusinfecties zo veel mogelijk te voorkomen.

Conclusies

De veelheid aan literatuur die de relatie tussen astma en COVID-19 beschrijft, neemt nog wekelijks toe. Samenvattend lijkt er op basis van de huidige beschikbare studies geen verhoogd risico te bestaan op een SARS-CoV-2-infectie noch op ernstig COVID-19 bij mild en matig astma. Patiënten met ernstig astma hebben daarentegen mogelijk wel een verhoogd risico op COVID-19 gerelateerde mortaliteit. Daarnaast lijken type 2 inflammatie en inhalatiecorticosteroïden een beschermend effect te hebben bij SARS-CoV-2-infectie, terwijl er tot dusver geen signalen zijn dat de astma biologicals tot slechtere COVID-19 uitkomsten leiden. Het wordt daarom geadviseerd om astma medicatie (inclusief biologicals) voor te blijven schrijven volgens de geldende richtlijnen. Tot slot is er wereldwijd sprake van een afname van (ernstige) astma exacerbaties gedurende de pandemie, waarbij verminderde transmissie van andere virussen als gevolg van de coronamaatregelen zeer waarschijnlijk een rol speelt. Wellicht kan men hiervan leren om zo in toekomstige griepseizoenen ten minste een deel van de jaarlijkse golf van virus-geïnduceerde astma exacerbaties te voorkomen.

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Chapter 8

Poor outcome of SARS-CoV-2 infection in patients with severe asthma on biologic therapy

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Abstract

Background

It is unclear whether asthma and asthma medications increase or decrease the risk of severe COVID-19, and this is particularly true for patients with severe asthma receiving biologics.

Objectives

The aim of this study was to assess incidence and disease course of COVID-19 in patients with severe asthma on biologic therapy (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab), as compared with COVID-19 data from the general Dutch population.

Methods

COVID-19 cases were identified through a prospective ongoing survey between March 17 and April 30, 2020, among all severe asthma specialists from 15 hospitals of the Dutch Severe Asthma Registry RAPSODI. From these cases, data was collected on patient characteristics, including co-morbidities, COVID-19 disease progression and asthma exacerbations. Findings were then compared with COVID-19 data from the general Dutch population.

Results

Of 634 severe asthma patients who received biologic therapy in RAPSODI, 9 (1.4%) were diagnosed with COVID-19. Seven patients (1.1%) required hospitalization for oxygen therapy, of which 5 were admitted to the intensive care for intubation and mechanical ventilation. One patient died (0.16%). All intubated patients had ≥1 co-morbidities. Odds (95%CI) for COVID-19 related hospitalization and intubations were 14 (6.6-29.5) and 41 (16.9-98.5) times higher, respectively, compared to the Dutch population. One patient presented with an asthma exacerbation.

Conclusion

Patients with severe asthma using biologic therapy showed to have a more severe course of COVID-19 compared to the general population. This may be due to co-morbidities, the severity of asthmatic airway inflammation, the use of biologics, or a combination of these.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an ongoing crisis, and currently, second waves are a major concern in many parts of the world [1]. From the earliest observations it has appeared that the course of COVID-19 is heterogeneous, varying from asymptomatic infection to severe pneumonia in 20% of cases including 5% developing critical disease [2]. Several risk factors for poor outcome of COVID-19 have been identified, including older age, diabetes, cardiovascular disease and obesity [3-5]. Since the outbreak there has been much debate about the extent to which asthma is a risk factor for susceptibility to SARS-CoV-2 infection or severe disease progression of COVID-19, and results of studies addressing these issues vary substantially [6-12]. Recent large studies and meta-analyses however suggest that asthma patients in general may not be at risk for severe COVID-19 due to a potential protective effect of type-2 inflammation [13-17].

In most studies COVID-19 asthmatics had mild to moderate disease, and only a few reports have been published on patients with severe asthma and COVID-19 [15,18-22]. A growing number of these patients with severe asthma use monoclonal antibodies targeting immunoglobulin E (IgE), IL-5, IL-5 receptor alpha (Rα) or IL-4Rα [23]. Currently, it is unknown whether severe asthma patients who use biologics have increased susceptibility to SARS-CoV-2 infection, or increased risk of a more severe course of COVID-19. Neither is it known whether SARS-CoV-2 infection is a trigger of acute asthma exacerbations in these patients. In the present study we aimed to explore; (1) the incidence of COVID-19 cases in patients with severe asthma on biologic therapy included in the Dutch Severe Asthma Registry RAPSODI; (2) the frequency of asthma exacerbations at COVID-19 diagnosis; (3) the proportion of these COVID-19 positive patients needing hospitalization or ventilatory support; and (4) the incidences of (severe) COVID-19 and COVID-19 related death compared to the RAPSODI population not on biologic treatment and the general Dutch population.

Methods

This was a prospective study in which data on COVID-19 were collected from patients included in the Dutch Severe Asthma Registry RAPSODI (Registry of Adult Patients with Severe asthma for Optimal Disease management) as from May 2016. These patients were all diagnosed with severe asthma according ERS/ATS guidelines and included in the registry after having provided informed consent. There were no exclusion criteria for enrollment in the registry. COVID-19 cases were identified through a prospective ongoing survey between March 17th and April 30rd, 2020, among all severe asthma

specialist at the 15 RAPSODI hospitals. A COVID-19 diagnosis was defined as a positive PCR for SARS-CoV-2, typical symptoms <10 days after contact with a confirmed case, or typical symptoms with positive SARS-CoV-2 serology results afterwards. Patient characteristics including co-morbidities, as well as the course of COVID-19 from patients diagnosed with COVID-19 were collected. Information on COVID-19 in the Dutch population in the period March 1st 2020 and 30th April 2020 was derived from the Dutch National Institute for Public Health and the Environment and the Statistics Netherlands' database.[24-26] Consent for participation in this study was obtained from all COVID-19 patients. Ethical approval for the study was obtained under nr. W20_155 # 20.169.

Analysis

First we collected all cases of COVID-19 between March 1st 2020 and April 30th 2020 among patients included in RAPSODI who were treated with biologics and calculated the incidence of COVID-19 in this population. Then we assessed the proportion of these COVID-19 patients who presented with an asthma exacerbation, were admitted to the hospital, were intubated and died. Finally, we compared the incidence rates of confirmed COVID-19 cases, hospitalizations, intubations and mortality with the RAPSODI population not treated with biologics and the general Dutch population, and calculated odds ratio's. We expected only small numbers of COVID-19 cases in our study population and therefore did not plan a regression analysis for adjusting for confounders. P values <0.05 were considered statistically significant.

Results

COVID-19 incidence

At the start of the COVID-19 pandemic in the Netherlands, on March 1st 2020, the RAPSODI database contained data from 707 well-characterized patients of which 634 were treated with a biologic for asthma (19% omalizumab, 39% mepolizumab, 16% reslizumab, 19% benralizumab, 7% dupilumab) and were frequently monitored. Nine of these 634 severe asthma patients in the RAPSODI database (1.42%) were diagnosed with COVID-19, of which eight were laboratory confirmed (1.26%). Characteristics of these 9 patients are summarized in the upper panel of Table 1. Most of them were treated with an anti-IL-5 biologic (mepolizumab, reslizumab, benralizumab). Co-morbidities known to increase the risk for severe COVID-19, such as obesity, diabetes or cardiovascular disease, were present in two-thirds of cases.

COVID-19 disease course

Seven out of nine COVID-19 patients were hospitalized because of hypoxemia, requiring oxygen therapy by nasal canula or non-rebreather mask, five of these (71%) were admitted to the intensive care unit for intubation and mechanical ventilation, and one patient died (14%), as shown in the lower panel of Table 1. None of the patients received Continuous Positive Airway Pressure (CPAP), Non-Invasive Ventilation (NIV), or Extracorporeal Life Support (ECLS). Asthma symptoms (wheeze) at COVID-19 diagnosis were observed in one patient.

COVID-19 incidences compared to patients in RAPSODI not treated with biologics and the general Dutch population

Only 1 of the 73 (1.73%) patients included in RAPSODI who were not treated with biologics was diagnosed with COVID-19, which made any comparisons with the patients on biologic therapy trivial. This patients was a 50 year old male, who used maintenance prednisolone (10 mg/day), had a normal BMI and no other relevant co-morbidities. He was hospitalized for 3 days because of an ongoing exacerbation asthma. The positive PCR for SARS-CoV-2 infection was quite unexpected since he had no other symptoms typical for COVID-19.

Compared to the general Dutch population the incidence of COVID-19, hospitalization or intubation for COVID-19, and COVID-19 related mortality were higher in the RAPSODI population on biologic therapy (Table 2), with corresponding odds ratio's for contracting COVID-19 of 4.6 (95% confidence interval (CI) 2.3-9.2, p value <0.0001), for hospitalization of 14.0 (95% CI 6.6-29.5, p value <0.0001), for intubation of 40.8 (16.9-98.5, p value <0.0001), and for mortality of 5.0 (95% CI 0.7-35.8, p value 0.106).

Table 1. Clinical characteristics, treatments and outcomes in patients with severe asthma and COVID-19

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age category	60-65	55-60	55-60	55-60	60-65	55-60	45-50	65-70	45-50
Gender (m/f)	m	f	m	m	f	m	f	f	m
BMI	32	30	25	27	44	41	34	38	25
Asthma characteristics and treatment									
Asthma phenotype	early onset allergic eosinophilic	allergic	early onset allergic eosinophilic	late onset allergic eosinophilic	late onset non-allergic eosinophilic	early onset allergic eosinophilic	late onset non-allergic eosinophilic	early onset allergic eosinophilic	late onset non-allergic eosinophilic
ACQ-6 <1.5*	no	not known	yes	yes	yes	yes	no	yes	yes
FEV_1 (%pred)*	97%	not known	87%	73%	75%	78%	72%	113%	61%
Biologic	omalizumab	omalizumab	dupilumab	mepolizumab	mepolizumab	mepolizumab	reslizumab	benralizumab	benralizumab
OCS (mg/day)	5	0	0	0	0	0	7.5	0	12.5
Co-morbidities									
Known risk factors for severe COVID-19	obesity diabetes CVD	obesity diabetes CVD	none	none	obesity	obesity diabetes	obesity	obesity	none
COVID-19 diagnosis, treatment and outcome									
SARS-CoV2 confirmed	PCR	PCR	no	serology	PCR	PCR	PCR	PCR	PCR
Asthma exacerbation#	yes	no	no	no	no	no	no	no	no
OCS burst at start symptoms	yes	yes	no	no	no	no	yes	yes	yes
Admission to hospital for oxygen therapy	yes	yes	no	no	yes	yes	yes	yes	yes
Admission to ICU for intubation	yes	yes	no	no	yes	yes	no	yes	no
Days hospital admission	56	22	n/a	n/a	58	19	5	84	4
Days ICU admission	44	15	n/a	n/a	48	15	n/a	44	n/a
Death	no	no	no	no	no	yes	no	no	no

*Most recent FEV_1 or ACQ-6 score before COVID-19 infection; #Asthma exacerbation defined as wheezing, night time awakening, relieve of symptoms by bronchodilation. Abbreviations: *ACQ-6*, asthma control questionnaire – 6 item score; *BMI*, body mass index; *CVD*, cardiovascular disease; *ICU*, intensive care unit; *OCS*, oral corticosteroids.

Table 2. Incidences of COVID-19, hospitalization, intubation and death

	RAPSODI population age range 19-89yr n= 634	**Dutch population age category 20-90yr** n=13,363,687	**Dutch population age category 45-65yr** n=4,840,946
COVID-19 cases* - %	1.26%	0.28%	0.28%
hospitalization for COVID-19 -%	1.10%	0.08%	0.07%
intubation for COVID-19 - %	0.79%	0.02%	n/a
COVID-19 related deaths - %	0.16%	0.03%	0.006%

RAPSODI is the Dutch Severe Asthma Registry.*Only laboratory confirmed cases were considered for comparison with the general Dutch population. Abbreviations: *n/a*, not available.

Discussion

This study shows that the incidence of COVID-19 in 634 Dutch patients with severe asthma on biologic therapy was relatively high, and that the outcome of COVID-19 in these patients was poor. Compared to the general Dutch population with COVID-19 odds for hospitalization and intubations were 14 times and 41 times higher, respectively. A trend for a 5 times increased odds for mortality was also observed. Factors contributing to the increased severity of COVID-19 in these patients could not be determined due to the relative small number of cases, but comorbidities like obesity, severity of asthma, and the use of biologic therapy may all have played a role.

Our study is amongst the largest of 6 published reports on patients with severe asthma treated with biologics and shows the worst outcome of COVID-19. The other studies in asthma patients on biologic treatment reported cases of COVID-19, but out of a total of 19 confirmed COVID-19 patients admitted to the hospital, only 2 were intubated, and 2 died [15,18-22,38]. Compared to these other studies, the COVID-19 cases in our study were clearly more severe. We can only speculate about the causes for this higher incidence of severe cases, but one important difference was the relatively high proportion of patients in the RAPSODI population who had adult-onset asthma, were non-atopic and had been previously on chronic oral corticosteroid treatment [27].

A higher incidence of severe COVID-19 cases in our patients was however confirmed by the results from a study in unselected COVID-19 patients in one of the 15 RAPSODI hospitals in the same period [28]. In this study 198 COVID-19 patients were hospitalized because of hypoxemia, of which 75 (38%) were intubated, much less than the 71% of intubated cases among our RAPSODI patients. Based on these comparisons, we could be certain that the incidence of severe COVID-19 in the RAPSODI population was higher than expected from other studies in severe asthma patients treated with biologics or unselected COVID-19 patients.

A possible explanation for the higher incidence of severe COVID-19 cases amongst the RAPSODI patients may be the relatively high prevalence of obesity as compared to the general population (30% vs 15%), which is a known risk factor for severe COVID-19 and commonly seen in patients with severe asthma as a result of frequent OCS use [29,30]. Other reports have also suggested that co-morbidities may play an important role in severe COVID-19 progression in patients with asthma [7,9].

Still, it cannot be excluded that the use of biologics itself has contributed to a more severe course of COVID-19 in our patients. All currently available biologics for severe asthma are known to block different pathways involved in type 2 inflammation. At present, the role of type 2 immune responses, and in particular that of eosinophils in anti-viral defense against SARS-CoV-2 has not yet been elucidated [31,32]. There is some evidence that type 2 inflammation can reduce susceptibility to infection with SARS-CoV-2 and mitigate the course of COVID-19. One hypothesis is that this occurs by decreasing expression levels of the angiotensin-converting enzyme-2 (ACE-2) receptor used by SARS-CoV-2 to enter cells. Studies have shown that ACE2 receptor levels are negatively associated with Th2-gene expression, allergen exposure and interleukin (IL)-13 [33,34]. Another hypothesis is that a type 2 inflammatory milieu inhibits interferon responses, thereby preventing the hyper-inflammatory state observed in severe COVID-19 cases [17,35]. Thus, since asthma biologics block type 2 pathways, it is conceivable that they could negatively affect these potentially protective effects of a type 2 inflammatory environment [36,37].

Only one patient not on biologic therapy contracted COVID-19 in the study period, making it difficult to draw definitive conclusions about the role of biologic therapy on COVID-19 severity.

A strength of this study is that we used objective measures of severe disease (hospitalization, intubation and death) to estimate the incidence of severe COVID-19 among our asthma patients on biologic therapy, and that we were able to compare these incidences with that of the general Dutch population as well as unselected COVID-19 patients in one of the RAPSODI hospitals. A limitation of this study is the possibly underestimated incidence of COVID-19 in the RAPSODI population, because, as in other real-life studies, asymptomatic patients or those with only mild symptoms were not tested during the first COVID-19 wave. In addition, strict shielding as recommended by the Dutch Institute for Public Health and Environment and the World Health Organization, in particular for patients with chronic lung diseases, may have influenced infection rate. Still, COVID-19 incidence in the RAPSODI population was more than 4 times higher than in the general Dutch population, while the incidence of severe COVID-19 requiring hospitalization or intubation was increased even more.

Another limitation of our study is that it was not possible to assess for predictors of severe outcome and adjust for confounding factors such as co-morbidities due to the small number of COVID-19 positive cases. However, since the known risk factors for severe COVID-19 (obesity, diabetes, hypertension) are relatively common in patients with severe asthma due to high oral corticosteroid exposure it may be difficult to disentangle which risk factor is the most important for developing severe COVID: the severity of the asthma, the use of biologics or the steroid-induced co-morbidities.

Our study has clinical implications. Because patients with severe asthma on biologic therapy may have a higher risk of hospitalization and intubation, which is often associated with long-term dysfunction of vital organs and loss of quality of life, it is important to coach these patients during their self-isolation, to secure access to care and medication, including biologics, and to ensure that they will be a priority in a future vaccination program.

Conclusion

This multicenter study in 634 well-characterized patients with severe asthma on biologic therapy shows that these patients may not only be more likely to contract COVID-19 but also to develop more severe COVID-19, with higher rates of hospitalizations, intubations and death as compared to the general Dutch population. The reasons why these patients with severe asthma on biologic therapy progressed to more severe COVID-19, and why the findings of this study differ from other reports are still uncertain. Only by analyzing pooled data from multiple cohorts it will become clear to what extent patients on asthma biologics are at increased risk for severe COVID-19 and whether this would be due to the severity of asthmatic inflammation, the presence of co-morbidities, the use of biologic therapies or a combination of these.

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Chapter 9

The effect of the COVID-19 pandemic on severe asthma care in Europe – will care change for good?

Eger K*, Paroczai D*, Bacon A, Schleich F, Sergejeva S, Bourdin A, Vachier I, Zervas E, Katsoulis K, Papapetrou D, Kostikas K, Csoma Z, Heffler H, Canonica GW, Grisle I, Bieksiene K, Palacionyte J, ten Brinke A, Hashimoto S, Smeenk FWJM, Braunstahl GJ, van der Sar S, Mihălțan F, Nenasheva N, Peredelskaya M, Zvezdin B, Čekerevac I, Hromiš S, Ćupurdija V, Lazic Z, Milenkovic B, Dimic-Janjic S, Yasinska V, Dahlén B, Bossios A, Lazarinis N, Aronsson D, Egesten A, Munir AKM, Ahlbeck L, Janson C, krgat S, Edelbaher N, Leuppi J, Jaun F, Rüdiger J, Pavlov N, Gianella P, Fischer R, Charbonnier F, Chaudhuri R, Smith SJ, Doe S, Fawdon M, Masoli M, Heaney L, Haitchi HM, Kurukulaaratchy R, Fulton O, Frankemölle B, Gibson T, Needham K, Howarth P, Djukanovic R, Bel EH, Hyland M

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Submitted

Abstract

Background

The COVID-19 pandemic has put pressure on health-care services forcing the reorganization of traditional care pathways. We investigated how physicians taking care of severe asthma patients in Europe reorganized care, and how these changes affected patient satisfaction, asthma control and future care.

Methods

In this European-wide cross-sectional study, patient surveys were sent to patients with a physician-diagnosis of severe asthma, and physician surveys to severe asthma specialists between November 2020 and May 2021.

Results

1101 patients and 268 physicians from 16 European countries contributed to the study. Common physician-reported changes in severe asthma care included use of video/phone consultations (46%), reduced availability of physicians (43%) and change to home-administered biologics (38%). Change to phone/video consultations was reported in 45% of patients, of whom 79% were satisfied or very satisfied with this change. Of 709 patients on biologics, 24% experienced changes in biologic care, of whom 92% were changed to home-administered biologics and of these 62% were satisfied or very satisfied with this change. Only 2% reported worsening asthma symptoms associated with changes in biologic care. Many physicians expect continued implementation of video/phone consultations (41%) and home administration of biologics (52%).

Conclusions

Change to video/phone consultations and home administration of biologics was common in severe asthma care during the COVID-19 pandemic, and was associated with high satisfaction levels in most but not all cases. Physicians expect these changes to continue in future severe asthma care, though satisfaction levels may change after the pandemic.

Introduction

Severe asthma, affecting around 3.7% of adults with asthma in Europe, is a heterogeneous chronic respiratory disease characterized by persistent symptoms, impaired lung function and frequent exacerbations most commonly triggered by viral infections, resulting in disease worsening and increased vulnerability [1, 2]. Treatment depends on complex regimes of high-dose maintenance medications, including biologics [3]. Traditional models of care for patients with severe asthma require frequent attendance to specialist centers and review by a multidisciplinary team to assess asthma control, monitor lung function and inflammation parameters, evaluate response and adherence to medication, check for adverse effects, and dispense or administer medication such as oral corticosteroids (OCS) and biologics [4, 5].

The coronavirus disease 2019 (COVID-19) pandemic has placed major challenges on health-care services, forcing reorganization of traditional care pathways and reducing the capacity for face-to-face consultations globally [6]. The crisis created considerable challenges to maintain access to and delivery of effective severe asthma care for many vulnerable patients. Several expert-opinion papers have provided recommendations for reorganization of severe asthma care during the pandemic, though, large-scale real-world data on how physicians managed in practice and the resultant impact on severe asthma patients are lacking [7–11].

The 'Severe Heterogeneous Asthma Research collaboration, Patient-centered' (SHARP), is a Clinical Research Collaboration of the European Respiratory Society (ERS) that forms a network of severe asthma experts and patients from different European centers to promote patient-centered severe asthma research on a pan-European scale [12]. The aims of this European-wide survey-based study by SHARP are to investigate the effect of the pandemic on the organization of severe asthma care (1) from the physician-perspective; (2) from the patient-perspective, including the impact of changes in care and treatments on satisfaction with care and asthma control; and (3) to evaluate which aspects of reorganized care physicians expect to be continued in future care.

Methods

Design

This was a cross-sectional study in which a patient survey was sent to patients with severe asthma, and a physician survey was sent to severe asthma specialists. The survey was launched on 30 November 2020 and closed on 9 May 2021. Members of the

European Lung Foundation's asthma Patient Advisory Group (PAG) and representatives of national respiratory patient organizations were actively involved in the conception and design of the study (details in supplementary file 1) [13].

Survey development and setting

The surveys were developed in an iterative manner by the authors, involving physicians (severe asthma experts), psychologists and patients. The patient surveys were translated by professional translators into the native languages of the 16 countries. Physicians were asked to recruit severe asthma patients from their outpatient clinics for the patient survey, and to complete the physician survey. Both online and paper versions of the patient survey were available, while only an online version was used for the physician survey. SurveyMonkey (SurveyMonkey, Momentive Inc, USA) was used for the online survey. Paper versions of the patient survey were used if online versions were not available, and results from these paper version surveys were transferred into the SurveyMonkey system by the local research team. Data collection was anonymous.

Patient and physician selection

Patients were eligible for inclusion if they had physician-diagnosed severe asthma and had been followed up in a severe asthma clinic for at least 6 months from the beginning of the COVID-19 pandemic. Participating physicians included national leads from SHARP member countries and physicians in their Respiratory Societies, who were identified by the national leads to have significant experience treating severe asthma patients.

Survey content

The patient survey consisted of multiple-choice questions including demographics, medication use, changes in care and (biologic) treatments, patient satisfaction with any changes in care or treatments, and patient perceptions of any change in asthma control induced by changes in care or treatments. Full patient and physician surveys are included in the supplementary material (supplementary file 2 and 3, respectively). A scale ranging from 1 to 5 was used for answering questions about satisfaction, with a higher score meaning a higher level of satisfaction. 'Satisfaction with care' was then calculated as a mean of the scores of 7 questions (question 16A-G, in which 16C-G were reverse coded), 'satisfaction with changes in care' as a mean of the scores of 2 questions (16H-I), and 'satisfaction with changes to biologic treatments' consisted of the score of a single question (16J). A scale ranging from 1 to 5 was used for answering questions about patients' perceived change in asthma control, with a higher score meaning a worsening in asthma. Change in asthma control due to 'changes in care' was then calculated as a mean of the scores of 3 questions (question 17A-C) and change in asthma control due to 'changes in biologic treatment' consisted of the score of a single question

(17D). Questions 17A-D comprised statements indicating that asthma symptoms had got worse, with responses 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree. The physician survey contained multiple-choice questions about the reorganization of severe asthma care and treatments, the challenges they faced in reorganization of care, and physicians' perspectives on which of these changes may be implemented in future care. The physician survey was conducted in English.

Ethics

Approval for the study was obtained from the medical ethical board of the Amsterdam University Medical Center (W20_463 # 20.512) and the ethical boards of every individual country where there was a requirement for ethics approval for survey-based studies. All patients and physicians provided digital or written informed consent for participation in this study.

Statistical analysis

Descriptive statistics and t-tests were used for comparisons between groups. P values ≤0.05 were regarded as a statistically significant difference. Statistical analyses were performed using IBM SPSS v.25 software (IBM Corp., Armonk, NY, USA).

Results

Patient and physician participation

The physician survey was completed by 268 severe asthma specialists from 16 countries in Europe. Of 1119 returned patient surveys, 1101 were complete and included for analysis. Numbers of participating physicians and patients per country; and baseline patient characteristics of included patients are shown in Table 1.

Physician-reported changes in care during the COVID-19 pandemic

Ninety percent (242 of 268) of participating physicians reported at least one change in severe asthma care in their center during the COVID-19 pandemic, and the nature of the changes are shown in Table 2. Changes were either the result of "voluntary" physician-induced changes in reorganizations of severe asthma care, or due to "involuntary" pandemic-induced changes, mainly concerning reduced staff or resource capacity.

Table 1. Country breakdown of physician and patient respondents to questionnaires

Country	Physicians	Patients			
	n	n	Female n (%)	Use of biologics n (%)	Daily OCS n (%)
Belgium	13	102	57 (56)	86 (84)	9 (9)
Estonia	8	14	13 (93)	6 (43)	5 (36)
France	28	15	10 (67)	13 (87)	5 (33)
Greece	18	122	82 (67)	74 (60)	35 (29)
Hungary	40	110	71 (65)	71 (65)	22 (20)
Italy	31	52	38 (73)	28 (54)	13 (25)
Latvia	4	54	33 (61)	24 (44)	19 (35)
Lithuania	15	53	35 (66)	41 (77)	8 (15)
Netherlands	2	114	69 (61)	79 (69)	27 (24)
Romania	31	12	5 (42)	9 (75)	3 (25)
Russian Federation	13	55	34 (62)	11 (20)	9 (16)
Serbia	15	74	50 (68)	45 (60)	30 (41)
Slovenia	2	70	51 (73)	64 (91)	12 (17)
Sweden	9	122	60 (49)	67 (55)	34 (28)
Switzerland	19	57	25 (44)	46 (81)	19 (33)
United Kingdom	20	75	43 (57)	45 (60)	31 (41)
Total	**268**	**1101**	**676 (61)**	**709 (64)**	**281 (26)**

Number of returned physician surveys per country, and number and characteristics of participating patients per country. Data are presented as n (%). Abbreviations: *OCS*, oral corticosteroids.

Table 2. Physician-reported changes in delivery of care

Change in care	n (%)
Re-organization in care by physicians (i.e. voluntary)	
Change to video/phone consultations	122 (46)
Outpatient clinic continued with social distancing	142 (53)
Urgent consultations only	44 (16)
New patients postponed	32 (12)
Switch to home-administered biologics	102 (38)
Changes induced by the pandemic (i.e. involuntary)	
Reduced capacity outpatient clinic	109 (41)
Reduced capacity lung function lab	159 (59)
Fewer physicians available	115 (43)
Fewer nurses available	76 (28)

Changes in severe asthma care during the COVID-19 pandemic as reported by the participating severe asthma specialists (n=268). Data are presented as n (%).

Patient-reported changes in care during the COVID-19 pandemic and impact on satisfaction with care and asthma control

Of 1101 included patients, 494 (45%) experienced a change in severe asthma care. Table 3 shows the nature of these changes in care and the associated levels of satisfaction with care as well as changes in care. Patients for whom care had changed were significantly less likely to be satisfied with care compared to patients who experienced no changes in care (p <0.001). In a further analysis of only those patients who were changed to video/ phone consultations from face-to face the majority was satisfied, see Figure 1.

Table 3 also shows change in perceived asthma control. For those patients who reported a change, the mean score was 1.9 indicating that, on average, they disagreed with the three statements indicating poorer control. Reports of different types of change also showed mean levels indicating disagreement with the assertion that asthma symptoms had got worse.

Table 3. Satisfaction scores with types of change in care and asthma control

		Satisfaction with care	Satisfaction with changes in care	Effect on asthma control attributed to changes in care
	n (%)	mean (SD)	mean (SD)	mean (SD)
No change	607 (55)	4.42 (.61)*	-	-
Change	494 (45)	3.85 (.72)*	3.68 (.93)	1.90 (.84)
Phone/video consultations	212 (45)	3.96 (.67)	3.81 (.87)	1.80 (.78)
Monitored my asthma at home	24 (5)	3.55 (.76)	3.65 (.86)	2.24 (.70)
The location of my appointments was changed	43 (9)	3.90 (.68)	3.78 (.91)	1.86 (.87)
Attended alternative unit (e.g. ED)	10 (2)	3.66 (.92)	3.55 (1.28)	2.50 (1.25)
I chose to cancel appointments	61 (13)	3.60 (.74)	3.30 (1.00)	2.07 (.96)
Cancelled or postponed by clinic	117 (25)	3.79 (.74)	3.55 (.97)	1.91 (.85)

Patient-reported changes in severe asthma care during the COVID-19 pandemic and associated levels of satisfaction with care and changes in care, and patient-perceived effect on asthma control. Higher satisfaction scores indicate better satisfaction (range 1-5); higher asthma control scores indicate greater agreement with statements that changes in care induced worsening of asthma control (range 1-5, 1 = strongly disagree and 5 = strongly agree). Data are expressed as n and percentages (%), or mean and standard deviation (SD). *t (1068) = 15.82, $p < 0.001$, d = 0.96. Abbreviations: *ED*, Emergency Department.

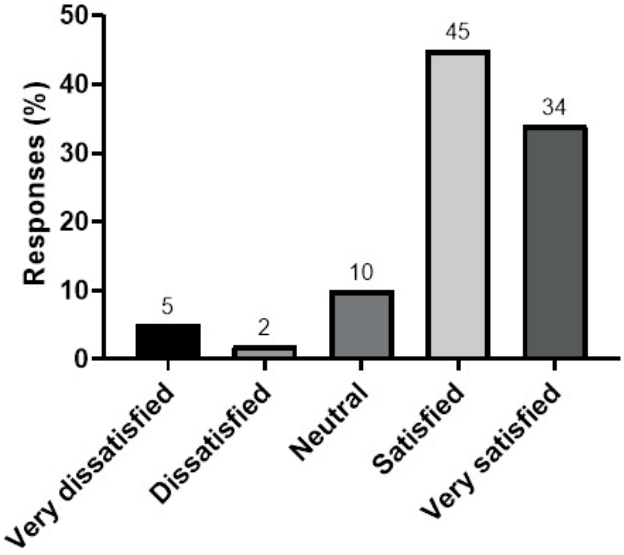

Figure 1. Satisfaction with change to video/phone consultations. A change to video/phone consultations was reported by 212 patients, of whom 207 indicated their satisfaction level with this change. Data are expressed as percentages (%).

Patient-reported changes in biologic care during the COVID-19 pandemic and impact on satisfaction with care and asthma control

Of 709 patients using asthma biologics at the start of the pandemic, 167 (24%) reported a change in their biologic treatment. The different types of changes in biologic care, and associated satisfaction ratings and impact on asthma control are presented in Table 4. Patients on biologics reporting a change in provision of biologic care were significantly less satisfied with care, than those who reported no change in provision of biologic care ($p < 0.001$). In a further analysis of patients who experienced a change in biologic care during the pandemic, the large majority of patients reported a switch to home-administered biologics. Figure 2 shows that a small percentage of patients were not satisfied with this change. Only 3 of 153 patients (2%) of patients who switched to home-administration of their biologic, agreed or agreed strongly that their symptoms had worsened because of this change.

Table 4 also shows the mean score of responses to a single statement indicating that change in biologic care produced a worsening of asthma control. On a scale ranging from 1 to 5 (in which 1 = strongly disagree and 5 = strongly agree), a mean score of 1.9 shows that on average patients who were on biologics disagreed with this statement. Ninety-two percent of those patients reporting a change in biologic treatment reported

that the change was due to home administration, and for these patients the mean was 1.76 indicating a slightly greater trend towards strong disagreement with the statement that asthma symptoms had worsened.

Table 4. Satisfaction scores with types of change in biologic care and asthma control

		Satisfaction with care	Satisfaction with changes in care	Effect on asthma control attributed to changes in biologic treatment
	n (%)	**mean (SD)**	**mean (SD)**	**mean (SD)**
No change	542 (76)	4.40 (.59)*	-	-
Change	167 (24)	3.93 (.68)*	3.72 (1.08)	1.90 (.88)
Switch to home administration	153 (92)	3.96 (.67)	3.90 (.87)	1.76 (.74)
Treatment less frequent	7 (4)	3.63 (.84)	3.93 (1.02)	2.05 (.83)
Treatment postponed	3 (2)	3.05 (.33)	3.17(.29)	3.22 (.69)
Treatment stopped	4 (2)	4.05 (.46)	3.83 (.53)	2.22 (1.57)

Patient-reported changes in biologic care during the COVID-19 pandemic and associated levels of satisfaction with care and changes in care, and patient-perceived effect on asthma control. Higher satisfaction scores indicate better satisfaction (range 1-5); higher asthma control scores indicate greater agreement with a statement that changes in biologic care induced worsening of asthma control (range 1-5, 1 = strongly disagree and 5 = strongly agree). Data Of 709 patients on biologics, 26 did not complete the questions concerning satisfaction with care. Data are expressed as n and percentages (%), or mean and standard deviation (SD). *$t(674) = 8.47$, $p < 0.001$, $d = 0.72$

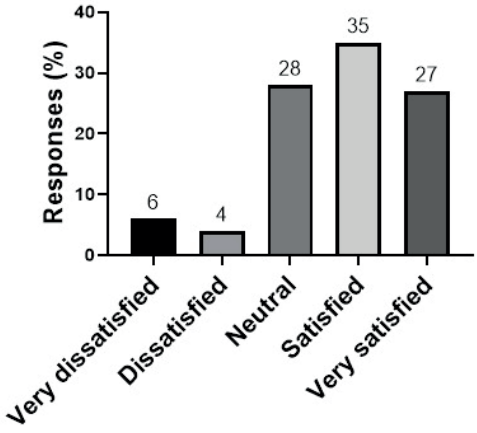

Figure 2. Satisfaction with change to home-administered biologics. Satisfaction with change to home-administered biologics in patients reporting this change in their biologic care (n=153). Data are expressed as percentages (%).

Physicians' expected changes to future severe asthma care

The majority of participating physicians (78%) expect that certain aspects of reorganized care will be continued in the future. Figure 3 presents physicians' beliefs about how severe asthma care will change as a result of the COVID-19 pandemic.

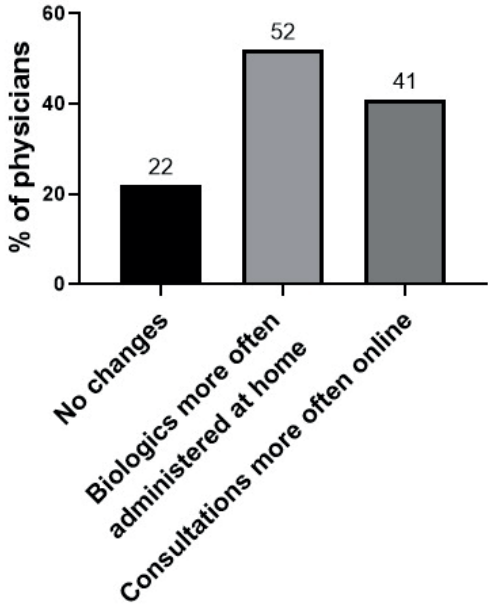

Figure 3. Physicians' expected changes to future severe asthma care. Physicians' beliefs about how asthma care will change following the pandemic (n=268). Data are shown as percentages (%).

Discussion

The results of this European-wide survey showed that both physicians and patients reported changes in severe asthma care during the COVID-19 pandemic. Physicians expected these changes to outlast the pandemic, and the majority of patients were satisfied by the changes that were made, the most common changes being the use of video/telephone consultations and home administration of biologics. There was no evidence that changes led to poorer perceived asthma control.

Although this study is the first that has investigated the effect of the pandemic on severe asthma care, our results can be compared to other disease areas. A global survey from the World Health Organization showed that more than 50% of 163 participating countries reported disrupted outpatient services for non-communicable diseases with

limited access, reduced staff capacity, alternate locations or different modes of care [6]. Consistent with the results of our study, replacement of face-to-face consultations into telemedicine deployments were reported in approximately 60% of countries. Several other studies investigated patient satisfaction with video/phone consultations during the COVID-19 pandemic, both in allergy/immunology and other services (e.g. rheumatology, inflammatory bowel disease, oral/maxillofacial surgery, urology), and all confirmed high satisfaction levels in the majority of patients [14–20]. In addition, some other studies, mainly involving allergy/immunology clinics, reported increased prescriptions of home-administered biologics [21–23]. Apparently, even patients requiring complex care, including those with severe asthma, are willing to switch to a different type of care if circumstances demand it.

In our study changes in asthma care resulted from decisions made either by the hospital, the doctor or by the patients themselves, and changes took various forms. Some of the changes were due to reduced staffing, and low staffing will impact care irrespective of whether there is a pandemic. There was evidence of reduced satisfaction in care in those patients experiencing a change compared to those not experiencing a change, but it does not follow that change caused reduced satisfaction as other unknown factors also contribute to satisfaction levels. We found no evidence that any one type of change was associated with lower satisfaction than any other.

Slightly more than half of physicians in our study reported that the change to home administration of biologics would be more frequent in future care. In our study we found no evidence that home administration was associated with better or worse asthma control for the group as a whole. Although the majority were satisfied with that change, a small minority were not satisfied indicating the need to personalize this aspect of patient care post-pandemic.

Telemedicine in the field of asthma is not new, and several studies including meta-analyses suggested positive effects of telemedicine on asthma control and quality of life in asthma patients, though numerous human-related, technical and reimbursement barriers hampered widespread implementation [24–27]. The emergence of the COVID-19 pandemic seems to have accelerated the transition towards telemedicine modalities, although its precise role in future severe asthma care needs further exploration. In our study, satisfaction levels with video/phone consultations were high. Seventy-nine percent of patients were satisfied or very satisfied with this change, while only 7% of patients were not satisfied. Preferences in the mode of consultations may vary between patients, or may vary over time in individual patients. In addition, previous reports suggested benefits to telemedicine modalities in asthma patients living in rural/remote areas, while other studies suggested decreased benefits in vulnerable patient

populations, including those with lower socioeconomic status, with language barriers or poor internet access [28–30]. Better understanding of patient characteristics associated with dissatisfaction or poorer clinical outcome, would allow for accurate patient selection and a personalized approach to telemedicine deployments in severe asthma patients. It is conceivable that a hybrid form of care delivery will emerge in future severe asthma care, in which virtual and face-to-face consultations are alternated, tailored to individual patient preferences and needs.

Limitations of this study include a possible underestimation of the proportion of patients with changes in care. We made no distinction between phone or video consultations, which are quite different modalities regarding logistics and patient-physician interaction, but a recent study in an allergy/immunology service evaluating patient satisfaction with in-person, video or phone consultations during the pandemic did not find a significant difference in satisfaction levels between these encounter modalities [19]. Lastly, we did not make comparisons between countries, because multiple factors could influence the results.

Conclusions and implications for clinical practice

Although severe asthma specialists across Europe reported numerous challenges in reorganization of severe asthma care, this reorganization was achieved with high levels of patient satisfaction and just limited effects on asthma control. Video/phone consultations and home-administered biologics were shown to work well for both physicians and most patients. For the small minority of patients who were dissatisfied, either face-to-face consultations are needed or assistance to improve their satisfaction with this mode of communication, consistent with previous research [29–31]. It remains to be seen whether the level of satisfaction with video/phone consultations will remain high after the pandemic. A personalized approach may be the way forward for a sustainable implementation of telemedicine modalities and home administration of injectable biologics in severe asthma care.

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Supplementary material File 1: Guidance for Reporting Involvement of Patients and the Public (GRIPP)-2 form

(BMJ 2017; 358 doi: https://doi.org/10.1136/bmj.j3453; [13])

Section and topic	Item
1: Aim Report the aim of the study	To investigate the effect of the coronavirus pandemic on severe asthma care in Europe from physician and patient perspectives. To evaluate which changes in care are expected to continue in future.
2: Methods Provide a clear description of the methods used for PPI in the study	Members of European Lung Foundation's asthma Patient Advisory Group (PAG) and representatives of national respiratory patient organizations were invited to join the research team. A patient member of the PAG developed the initial concept of the study, which was then led by a scientific member of SHARP. Members of the PAG and patient organisation representatives were involved in refining the scope of the survey, suggesting answer fields and domains, reviewing the language used in the survey for accessibility and understanding, and reviewing patient recruitment, information and consent materials. They piloted the electronic survey in English, before translation. Two patient representatives were involved in the study team during analysis and write-up. They reviewed survey data, suggested additional interpretations of the results and identified areas for future research. The patient representatives reviewed drafts of manuscript and are co-authors.
3: Results Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	PPI contributed to the study in several ways, including: - Suggesting the concept of the study by identifying the need to understand the pandemic's impact on severe asthma care in Europe and working with the study team to refine and further develop the study aims. - Refining and improving the patient survey by suggesting answer options and additional themes to explore, for example when asking how a patient's treatment with biologic medications changed, patient representatives suggested additional answer options including 'I was afraid to travel to the hospital'. They also suggested additional questions: 'I was reluctant to access asthma care because I did not want to bother my clinician' and 'I was reluctant to access asthma care because of fear I would get exposed to coronavirus'. - During study analysis and write-up, patient representatives challenged assumptions and highlighted additional important considerations for future research, for example of initial patient satisfaction with virtual appointments may not be sustained as the pandemic restrictions become a 'new normal' and the sense of everyone adapting to an emergency wanes.

Section and topic	Item
	Patient and public involvement in this study was effective and influenced important aspects of the study design and outcomes, as noted in section 3. Several factors may have contributed to this success. Firstly, the patient representatives are members of the European Lung Foundation's asthma patient advisory group and have been involved in the overall SHARP research consortium since the outset, some for nearly 5 years. Beyond this, many have been involved in asthma research and patient involvement through EU projects and national patient organisations for many years. They are experienced patient advocates. Other patient representatives were staff or volunteers of national patient organisations who are familiar with international collaboration and inputting into research from a patient perspective. Secondly, SHARP is a patient-centred research consortium, with two patient co-chairs sitting alongside two academic/clinical chairs. This has helped to embed a culture of patient involvement across the project and consortium members are used to welcoming patients to meetings and having their input during discussions. Patient representatives are invited to all consortium meetings.
4: Discussion Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	In this way, the consortium was well set-up in terms of patient involvement in order to respond quickly to the emerging pandemic. Following a patient representatives' suggestion to initiate a project to understand the impact of the pandemic on severe asthma care and the approval of the project, patients were then involved from the outset in all meetings and project activities. Nevertheless, there were challenges. Many of the individual and patient organisation representatives dropped out after the first few meetings, once the project concept had been agreed and the survey design was approaching finalisation. Reasons for this included an explosion of work for patient groups caused by the pandemic, virtual meeting fatigue and prioritising personal mental and physical health needs. One representative also felt frustration that their feedback was not being taken on board or given the same weight as the professional team members, and decided to step down from the project. The patient involvement lead from European Lung Foundation was not able to attend all project calls and therefore was not able to provide the level of facilitation and oversight as may have been needed to ensure patient views were included. The patient representatives involved came from the UK, Ireland and Netherlands, supported by patient organisations from France, Ireland, UK and Spain. It may have been beneficial to have input from a more diverse group, with experience of different healthcare systems in order to ensure the survey took account of different national responses to the pandemic, and to address health and socio-economic inequalities.
5: Reflections Critical perspective—Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	Patient involvement was well-embedded within the study from the outset, with patients as equal members of the study team from day 1. Their input materially changed the study design, analysis and interpretation. The key challenge was sustaining involvement throughout, however it was more critical to have a broad number of patient contributors at the survey design phase which we achieved. There was inconsistency in ensuring patient suggestions were considered and incorporated, or a satisfactory explanation was given as to why this could not be done – perhaps due to a lack of patient input oversight from the study team.

Supplementary material File 2: Patient survey

Dear Sir or Madam,

The purpose of this survey is to understand whether and how the coronavirus outbreak (COVID-19) has changed severe asthma care and how it has affected the well-being of patients with severe asthma. This data will help us improve the care of asthma patients in the future. The questionnaire is anonymous, and answers will be kept confidential. The survey contains 17 questions and takes approximately 5 minutes to complete.

When responding to the questions, please report about your situation during the first wave of the COVID-19 pandemic.

In case you have further questions on this survey, please contact [National Lead Contact].

Thank you very much for helping improve severe asthma care,

The SHARP team.

.....☞.....☞.....☞.....☞.....☞.....☞.....☞.....

1. Do you agree to answer the following questions anonymously for scientific research?
   - □ No, I don't agree, and will therefore not complete this survey
   - □ Yes, I agree

2. Which country do you live in? .....

3. What is your age?
   - □ 18-40 years
   - □ 40-65 years
   - □ >65 years

4. What is your gender?

☐ Male
☐ Female
☐ Prefer not to say

5. Do you think you had COVID-19?

☐ No
☐ Yes but I was not diagnosed by a doctor and was not tested
☐ Yes and I was diagnosed by a doctor, but was not tested
☐ Yes and I had a positive test result
☐ Yes and I was admitted to hospital with a diagnosis of COVID-19
☐ Yes and I was admitted to hospital intensive care unit with a diagnosis of COVID-19
☐ I don't know

6. At the beginning of the coronavirus outbreak in Europe (February 2020) did you use asthma inhalers (relievers + preventers) every day?

☐ No
☐ Yes

7. At the beginning of the coronavirus outbreak in Europe (February 2020) did you use prednisolone (or similar) steroids tablets every day?

☐ No
☐ Yes

8. Did your appointments at the asthma clinic change during the coronavirus outbreak?

☐ No
☐ Yes

9. If you answered yes to the previous question (*tick all that apply*):

☐ Not applicable, my appointments stayed the same
☐ My appointments were cancelled or postponed
☐ I chose myself to cancel my appointments
☐ The location of my appointments was changed
☐ My lung function test was cancelled
☐ I monitored my asthma at home with a peak-flow meter or other device
☐ My appointments were changed into telephone or video consultations
☐ My asthma problems were resolved in other units (e.g. emergency ward)
☐ Other (please specify): .....

10. If you had appointments by telephone or video, were you satisfied?

very dissatisfied	dissatisfied	neither satisfied nor dissatisfied	satisfied	Very satisfied	not applicable
□	□	□	□	□	□

11. Did the frequency of contact with your asthma doctor or nurse change during the corona outbreak?

□ No, contact remained the same
□ Yes, I completely lost contact
□ Yes, I had less contact
□ Yes, I had more contact

12. At the beginning of the coronavirus outbreak did you use biologic medications* (injections) for your asthma and did the treatment change?

□ Not applicable, I did not use biologic medications
□ Yes, I used biologic medications
□ I was supposed to start a biologic treatment, but this was postponed

** Biologic medications for severe asthma include:*
Xolair (omalizumab); Nucala (mepolizumab); Cinqaero (reslizumab); Fasenra (benralizumab) Dupixent (dupilumab)

13. If you used biologic medications for your asthma at the beginning of the coronavirus outbreak, how did the treatment change during the pandemic? (*tick all that apply*)

□ My treatment was unchanged
□ My treatment was postponed
□ My treatment stopped
□ I received less frequent treatments
□ I switched to administering my injections myself at home
□ Other (please specify): .....

14.If your treatment with biologic medications changed, what was the reason? (*tick all that apply*)

□ Not applicable, my treatment was unchanged
□ It was decided by the clinic
□ I had to stay home because of COVID-19 symptoms
□ I was not able to get transport to the hospital
□ I was afraid to travel to the hospital
□ My biologic medications were not available at the pharmacy
□ The pharmacy was unable to deliver medication to my home
□ I was not able to collect my biologic medication at the pharmacy
□ I was afraid to pick up my biologic medication at the pharmacy
□ Other

15. Apart from biologic medications (injections), did you have trouble getting your other asthma medications?

☐ No
☐ Yes

16. To what extent do you agree with the following statements **during the coronavirus outbreak**

A. My care was good

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

B. It was easy to get in contact with my asthma doctor or nurse at the asthma clinic

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

C. I received less care for my asthma than I needed

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

D. It was difficult to access asthma care

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

E. I was reluctant to access asthma care because of fear I would get exposed to coronavirus

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

F. I was reluctant to access asthma care because I did not want to bother my clinician

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

G. It was difficult to get my asthma medication

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

H. I was satisfied with changes in my asthma care

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

I. I was satisfied with changes in getting my asthma inhalers

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

J. I was satisfied with changes in my biologic treatment

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree
☐	☐	☐	☐	☐

17. How did changes during the coronavirus outbreak affect your asthma?

A. Changes in type of contact with my asthma doctor or nurse made my asthma worse

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree	not applicable
☐	☐	☐	☐	☐	☐

B. Changes in frequency of appointment with my doctor or nurse my asthma worse

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree	not applicable
☐	☐	☐	☐	☐	☐

C. Changes in access to my asthma inhalers made my asthma worse

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree	not applicable
☐	☐	☐	☐	☐	☐

D. Changes in my biologic treatment made my asthma worse

strongly disagree	disagree	neither agree or disagree	agree	Strongly agree	not applicable
☐	☐	☐	☐	☐	☐

All answers are collected anonymously and treated in strict confidence. The results from the survey will be kept in accordance with the privacy laws of the country in which the data is collected and in compliance with data protection rules.

By submitting my answers, I agree that my data will be used anonymously for research purposes.

Thank you for your time and engagement.
Thank you for taking the time to complete this survey.

Supplementary material File 3: Physician survey

Dear colleague,

The purpose of this SHARP survey is to better understand how the coronavirus outbreak has changed severe asthma care and how it has affected the well-being of patients with severe asthma. This data will help improve the care of severe asthma patients in the event of a 2nd wave. All answers are collected anonymously and treated in strict confidence. Results from the survey will be kept in accordance with the privacy laws of the country in which the data will be collected and in compliance with GDPR data protection rules. The survey contains 15 questions and takes approximately 5-10 minutes to complete.

Thank you very much for your time and help!

The SHARP team.

Do you agree to answer the following questions anonymously for scientific research?

☐ No, I don't agree, and will therefore not complete this survey

☐ Yes, I agree

1. In which country is your hospital/clinic located?

.....

2. Was severe asthma care reorganised in your clinic during the COVID-19 outbreak

□ No
□ Yes, the organisation of consultations changed

(tick all that apply)

□ Consultations continued but with social distancing measures

□ Consultations continued but at a reduced capacity

□ Consultations continued at another location

□ Only urgent consultations were held

□ Consultations for new patients were postponed

□ Consultations switched to telephone, video or e-mail
□ Other: :.....

□ Yes, the organisation of other disciplines/departments changed

(tick all that apply)

□ Respiratory nurses assisted more than before in severe asthma care

□ Pulmonary function tests were cancelled

□ Pulmonary function tests were performed at reduced capacity

□ Other: :.....

□ Yes, the delivery / administration of biologic medications changed

(tick all that apply)

□ Not applicable (biologics are not available in our clinic)

□ Administration of biologics was cancelled or postponed

□ Clinical administration of biologics was switched to self-administration at home

□ In-hospital administration of IV biologics was switched to subcutaneous administration

□ Initiation of biologics was postponed

□ Other: :.....

□ Yes, new IT technologies were introduced to improve communication between hospitals, clinic, GP practices or other care givers.
If yes, please provide some explanation:.....

3. Did the frequency of contact with your severe asthma patients change during the COVID-19 outbreak?

☐ No
☐ Yes, I had less contact
☐ Yes, I had more contact
☐ Other: :.....

4. Were doctors or nurses from your department assigned to special COVID-19 units, and did this affect severe asthma care?

☐ No
☐ Yes, fewer physicians were available for severe asthma care
☐ Yes, fewer nurses were available for severe asthma care
☐ Yes, fewer nurses were available for administration of biologics
☐ Other: :.....

5. Did you receive guidance/instructions on whether and how to change severe asthma care in your department?

☐ No, we could decide ourselves
☐ Yes, we received instructions from our hospital / centre
☐ Yes, we received guidelines from our government
☐ Other: :.....

6. Did you observe that asthma control in your severe asthma patients **worsened** due to changes in severe asthma care?

☐ No
☐ Yes, certainly in many patients
☐ Yes, certainly in some patients
☐ Yes, possibly in some patients
☐ Other: .....

7. Did you observe that asthma control in your severe asthma patients **improved** due to changes in self-isolation?

☐ No
☐ Yes, certainly in many patients
☐ Yes, certainly in some patients
☐ Yes, possibly in some patients
☐ Other: .....

8. Do you expect some changes in organization of asthma care will continue after the corona crisis? *(tick all that apply)*

☐ No
☐ Yes, consultations will more often take place on-line
☐ Yes, biologics will more often be self-administered at home
☐ Other: :.....

9. Do you have any specific advice for your colleagues on how best to organize asthma care during a possible 2nd wave? If yes, please provide your advice in the open field.

☐ No, not really
☐ Yes, open field for text:.....

Chapter 10

General discussion

Topic of the thesis

The field of severe asthma finds itself in an exciting era. In recent years, the treatment regimen for patients with severe asthma has been expanded with several biologic therapies, in addition to inhaler therapy and oral corticosteroids (OCS). These biologic therapies target type 2 inflammatory pathways. Phase 3 clinical trials have shown that these asthma biologics significantly reduce exacerbations and chronic OCS use in patients with severe eosinophilic asthma [1–9]. However, many questions regarding real-world treatment of severe asthma, including biologic therapies, remain unanswered.

Therefore, the overarching aim of this thesis was to explore some of the key research questions related to the real-world treatment of severe asthma. First, we evaluated suboptimal use of inhaler therapy in asthma patients consuming high doses of OCS in order to reveal targets for OCS use reduction and to assess the proportion of patients who may be potential candidates for biologic therapy. Further, we evaluated the long-term response to anti-IL-5 biologics and characterized the nature of residual disease manifestations, allowing analysis of predictors and increasing insight in the pathophysiology of severe asthma. Next, we focused on safety of switching between biologics, to raise awareness about potentially severe complications of switching from anti-IL-5 biologics to dupilumab and to describe potential treatment strategies of these complications.

Initially, this thesis focused on OCS and biologic use in what later appeared to be "normal" circumstances. With the emergence of the coronavirus disease 2019 (COVID-19) pandemic circumstances changed globally, and with that the definition of "normal". Rapid generation of real-world data greatly contributed to insights into various aspects of the COVID-19 pandemic. Because of this thesis' topic, we could directly respond to the new challenges in severe asthma management posed by the pandemic. New research questions that were added to the thesis were related to outcomes of COVID-19 in (severe) asthma patients and the role of biologic therapy, and to the impact of the pandemic on (long-term) severe asthma care reorganization in Europe. This knowledge may contribute to severe asthma management recommendations during pandemic conditions.

The thesis is divided into two parts, reflecting the different circumstances in which the studies were performed. Part I includes studies evaluating severe asthma treatment in the "normal" circumstances, i.e. "before the COVID-19 pandemic", whereas part II includes studies evaluating severe asthma care and treatments "during the COVID-19 pandemic".

Main findings and their relation to previous literature

Part I Evaluation of severe asthma treatment before the COVID-19 pandemic

New targeted therapies

In the past six years, two new classes of biologics have entered the market in addition to the anti-immunoglobulin E (IgE) biologic omalizumab, which has been available since 2003. These are the anti-interleukin (IL)-5 biologics targeting the IL-5 pathway (mepolizumab, reslizumab, benralizumab), and the anti-IL-4-receptor-alpha monoclonal (dupilumab) targeting both the IL-4 and IL-13 pathway. These new steroid-sparing therapies finally represented an alternative for OCS in severe eosinophilic asthma patients who have been dependent on intermittent or chronic OCS use for many years. In **chapter 2** we provided an overview of the chronology of development, targets, clinical effects and approval label of the currently available asthma biologics, and gave a brief update on upcoming promising treatments for severe asthma in a narrative review. The emergence of asthma biologics has significantly improved the quality of life of many patients with severe asthma [10, 11].

OCS overuse and relevance of inhaler therapy assessment before asthma biologic initiation

Asthma biologics are expensive drugs (~12.000-16.000 euro/year) [12]. It is therefore highly relevant that the evaluation of its indications proceeds adequately and thoroughly. This evaluation starts with correctly labeling patients with a diagnosis of severe asthma, which means by definition that all conservative treatment strategies to improve asthma control should have been addressed, including optimization of adherence to high-dose inhaler therapy and inhaler technique. Patients who still need treatment with ≥400-420mg prednisone-equivalent per year (i.e. ≥2 exacerbations per year or chronic OCS use), despite optimization of all modifiable factors, qualify as potential biologic candidates [13–15].

In **chapter 3** we assessed the prevalence of asthma patients on intensive inhaler therapy using high cumulative doses of OCS (≥420mg prednisone-equivalent per year), and the proportion of these patients who were using their inhaler therapy sub-optimally (poor adherence or inadequate inhaler technique), and the proportion of patients who used their inhaler therapy adequately and thus were potential candidates for biologic therapy. For this study, data from a large pharmacy database were combined with clinical data derived from patient surveys. We found that nearly 30% of patients on intensive inhaler therapy used high cumulative doses of OCS (7% of the total asthma population), with a median cumulative OCS dose being as high as 750 mg prednisone-equivalent a year. Nearly 80% of these patients showed suboptimal adherence to

inhaler therapy (<80% prescription filling) or inadequate inhaler technique (≥1 critical mistake during use of inhaler). Only 1 in 5 patients therefore qualified as potential biologic candidate, while for the others optimization of inhaler therapy usage should be a priority first. These results imply that OCS overuse could probably be reduced in many patients.

Multiple other studies have shown that OCS overuse is common in asthma patients, spanning the full spectrum of patients on low- to high-dose ICS [16, 17]. Increasing evidence suggests a dose response relationship between the cumulative OCS dose, calculated by the sum of both short- and long-term OCS prescriptions, and the risk of OCS-induced morbidities [18, 19]. In asthma patients, life-time cumulative doses starting from 500 mg prednisone-equivalent have been associated with an increased risk of type 2 diabetes, while life-time exposures exceeding 1000 mg have been associated with multiple OCS-induced morbidities including cardiovascular disease, osteoporosis and cataract [18]. One short rescue course for treating an exacerbation provides about ~200 mg of prednisone-equivalent, and a life-time cumulative dose of 500 mg prednisone-equivalent in asthma patients is therefore quickly reached. In addition, also ICS may add to this risk of steroid-induced morbidities in a similar dose-response relationship [20, 21]. It is therefore recommended to reduce OCS use to the lowest possible dose, which can be achieved by addressing factors known to improve asthma control, including optimization of inhaler therapy adherence and inhaler technique [22].

Multi-dimensional assessment in specialized asthma centers have shown to be effective in reducing OCS use in uncontrolled asthma patients [23–25]. In this same setting indications for biologic therapies could be evaluated. Several expert-based publications therefore recommend to timely refer patients who use high cumulative doses of OCS. However, the recommended threshold dose for referral of 1000 mg prednisone-equivalent in 1 year, as stated in these publications, seems relatively high, since patients with for instance 2 exacerbations per year for several years in a row, may be missed [26, 27]. More than half of high OCS users in our study would not fulfil this criterion for referral to specialist care. The need for clear criteria for referral in asthma patients on high-dose inhaler therapy and/or recurrent exacerbations (i.e. GINA step 4 + ≥2 exacerbations/year, or GINA step 5) was also emphasized by results from two recent studies from the United Kingdom (UK), one of which showing that a large number of these potentially severe asthma patients were under-recognized in primary care (i.e. 8% of the asthma population), and the other study showing that <20% of patients using ≥3 OCS courses per year were referred to specialist care [28, 29]. Our study confirms this under-recognition of potentially severe asthma patients in primary care, since 25% of patients using high OCS doses were not consulting a respiratory physician. Another

recent study from the UK showed that the majority of asthma patients in primary care are likely to have an eosinophilic phenotype. About half of patients in this study even had a 'high likelihood' of having the eosinophilic asthma phenotype, which was associated with intensive treatment (GINA step 4 or 5) and recurrent exacerbations, exactly representing the patient category who may benefit from biologic therapy [30].

Although the first assessment of adequate inhaler therapy usage could take place in primary care setting, these results support early referral of patients on high-dose asthma medication and high OCS use to specialist care for multidimensional assessment and initiation of biologics if appropriate. The results from **chapter 3** contributed to these previous studies by confirming the high prevalence of worrying OCS overuse in asthma patients, and by revealing targets for OCS use reduction. In addition, our study stressed the importance of adequate assessment of inhaler therapy usage, including adherence and inhaler technique, before a step-up to expensive therapies such as asthma biologics is being considered.

Evaluation of response to asthma biologics: defining a super-responder

Patients with persistent eosinophilic inflammation and recurrent exacerbations or chronic OCS use despite optimization of all modifiable factors, qualify for treatment with one of the OCS-sparing biologics, such anti-IL-5's [31]. Multiple real-world studies, including registry-based studies, confirmed the clinical effects of the anti-IL-5 biologics as observed in the phase 3 trials, and showed significant reductions in exacerbations and chronic OCS use in patients with severe eosinophilic asthma [32–40]. At group level, the therapy is therefore clearly effective. In daily practice however, it is noted that the response to biologics differs between patients, and it could be questioned what these results on group level imply for the disease burden in the individual patient. A response definition solely based on the endpoints of the phase 3 studies may not sufficiently reflect this disease burden and may not give full insight in remaining "treatable traits" [41]. A more comprehensive response definition covering all important aspects of asthmatic disease may be more appropriate. For the individual patient it is important whether exacerbations still occur, whether chronic OCS use is still necessary, whether exhaled nitric oxide (FeNO) remains high, whether respiratory symptoms persist, whether lung function remains impaired, or whether co-morbidities (e.g. nasal polyposis, atopic dermatitis) remain uncontrolled.

In **chapter 4** we assessed response to anti-IL-5 biologics using a composite definition of response, including all these different components, by using real-world data derived from the Dutch severe asthma registry "RAPSODI". It was shown that 14% of patients had a complete response after two years anti-IL-5 treatment, with resolution

of symptoms and exacerbations, elimination of chronic OCS therapy, low FeNO and absence of uncontrolled co-morbidities. We labeled these patients "super-responders". Two other studies classified response to anti-IL-5 therapies, and assessed the prevalence of super-responders. However, the authors of these studies used different definitions of super-response. In the studies by Harvey *et al*. and Kavannagh *et al*., definitions were either based on improvement of asthma control questionnaire (ACQ) scores, or complete resolution of exacerbations and elimination of chronic OCS therapy, respectively [42, 43]. Interestingly, a recent Delphi-consensus based study showed that a group of international asthma experts would prefer to use a more complicated definition for super-response. Major and minor criteria were formulated, and to qualify as a super-responder, a patients should fulfill ≥3 criteria, including 2 major criteria. Major criteria were the following: 1. Exacerbation elimination (for 12 months), 2. Major improvement in patient-reported asthma control based on ACQ or asthma control test (2x mean clinically important difference), 3. OCS elimination or weaning to the point of adrenal insufficiency, and minor criteria were; 1. Reduction of 75% in exacerbations, 2. Achieving well-controlled asthma, 3. ≥500 ml improvement in FEV_1 [44]. These super-response definitions partly correspond to the definition we used in our study. Remarkably, some of these other definitions included parameters that should show a certain degree of improvement compared to baseline values, for example with regard to ACQ and FEV_1. As a consequence, when using these definitions, patients could be classified as a super-responder, while still having a high ACQ or impaired lung function. It could therefore be argued that the achieved endpoint is actually more clinically relevant than a change in endpoints from baseline.

In addition, the treatment response definitions used in other studies did not include parameters regarding co-morbidities. This probably also explains the differences in identified predictors for a super-response. The presence of nasal polyps in the study of Kavannagh *et al*. appeared to be predictive of a super-response, which is in line with several post-hoc analyses of phase 3 studies of the anti-IL-5 biologics showing better clinical responses in severe eosinophilic asthma patients suffering from nasal polyps [43, 45, 46]. However, our study suggested that the absence of nasal polyps was predictive of super-response. This notable difference could probably be fully explained by our definition of response, in which the persistence of uncontrolled nasal polyps disqualified patients as super-responders. An increasing number of asthma biologics have currently been registered for common type 2 co-morbidities in asthma, for instance dupilumab, omalizumab and mepolizumab for the treatment of nasal polyps, and dupilumab for the treatment of atopic dermatitis. It seems therefore plausible to include these co-morbidities in response definitions. This would allow to include the treatment effects on both asthma and co-morbidities in the analysis of predictors of (super-)response. In addition, it could be questioned, whether a patient would him/

herself consider a super-responder, if respiratory symptoms were resolved and OCS use was eliminated, but bothersome upper respiratory symptoms persisted. Although this patient-perspective is not included in any of the studies assessing super-response, it seems more relevant for patients to use a comprehensive response definition, including all aspects that determine disease burden and/or prognosis.

Evaluation of response to asthma biologics: mechanisms of partial response

Patients with residual disease manifestations were labeled as partial responders in our study. A partial response was found in nearly 70% of patients, with most common residual disease manifestations being persistent airflow limitation (59%), uncontrolled sino-nasal disease (58%) and ongoing asthma symptoms (48%). Blocking the anti-IL-5 pathway was apparently insufficient to suppress all different disease manifestations in these patients. This may be a result of under-dosing in case of very severe inflammation, or insufficient plasma drug levels due to unfavorable pharmacokinetic effects in these patients. Also non-adherence to inhaler therapy should be considered in partial responders, since up to half of patients receiving biologic therapy were previously reported to show non-adherence to inhalers, which was associated with poorer outcomes in some patients [47, 48]. However, a partial treatment response may be a signal that other mechanisms than the IL-5 pathway play a role in the pathogenesis of the residual disease manifestations after long-term anti-IL-5 treatment.

In **chapter 4**, some potential mechanisms for partial response were discussed. For instance, FeNO is known to be driven by the IL-4/IL-13 pathway, and also airway remodelling may be related to IL-13 [49, 50]. Moreover, the IL-4/IL-13 pathway may contribute to inflammation of certain co-morbidities, for example nasal polyps. A recent phase 2 study looked into cytokine and FeNO levels in asthma patients with and without nasal polyps. Besides higher serum IL-5 levels, the authors also found higher serum IL-13 and FeNO levels in asthma patients with nasal polyps compared to asthma patients without nasal polyps [51]. A role for the IL-4/IL-13 pathway in upper airway disease is also apparent from **chapter 5**, which described a number of patients whose asthma responded well to anti-IL-5 biologics, but still suffered from bothersome upper airway symptoms and therefore switched to dupilumab. It later appeared that dupilumab was highly effective in suppressing these upper airway symptoms, and that symptoms returned after dupilumab was discontinued. These findings all imply that distinct inflammatory pathways may be dominant in upper and lower airways, and that blocking one single pathway may not be sufficient for treating all symptoms.

In summary, by using a broad definition of response including inflammation (OCS use, FeNO), symptom control, lung function and co-morbidities, **chapter 4** contributed to previous literature by providing insight into the heterogeneous response to anti-IL-5 biologics, with response ranging from super- to non-response. In addition, the study provided insight into possible predictors of super-response and residual disease manifestations after long-term anti-IL-5 treatment, the latter of which may not all be driven by IL-5 inflammation and represent the unmet needs in partial responders.

Complications of switching between biologics

In case of a partial response to biologic therapy, physicians may decide to switch to another biologic in order to achieve a better treatment response. This was also confirmed by the results from **chapter 4,** which showed that switches between anti-IL-5 biologics occurred in 41% of patients during the 2-year study period, the most common reason being an incomplete treatment response. An important question, however, is whether switching between biologics is safe. Phase 3 studies of the asthma biologics excluded patients who had recently used any other biologic. Real-world studies are therefore an important source of information about safety of switching between biologics. Switching between anti-IL-5's, and from anti-IgE to anti-IL-5 biologics appears safe, since complications of switching were not observed in **chapter 4,** nor in other real-world or observational clinical studies [52–54]. However, in case anti-IL-5 biologics are switched to dupilumab, problems can arise in rare cases, as shown in **chapter 5**. In this chapter we presented a case series of severe OCS-dependent asthma patients who switched from anti-IL-5 biologics to dupilumab, and subsequently developed serious eosinophilic complications, including severe worsening of asthma, eosinophilic pneumonia and/or severe thrombo-embolic events.

Hypereosinophilia was observed in a small minority of patients in the phase 3 studies of dupilumab, which was however an asymptomatic finding in nearly all patients. Blood eosinophils levels were suggested to be increased due to reduced recruitment to tissues resulting in accumulation of eosinophils in the blood compartment [55]. Eosinophil levels returned to baseline levels after approximately 4 months [7, 8]. Two real-world cohort studies investigating real-world effectiveness of dupilumab, included patients who were previously treated with anti-IL-5 biologics. One of these studies included 38 patients, of which 64% were OCS-dependent, and 84% were previously treated with an anti-IL-5 biologic [56]. Asymptomatic eosinophilia of ≥1000 cells/µl developed in 13% of patients. Interestingly, the authors described one case in their cohort who clinically deteriorated after having switched from benralizumab to dupilumab, and required high-dose OCS (50 mg/day) to recover, similar to our patients. The other study included 64 severe asthma patients, of which 76% were OCS-dependent at baseline, and 84% had been treated with mepolizumab before [57]. Duration between discontinuation

of mepolizumab and initiation of dupilumab was however not mentioned. Eosinophil levels rose ≥1500 cells/µl in 25% of patients, and ≥3000 cells/µl in 6.3% of patients, all of which without clinical consequences, although 12% of patients had persistent hypereosinophilia (≥1500 cells/µl) after 6 months.

It is currently unknown why in some patients eosinophils circulate in the blood compartment in large numbers without clinical consequences, while in others these eosinophils infiltrate tissues, become activated and cause local inflammation. One hypothesis is that the patients in our case series had underlying ANCA negative eosinophilic granulomatosis with polyangiitis (EGPA), and that eosinophilia was enhanced because the anti-IL-5 induced inhibitory effect on eosinophils diminished, while dupilumab simultaneously promoted eosinophilia. Remarkably, a recent case study reported on two pediatric EGPA patients who were switched to dupilumab after anti-IL-5 failure, without any eosinophilic complications. However, dupilumab was started while continuing anti-IL-5's for a short period of time [58]. This may be a treatment strategy to prevent eosinophilic complications. However, it is currently unknown which patients are at an increased risk for complications when switching from anti-IL-5 to dupilumab. In addition, it is also not known whether there are any safety concerns with dual treatment with biologics. A future solution for these patients may be in the upcoming biologics that interfere upstream in the inflammatory cascade, such as tezepelumab. Tezepelumab targets the epithelial-derived alarmin 'thymic stromal lymphopoietin' [59]. In a recently published phase 3 clinical trial, tezepelumab significantly reduced exacerbations, as well as blood eosinophils, IgE and FeNO levels, indicating suppression of multiple inflammatory pathways [60]. By targeting several inflammatory pathways at a time, upstream biologics may block pathways involved in inflammation of both upper and lower airways, without increasing eosinophil levels.

Since the current literature on complications of switching between biologics concerns scarce case reports only, it is clear that more real-world data and mechanistic studies are needed to increase the understanding of predictors of the observed complications and potential treatment strategies. A final remark on this topic is that the number of case reports with dupilumab-associated eosinophilic complications without preceding (recent) anti-IL-5 treatment is increasing [61–64].

What we can learn from our case series, is that despite the fact that phase 3 and long-term extension studies of the currently available asthma biologics have not shown any important safety issues so far, intervening in type 2 inflammatory pathways is not always safe. Alertness to rare or serious complications is recommended, especially when switching anti-IL-5 biologics to anti-IL-4/13 biologics. Patients who make this switch should be closely monitored.

Risk of poor COVID-19 outcomes in (severe) asthma patients

With the outbreak of the COVID-19 pandemic, new questions suddenly became relevant regarding risks of COVID-19 in (severe) asthma patients and safety of asthma medications. The first studies from China suggested reduced susceptibility to infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while shortly thereafter the American Center of Disease Control (CDC) reported a high prevalence of asthma patients among COVID-19 patients [65–67]. Numerous smaller and larger publications followed on the risks for (severe) asthma patients of SARS-CoV-2 infection and severe COVID-19 disease course, many of which showed conflicting results. In **chapter 6** we discussed two large real-world studies in an editorial of the European Respiratory Journal [68, 69]. Because of the varying findings between studies, meta-analyses had to be awaited.

In **chapter 7** we provided an update on the recent literature on COVID-19 in asthma, including the two largest meta-analyses published by that time. These two meta-analyses, including 600,000 and 1 million patients, showed large differences between studies from different regions, but overall, reported no increased risks of SARS-CoV-2 infection or severe COVID-19 disease course in asthma patients, and possibly even a lower risk of COVID-19 related mortality [70, 71]. However, the heterogeneity of the included studies with wide variations in sample size, definitions of asthma, local testing policies, criteria for hospitalization and intensive care unit (ICU) admission, and the fact that also preprints were included, presented important limitations of these meta-analyses [72]. In the period thereafter, four large well-conducted studies (one from China, two from the UK, and one from France) were published in leading journals, which did find an increased risk of severe COVID-19 disease course in asthma patients. These studies included 15.000-90.000 hospitalized COVID-19 patients [73–76]. One of these studies reported a significant increased risk of hospitalization for COVID-19 in asthma patients, and three of these studies found significant increased risks of receiving critical care for COVID-19 in asthma patients compared to patients without asthma. None of these four studies showed an increased risk of COVID-19 related mortality, and one study even found a lower mortality risk in asthma patients. Two of these studies also investigated risks in severe asthma patients (defined as patients using ≥3 asthma medications). In one study, patients with severe asthma had a significantly increased risk of hospitalization and ICU admission (both ~30%), while there was a trend towards increased mortality. The other study reported a significant increased mortality risk (96%) in severe asthma patients aged 16-49yr compared to patients without asthma. These results are consistent with another large study from the UK, in which the use of

high-dose ICS in asthma patients (compatible with severe asthma) was associated with higher COVID-19 related mortality compared to the use of bronchodilators only (i.e. mild asthma) [77].

Based on these studies, asthma patients in general may have an increased risk of severe COVID-19 disease course, but no apparent increased mortality risk, while patients with severe asthma may have slightly higher risks, including an increased risk of COVID-19 related mortality. However, these risks of poor COVID-19 outcomes in severe asthma patients are just modestly increased as compared to other chronic respiratory diseases, such as chronic obstructive pulmonary disease or interstitial lung diseases [75, 78].

The role of type 2 inflammation and asthma biologics in COVID-19 risks

The next important question concerned the COVID-19 risks for severe asthma patients treated with biologics blocking type 2 inflammatory pathways or inducing eosinopenia in case of anti-IL-5 therapy. Early on in the pandemic, the first observations were reported of remarkably low eosinophil levels in patients with severe COVID-19 [66, 79]. In addition, recovery of eosinophil levels was found to be associated with clinical recovery from COVID-19 [80, 81]. In addition to the question of what role eosinophils played in the pathogenesis of severe COVID-19, concerns arose about the course of COVID-19 in the severe asthma population treated with biologics. Shortly thereafter, the first autopsy studies in deceased COVID-19 patients were published, which showed no tissue infiltration of eosinophils [82–84]. Subsequently, no eosinophils were found in bronchoalveolar lavage fluid from COVID-19 patients, nor increased levels of IL-5 or other type 2 cytokines [85]. These findings made it less likely that eosinophils or type 2 inflammation played important roles in the fulminant disease course and hyperinflammation as observed in severe COVID-19 patients. Eosinopenia in severe COVID-19 may therefore be a secondary phenomenon, possibly explained by multiple factors such as reduced eosinophilopoiesis, defective egression from the bone marrow, increased apoptosis, or hemophagocytosis due to macrophage activation in the cytokine storm [86–88].

While the role of eosinophils in the anti-viral defense in early SARS-CoV-2 infection remains to be elucidated, and is unlikely in the hyper-inflammatory state observed in later phases of infection, there are signals of an association between COVID-19 and type 2 inflammation, with a possible protective effect of pre-existing type 2 inflammation [86]. In some recent studies, asthma patients with higher pre-existing eosinophil levels had better COVID-19 outcomes, and patients with allergic asthma had better outcomes than patients with non-allergic asthma [89–92]. As described in **chapter 7**, there are several possible mechanisms by which type 2 inflammation may have protective effects

in SARS-CoV-2 infection, for instance by downregulating the entry-receptor of the virus (angiotensin converting enzyme-2 receptor) or by counterbalancing the anti-viral interferon-mediated immune response [93–95]. Further research will have to show to what extent differences in inflammatory phenotype affect COVID-19 outcomes in asthma patients, and which mechanisms are responsible for this.

The question remains what the COVID-19 risks are for severe asthma patients treated with biologics that switch off parts of the potentially protective type 2 inflammation or cause eosinophil depletion. For this reason, in **chapter 7**, we evaluated the number of COVID-19 cases in the first wave of the pandemic among patients on biologic therapy included in the Dutch severe asthma registry (RAPSODI) by surveying all involved physicians. We described the patient characteristics and disease course of the COVID-19 cases, and assessed the COVID-19 risks in RAPSODI patients compared to the general Dutch population. We identified nine patients infected with SARS-CoV-2 in RAPSODI, of which seven were hospitalized, and one had an asthma exacerbation. Of the hospitalized patients, five had to be admitted to the ICU and one patient died. The odds for admission and intubation were significantly increased in the RAPSODI severe asthma population treated with biologics compared to the general Dutch population, namely 14 and 41 times, respectively.

Several other severe asthma registries have published their experiences regarding the risk of more severe COVID-19 in severe asthma patients on biologic treatment. For example, large Belgian, Italian, and Spanish studies reported no increased risk [69, 96–101]. It is unknown why the RAPSODI study showed contradictory findings. Several factors may have played a role, such as differences in patient characteristics including phenotype, co-morbidities (e.g. obesity, cardiovascular disease), or treatments (e.g. previous chronic OCS use, type of biologic), or methodological differences (inclusion of a relatively high proportion of non-PCR confirmed COVID-19 cases may have resulted in underestimation of severe COVID-19 cases in some studies). Relatively many patients in RAPSODI were found to be obese (30%) and almost all patients with severe COVID-19 in RAPSODI had one or more co-morbidities known to be risk factors of a severe disease course. This may have contributed to the high prevalence of severe COVID-19 in the RAPSODI population, although it is unknown how the prevalence of co-morbidities in RAPSODI relate to this prevalence in the other registries. The role of biologic treatment in the observed severe COVID-19 disease course cannot be determined from our study, but in view of the results of the other studies, biologic treatment for asthma does not appear to be an important risk factor for severe COVID-19.

Another relevant observation in the RAPSODI study is that asthma exacerbations hardly occurred during SARS-CoV-2 infection, which was also reported in the other registry-studies. This is noteworthy because other viruses are known to trigger asthma exacerbations, although similar low exacerbation rates were observed in SARS-CoV-1 and MERS infections [102].

In conclusion, although asthma biologics block potentially protective type 2 inflammatory pathways, based on several large registry studies, treatment with these biologics does not appear to be associated with an increased risk of severe COVID-19. Co-morbidities, such as obesity and cardiovascular disease, may have contributed to the observed severe disease course in the COVID-19 cases in the RAPSODI population.

Re-organization of severe asthma care during the COVID-19 pandemic

One of the questions of particular importance for physicians and patients was whether severe asthma care could be ensured during the pandemic. While health-care systems worldwide were under heavy pressure due to the large number of severe COVID-19 patients, health-care professionals also faced the challenge of preserving chronic care, such as the care for severe asthma patients, as much as possible. Close monitoring of patients with severe asthma was especially important in the beginning of the pandemic, when it was still uncertain whether asthma patients and those on asthma biologics were at risk of severe COVID-19 or severe exacerbations triggered by the novel coronavirus. Several expert-based articles were published on how to reorganize a severe asthma clinic during the pandemic, however, real-world data was missing on how severe asthma specialists had managed the reorganization in their clinics, and whether this reorganization affected patients and future severe asthma care [103–105].

In **chapter 9**, a large-scale survey-based study among severe asthma patients and specialists from 16 different countries in Europe showed that severe asthma care changed for nearly 50% of severe asthma patients during the COVID-19 pandemic. Most common patient-reported changes were change into video/telephone consultations and, in patients on biologic therapy, change into home-administered biologics. Satisfaction levels with these changes were high, and nearly all patients reported no negative effect on asthma control due to these changes. Another relevant finding of the study was that many physicians expected the use of video/phone consultations and home administration of biologics to continue in future severe asthma care. Also in other areas, the COVID-19 pandemic seemed to have caused a shift to deployment of virtual consultations, with similar high levels of patient satisfaction [106–108]. Thus, based on our study, it can be concluded that asthma specialists in Europe successfully managed severe asthma care reorganization during the COVID-19 pandemic, despite all

challenges they faced, such as limited capacity of facilities or staff. And secondly, that the COVID-19 pandemic has probably been a driver for long-standing changes in severe asthma care. While telemedicine used to receive primarily attention in research setting, and may have been viewed with some skepticism by clinicians (and health insurers), it is now more relevant than ever due to the COVID-19 pandemic and appears to have finally found a definite place in everyday clinical practice.

Limitations of the thesis

The limitations of this thesis are mainly related to those of real-world studies in general [109]. These limitations include for instance differences in routine between health-care professionals, differences in their manner of documentation in patient records, missing data, lack of follow-up, input errors, etc. However, data in the studies of this thesis were provided by experienced asthma expertise centers, and it can therefore be assumed that diagnosis and treatment of severe asthma will be in accordance with current guidelines. In addition, lost to follow-up numbers were small, missing data or gross input errors could be adjusted or supplemented with data from patient records, and numbers of incomplete questionnaires were limited. There are some other limitations that relate to the individual studies, such as the asthma definition based on a self-reported diagnosis and the use of relatively 'outdated' data in chapter 1; the possibility of selection bias in chapter 2 as the study was conducted in only two severe asthma centers; the lack of detailed matching with the reference population in chapter 8; and the small contributions of some countries in chapter 9.

Specifically related to research on COVID-19 is that science in this area moves so fast and data is evolving so rapidly, that anything one writes down is almost instantly outdated. As a result, the conclusions regarding COVID-19 risks for asthma patients in the different studies in this thesis also showed a variable course, which relates to the chronology of publishing. In addition, many COVID-19 related studies have been set up and conducted in a very short time-frame, which comes with challenges and limitations, and besides, many health-care professionals had limited time for research activities due to crowded COVID-19 wards. These limitations also applied to the study in chapter 9. In retrospect, some questions in the surveys could have been formulated in a different or clearer way, and in addition, other questions would have been relevant as well. Despite these limitations, the study yielded relevant clinical results with a wide reach across Europe.

Clinical implications

The findings of this thesis have led to several implications for clinical practice. First, the results in chapter 1 emphasize that more attention should be paid to adherence and inhaler technique in asthma patients who require regular OCS for control of their asthma. It is important for clinicians to be aware that short courses of OCS are not harmless, but contribute to the cumulative dose associated with the long-term side effects of OCS. A "red flag system" implemented in the prescribing or dispensing system could help identify patients taking high cumulative OCS doses [22, 26]. In addition, alertness to OCS overuse is important in both primary and secondary care. Next, OCS overusing asthma patients should undergo a thorough assessment, in which any modifiable factor that may contribute to OCS overuse, including inadequate use of inhaler therapy, should be eliminated as much as possible. However, adherence to therapy remains a challenging aspect of asthma treatment [110]. Recently developed methods such as smart inhalers with sensors and feedback mechanisms, with or without concurrent FeNO suppression testing, may help monitor and improve use of inhaler therapy in future care [111, 112]. In addition, patient education should include the potential risks of regular OCS use, and the importance of adequate use of inhaler therapy for reducing OCS consumption [22]. If patients still require frequent OCS prescriptions, they should be referred for phenotyping and evaluation of the indication for biologic therapy, the latter only if the multidisciplinary team is convinced that the use of inhaled medication has been optimized as much as possible.

With regard to response to biologics, it seems desirable to systematically evaluate all different aspects of the disease. In this way, it becomes clear which aspects of the disease still need optimization, which is in line with the 'treatable traits' approach [41, 113]. If it is decided to switch to another biologic in partial responders, patients should be closely monitored, particularly when switching from anti-IL-5's to dupilumab. In case a patient, who made this switch, develops progressive pulmonary symptoms combined with high levels of blood eosinophilia, dupilumab should be discontinued immediately and OCS or anti-IL-5's should be resumed. In addition, physicians should realize that thromboembolic events in these patients may be manifestations of eosinophilic, EGPA-like complications. The case series in chapter 5 has one final clinical implication for all physicians prescribing biologics, namely that, since we interfere in immunity, we should always be aware of rare side effects or complications.

With regard to current knowledge concerning asthma and COVID-19 risks, there are indications that patients with severe asthma belong to a risk group for severe COVID-19, although these risks are probably not major. The question is what this means for advice regarding shielding and measures to prevent SARS-CoV-2 infection. The World Health

Organization and the Dutch National Institute for Public Health and the Environment (i.e. RIVM) labeled patients with any chronic lung disease as high-risk group, while the National Health Service from the UK and the American CDC, specifically mention patients with severe asthma as high-risk population [114–117]. In view of current evidence, it seems advisable that local anti-COVID-19 measures for high-risk groups are therefore followed by patients with severe asthma. In addition, patients with severe asthma should be advised to get vaccinated [72].

With regard to severe asthma medication during the COVID-19 pandemic, the advice based on available literature, is to continue or initiate biologic treatment as usual according to the current guidelines [103]. Furthermore, preventing uncontrolled asthma should have priority, since several studies now have shown that recent OCS use may be a risk factor for poor COVID-19 outcomes in asthma [74, 78, 118].

Another clinical implication of this thesis is that it showed that the COVID-19 pandemic induced changes in severe asthma care organization. It is expected that some of these changes, namely more frequent application of telemedicine deployments, such as phone/video consultations, and prescription of home-administered asthma biologics, will be continued in future health-care. This implies that the COVID-19 pandemic has accelerated the implementation of these remote care modalities in severe asthma management.

General conclusion and future perspectives

This thesis has contributed to answering a number of key issues regarding real-world severe asthma treatment, both in normal and pandemic conditions. Returning to the research questions of the thesis, a number of conclusions can be drawn.

First, this thesis has shown that excessive OCS use is common in asthma patients on high-dose inhaler therapy; that only a minority of high-dose OCS users qualify as potential candidates for biologics, and; that in the other patients more attention should be paid to therapy adherence and inhaler technique in order to reduce OCS overuse.

Second, it was shown that the response to anti-IL-5 biologics after two years treatment is heterogeneous, with a small proportion of patients having a complete response , i.e. super-response; that a super-response may be predicted by a shorter asthma duration and higher FEV_1; that the majority of patients on long-term anti-IL-5 treatment have a partial therapy response and suffer from residual disease manifestations, which

mainly consist of persistent airflow limitation and upper airway symptoms; and that an incomplete therapy response is the main reason for the frequently observed switches between anti-IL-5 biologics.

Third, in this thesis we described that serious eosinophilic complications may occur after switching anti-IL-5 biologics to dupilumab; that these complications could be treated with resumption of OCS or anti-IL-5 biologics; and that close monitoring of patients switching from anti-IL5's to dupilumab is important.

Fourth, based on current evidence, this thesis showed that severe asthma patients may have an increased risk of severe COVID-19 outcomes, however, there is insufficient evidence for a risk-increasing effect of asthma biologics, and current guidelines advise to continue asthma biologic treatment as usual.

And lastly, it was shown that nearly half of severe asthma patients in Europe experienced a change in severe asthma care, while only a minority reported a change in biologic treatment; that a change into video/phone consultations or a switch to home-administered biologics were commonly reported changes; that satisfaction levels with these changes were high, while asthma control was hardly affected; finally, that physicians expect that video/phone consultations and home-administration of biologics will be implemented in future severe asthma care.

Future perspectives regarding oral corticosteroid overuse

In addition to addressing key questions about real-world severe asthma treatment, the studies in this thesis also raise new questions that could be the subject of future studies. With regard to OCS overuse, the most important question is how to reduce steroid exposure as much as possible. This should start with prescribing OCS only for OCS-responsive asthmatic disease, which seems obvious but has not fully crystallized yet. It is for example not clear whether exacerbations should be phenotyped, and whether exacerbation treatment should be tailored to this phenotype. The benefit of phenotyping of exacerbations was recently suggested by a study investigating exacerbation phenotypes in patients on anti-IL-5 biologics [119]. Based on sputum eosinophil levels, two groups of exacerbation phenotypes in this patient population could be distinguished; 'eosinophil high' in 48% of exacerbations, and 'eosinophil low' in 52% of exacerbations, while FeNO levels >50 ppb were associated with 'eosinophil high' exacerbations, and FeNO <20 ppb with 'eosinophil low' exacerbations. In addition, 'eosinophil low' exacerbations were associated with high sputum neutrophils, higher CRP levels and more frequent pathogen-positive sputum cultures. The authors suggested that treatment with antibiotics may be more appropriate in patients with 'eosinophil low' exacerbations, while OCS are indicated in patients with 'eosinophil

high' exacerbations. Little is known about the benefit of phenotyping of exacerbations in mild/moderate asthma, or severe asthma patients not treated with biologics, although exacerbation phenotyping in COPD patients is a growing area of research [120]. Tailoring exacerbation treatment to exacerbation phenotype in the full spectrum of asthma patients therefore would be an important topic for future research, focusing on easily measurable biomarkers of type 2 inflammation such as FeNO, as this would be a useful tool in both primary and secondary care setting. In addition, further research is needed on how to optimally treat exacerbations without evidence of type 2 inflammation. Better understanding of exacerbation phenotype and tailored exacerbation management, will hopefully reduce intermittent OCS use in asthma patients.

Future perspectives regarding asthma biologics

Many research questions concerning response to biologics remain to be investigated, including questions on definitions of response, predictors and mechanisms of partial response. First, it seems highly relevant to reach broad consensus on a response definition. It may be valuable to investigate the patient perspective of this response definition, such as patient-reported outcomes regarding exercise tolerance, quality of sleep, fatigue/energy levels or other extra-pulmonary disease manifestations. The newly developed and validated Severe Asthma Questionnaire may be a useful tool in this setting, and also other studies investigating the most bothersome aspects in patients with severe asthma (BIPAR study) may reveal other relevant patient-reported outcome parameters [121, 122]. Second, regarding predictors of response, it seems that a large sample size is necessary for adequate analysis of predictors, such as pooled data from severe asthma registries, possibly combined with data from registries of patients on type 2 biologics for nasal polyposis or atopic dermatitis. Big data from registries might enable development of algorithms for predicting response to the different available biologics based on baseline patient characteristics. In the absence of head-to-head trials, this may support clinical decision-making regarding selection of asthma biologics. Third, regarding partial responses to biologics, characterizing residual inflammation of upper and lower airways may increase the understanding of residual disease manifestations during biologic treatment. This knowledge may also provide insight in the subset of patients who may benefit from treatment with upstream biologics or, possibly, a combination of biologics.

Future perspectives regarding severe asthma (care) and COVID-19

There are many unresolved questions regarding severe asthma and COVID-19 as well. These questions concern for example the effectiveness and safety of the COVID-19 vaccinations in severe asthma patients (on biologics); the consequences of SARS-CoV-2 infection for long-term asthma control; and the risk of long-term symptoms

after SARS-CoV-2 infection (long COVID) in severe asthma patients [123, 124]. Also, further research is needed on the deployment of telemedicine in severe asthma care, for instance regarding a personalized approach to telemedicine (which patient groups may be suitable for telemedicine applications); long-term patient satisfaction with telemedicine; and remote monitoring of severe asthma patients with home devices (e.g. peak flow devices, portable or smartphone spirometers and e-health applications) [125]. Real-world studies will probably play an important role in answering numerous of these research questions.

Future steps to optimize utilization of registry-based studies

Registries are increasingly used as an important source of real-world data. If we zoom in on the long-term feasibility and applicability of registries in general, a number of steps need to be taken. The great advantage of registries is their huge amount of data, which are simply extracted from routine health-care records. The disadvantage, however, is that entering that data is a labor-intensive activity. For the future, it would be of great value if data from electronic health-care records could be automatically transferred to the various registries, of course with adequate measures to protect personal information, and with appropriate informed consent. Until then, there are still many hurdles to overcome, including technical and legal ones, but the application of data from electronic health-care records for real-world research and registries is currently being explored by various organizations, including the U.S. Food and Drug Administration and the European Medicines Agency [126, 127]. Connecting different national registries for joint analyses is another technical challenge. The collaboration of European severe asthma registries (Severe Heterogeneous Asthma Registry Patient-Centred, i.e. SHARP) has developed an innovative tool that harmonizes data from the different European registries according to an international 'common data model', allowing local analysis of anonymized patient data followed by meta-analysis of the federated output, while maintaining privacy protection [128]. Therefore, SHARP represents an example of how such technical and legal challenges can be overcome, moving real-world research to the next level. In addition, it would be of great value if a biobank would be developed including (a subset of) the patients in the registries. This would enable translational research into mechanisms of, for example, super- or non-response, residual disease manifestations, complications of biologics, and risks of (severe) COVID-19.

In conclusion, this thesis showed that a wide variety of research questions related to severe asthma treatment can be addressed with real-world studies. Real-world studies are increasingly acknowledged to be complementary to traditional clinical trials. By bridging the gap between the highly-controlled clinical trial setting and the heterogeneous conditions of routine practice, these studies are of great added

value in supporting physicians in clinical decision-making. Particularly in the field of severe asthma, the (joint) severe asthma registries are a promising source of data for generating real-world evidence on current and expected severe asthma therapies.

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Chapter 11

Summary

The landscape of severe asthma therapy has changed significantly in recent years. Better understanding of severe asthma pathophysiology enabled the development of several targeted therapies. In addition to traditional medications for severe asthma, such as inhaled corticosteroids (ICS), oral corticosteroids (OCS), and the longer available anti-immunoglobulin E biologic (omalizumab), four new biologics have been approved since 2015. These are the anti-interleukin (IL)-5 biologics (mepolizumab, reslizumab, benralizumab) and the anti-IL-4-receptor-alpha biologic (dupilumab). In phase 3 clinical trials these biologics showed significant reductions in intermittent and chronic oral corticosteroid use. However, the tightly controlled setting of clinical trials limits generalizability of the results to routine clinical practice, i.e. the real-world setting, and many research questions regarding severe asthma treatment in this real-world setting remain unanswered. In addition, the coronavirus disease 2019 (COVID-19) pandemic raised numerous new research questions concerning severe asthma treatments in real-world setting. This thesis focused on several of these key research questions "before" (part I) and "during" (part II) the COVID-19 pandemic.

Part I Real-world evaluation of severe asthma treatment before the COVID-19 pandemic

In **chapter 2**, which is a narrative review, we provided an overview on the history of targeted therapies for severe asthma, failed and currently approved biologics, and promising new therapies under development, such as the new generation of upstream targeting biologics.

In **chapter 3** we investigated OCS overuse in asthma patients, the role of suboptimal use of inhaler therapy in these patients and the resulting implications for biologic therapy. In this cross-sectional study, data from a large pharmacy database were supplemented with data from surveys and, in a subset of patients, with observations from an inhaler technique assessment. The study showed that high cumulative OCS doses (defined as ≥420 mg prednisone-equivalent/yr) were used by nearly a third of patients with severe or uncontrolled asthma, and that the majority of these patients were either non-adherent to ICS or had insufficient inhaler technique. Only about 20% of high OCS users were therefore potential candidates for biologic therapy. These findings imply that the use of inhaler therapy in high OCS using asthma patients should be thoroughly assessed and optimized, before treatment with expensive asthma biologics are considered in these patients.

In **chapter 4** we evaluated treatment response to anti-IL-5 biologics (mepolizumab, reslizumab, benralizumab) in severe asthma patients after two years treatment, by using data from the Dutch severe asthma registry RAPSODI, supplemented with data

from electronic patient records. A super-response, defined by the absence of residual disease manifestations, was found in 14% of patients. Partial response, defined as the presence of residual disease manifestations was found in 69% of patients. Most common residual disease manifestations in partial responders were impaired lung function (59%), uncontrolled sino-nasal disease (58%) and uncontrolled asthma symptoms (48%). The remainder patients (11%) had stopped anti-IL-5 treatment <2yrs because of clinical worsening, and were labeled non-responders. Switches between anti-IL-5 biologics occurred frequently (41%), mostly because of an incomplete treatment response. These results imply that many severe asthma patients treated with anti-IL-5 biologics still suffer from bothersome conditions. Treatment strategies for optimization of such residual disease manifestations are an important avenue for further research. The currently investigated upstream targeting biologics may be a solution for a subset of partial responders.

In **chapter 5** we described four severe, OCS-dependent asthma patients who developed serious eosinophilic complications after switching from an anti-IL-5 biologic to dupilumab. These complications ranged from severe worsening of asthma, to eosinophilic pneumonia and life-threatening thromboembolic events. The exact pathophysiologic mechanisms underlying these complications remain to be elucidated. However, both treatment related effects on circulating eosinophils (reduction of anti-IL-5 induced inhibition, and simultaneous dupilumab induced enhancement) and patient related factors (e.g. undiagnosed ANCA negative eosinophilic granulomatosis polyangiitis) may have played a role. All cases largely recovered with high-dose OCS and restart of anti-IL-5 therapy. This case series stresses the importance of awareness of potential serious complications of switching between type 2 biologics, and suggests the need for close monitoring of OCS-dependent asthma patients switching from anti-IL-5 biologics to dupilumab.

Part II Real-world evaluation of severe asthma treatment during the COVID-19 pandemic

The second part of the thesis starts with **chapter 6**, in which we commented on two studies investigating COVID-19 related risks in asthma patients in an editorial. These studies suggested a slight increased risk in susceptibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in asthma patients, while severe COVID-19 disease progression appeared not to be related to asthma therapies such as ICS or biologics, but rather to older age and co-morbidities. However, definitive conclusions could not be drawn from these studies due to many bias factors, indicating the need for more well-conducted large-scale real-world studies.

In **chapter 7**, a narrative review providing recent insights related to COVID-19 and asthma, we addressed COVID-19 related risks in asthma patients and discussed results from two large meta-analyses. These meta-analyses showed no increased risk of contracting SARS-CoV-2 infection or developing severe COVID-19 in asthma patients. However, as discussed in the 'General discussion' chapter of this thesis, these meta-analysis had several limitations, and later large, well-conducted epidemiologic studies did show a slight increased risk of severe COVID-19 in asthma patients, as well as an increased risk of COVID-19 related mortality in patients with severe asthma. Furthermore, in this review, we discussed the possible protective effects of type 2 inflammation and ICS during SARS-CoV-2 infection, and the absence of safety issues related to the use of asthma biologics during the pandemic in the majority of studies. Lastly, we showed results from several observational studies reporting striking reductions in asthma exacerbations during the pandemic, suggesting at least some positive effects of the pandemic in this particular patient population.

In **chapter 8**, we investigated the incidence of (severe) COVID-19 cases in patients on biologic therapy in the Dutch severe asthma registry 'RAPSODI' compared to the Dutch population. The incidence of COVID-19 was relatively high in these RAPSODI patients, and additionally, odds for COVID-19 related hospitalization, intubation and death were 14, 41 and 5-fold increased, respectively, compared to the general Dutch population. Many of the COVID-19 cases in RAPSODI had one or more co-morbidities that are known risk factors for severe COVID-19. Based on this study, it was not possible to unravel which factors were causing severe disease progression in these patients; whether it be factors related to severe asthma, asthma biologics or co-morbidities. However, other registry-based studies showed no increased risk of severe COVID-19 in their population on asthma biologics, questioning the role of asthma biologics in severe disease progression in our patients. Finally, consistent with other studies, and unlike other viral infections, SARS-CoV-2 did not appear to be a major trigger for asthma exacerbations.

Chapter 9 presented results from a large European-wide survey-based study investigating the impact of the COVID-19 pandemic on severe asthma care from the physician- and patient-perspective. The majority of physicians reported changes in the organization of severe asthma care in their centers. Common changes were switches to video/phone consultations (45%) and switches to home-administered biologics (38%). These changes were also the most commonly reported by patients. Patients' satisfaction levels with these changes were high, and impact on asthma control was low. In addition, many physicians expect that the deployment of both video/phone consultations and home administration of biologics will be continued in future care.

The findings from this study therefore imply that asthma specialist throughout Europe managed reorganizations during the COVID-19 pandemic very well, and also, that the COVID-19 pandemic may have changed severe asthma care for good.

In conclusion, this thesis illustrates how real-world studies can be used to answer a wide range of research questions about severe asthma treatment. Real-world studies bridge the gap between the highly-controlled setting of clinical trials and the heterogeneous conditions of routine practice, and thus have the potential to support physicians in clinical decision-making in this diverse everyday clinical practice. The emergence of numerous severe asthma registries in recent years, and in particular the collaboration between these registries, are important steps forward in generating large amounts of real-world data. Registry-based studies are expected to provide important contributions to future real-world evidence on severe asthma therapies.

Chapter 12

Samenvatting

Het landschap van de behandeling voor ernstig astma is de afgelopen jaren wezenlijk veranderd. De toegenomen kennis op het gebied van de pathofysiologie van ernstig astma heeft geleid tot de ontwikkeling van nieuwe gerichte behandelingen, ofwel 'targeted therapies'. Naast de traditionele behandelingen voor ernstig astma, zoals inhalatiecorticosteroïden (ICS), orale corticosteroïden (OCS), en de sinds langere tijd beschikbare biological gericht tegen immunoglobuline E (omalizumab), zijn er sinds 2015 vier nieuwe ernstig astma biologicals op de markt gekomen. Deze nieuwe middelen zijn de anti-interleukine (IL)-5 biologicals (mepolizumab, reslizumab, benralizumab) en de anti-IL-4-receptor-alpha biological (dupilumab). In fase 3 studies lieten deze biologicals een significante afname zien in intermitterend en chronisch OCS gebruik in patiënten met een type 2 gedreven ernstig astma. Echter, de strikt gecontroleerde setting van deze klinische studies beperkt de mate waarin deze resultaten gegeneraliseerd kunnen worden naar de dagelijkse klinische praktijk, ofwel de real-world setting. Veel onderzoeksvragen over ernstig astma behandeling in deze real-world setting zijn nog onbeantwoord. Daarnaast heeft de coronavirus disease 2019 (COVID-19) pandemie meerdere nieuwe vragen opgeroepen over de real-world behandeling van ernstig astma. Focus van dit proefschrift ligt op een aantal van deze relevante onderzoeksvragen, van toepassing op de situatie "voor" (deel I) of "tijdens" (deel II) de COVID-19 pandemie.

Deel I Real-world evaluatie van ernstig astma behandeling voor de COVID-19 pandemie

Hoofdstuk 2 omvat een review waarin we een overzicht gaven van de ontwikkeling van de 'targeted therapies' voor ernstig astma, de middelen die in het ontwikkelingsproces zijn gefaald, en de biologicals die inmiddels zijn geregistreerd voor de behandeling van ernstig astma. Daarnaast benoemden we een aantal veelbelovende ernstig astma behandelingen die op moment van schrijven nog in de ontwikkelingsfase waren, zoals de biologicals die hoog in de inflammatoire cascade aangrijpen, ook wel 'upstream' biologicals genoemd.

In **hoofdstuk 3** onderzochten we overmatig gebruik van OCS in astma patiënten, de rol van suboptimaal gebruik van inhalatiemedicatie en de hieruit volgende implicaties voor behandeling met biologicals. In dit dwarsdoorsnede onderzoek werd data van een grote apothekersdatabase aangevuld met data van patiënten vragenlijsten en, in een deel van de patiënten, met een beoordeling van de inhalatietechniek. De studie liet zien dat bijna een derde van de patiënten met ernstig of ongecontroleerd astma hoge cumulatieve doseringen van OCS innamen (gedefinieerd als ≥420mg prednison-equivalent per jaar), en dat de meerderheid van deze patiënten ofwel de ICS niet trouw gebruikten of een inadequate inhalatietechniek hadden. Slechts ongeveer 20% van de hoge OCS gebruikers kwalificeerden om deze reden als mogelijke kandidaat

voor biological behandeling. Deze bevindingen impliceren dat het gebruik van inhalatiemedicatie bij patiënten die hoge dosis OCS gebruiken nauwgezet beoordeeld en geoptimaliseerd dient te worden, voordat behandeling met een dure biological wordt overwogen.

In **hoofdstuk 4** evalueerden we de behandelrespons op anti-IL-5 biologicals (mepolizumab, reslizumab, benralizumab) voor ernstig astma na twee jaar behandeling, door gebruik te maken van data van de Nederlandse ernstig astma database RAPSODI, aangevuld met data uit elektronische patiëntendossiers. Een super respons, gedefinieerd als het ontbreken van residuale ziektemanifestaties, werd gevonden in 14% van de patiënten. Een partiële respons, gedefinieerd als de aanwezigheid van residuale ziektemanifestaties, werd gevonden in 69% van de patiënten. De meest voorkomende residuale ziekteverschijnselen in partiële responders waren luchtwegobstructie (59%), ongecontroleerde sino-nasale ziekte (58%) en ongecontroleerde astma symptomen (48%). De overige patiënten (11%) waren gestopt met anti-IL-5 behandeling binnen twee jaar als gevolg van klinische verslechtering, en werden om die reden non responders genoemd. Veranderingen naar een andere anti-IL-5 biological ('switches') vonden regelmatig plaats (41%), vooral vanwege een incomplete behandelrespons. Deze resultaten impliceren dat veel ernstig astma patiënten behandeld met anti-IL-5 biologicals last blijven houden van residuale ziekteverschijnselen. Behandelstrategieën voor optimalisatie van deze resterende condities zijn een belangrijk onderwerp voor toekomstig onderzoek. Upstream biologicals zouden een oplossing kunnen zijn voor een deel van de partiële responders.

In **hoofdstuk 5** beschreven we vier patiënten met prednisonafhankelijk astma die ernstige eosinofiele complicaties ontwikkelden na een switch van een anti-IL-5 biological naar dupilumab. Deze complicaties varieerden van ernstige verslechtering van de astma controle, tot eosinofiele pneumonie of levensbedreigende trombo-embolische events. De exacte pathofysiologische mechanismen van deze complicaties zijn niet bekend. Zowel behandeling gerelateerde effecten op circulerende eosinofielen (reductie van anti-IL-5 geïnduceerde remming en gelijktijdig dupilumab geïnduceerde stijging) en patiënt-gerelateerde factoren (bijvoorbeeld een ongediagnosticeerde ANCA negatieve eosinofiele granulomateuze polyangiitis) zouden een rol kunnen hebben gespeeld. Alle casus zijn grotendeels hersteld met hoge dosis OCS en herstart van anti-IL-5 therapie. Deze patiënten serie benadrukt het belang van alertheid op potentiële, ernstige complicaties van switchen tussen type 2 biologicals, en suggereert de noodzaak van strikte monitoring van OCS-afhankelijke astma patiënten die switchen van een anti-IL-5 biological naar dupilumab.

Deel II Real-world evaluatie van ernstig astma behandeling tijdens de COVID-19 pandemie

Het tweede deel van het proefschrift start met **hoofdstuk 6**, waarin we in een editorial twee studies becommentarieerden die COVID-19 gerelateerde risico's in astma patiënten onderzochten. Deze studies suggereerden een licht verhoogd risico op vatbaarheid voor severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectie in astma patiënten, terwijl ernstige COVID-19 ziekteprogressie niet gerelateerd leek aan astma behandeling zoals ICS of OCS, maar eerder aan hogere leeftijd en co-morbiditeit. Harde conclusies konden echter niet getrokken worden uit deze studies als gevolg van meerdere bias factoren, benadrukkend dat grootschalige, goed uitgevoerde real-world studies moesten worden afgewacht voor het inschatten van de COVID-19 gerelateerde risico's voor astma patiënten.

In **hoofdstuk 7**, een review over recente inzichten in COVID-19 en astma, bespraken we COVID-19 gerelateerde risico's voor astma patiënten en bediscussieerden we resultaten van twee grote meta-analyses. Deze meta-analyses toonden geen verhoogd risico op het oplopen van een SARS-CoV-2 infectie of het ontwikkelen van ernstig COVID-19 in astma patiënten. Echter, zoals beschreven in de 'General discussion' van het proefschrift, hadden deze meta-analyses meerdere limitaties, en latere, grote, goed uitgevoerde epidemiologische studies lieten wel een licht verhoogd risico zien op ernstig COVID-19 in astma patiënten, evenals een verhoogd risico op COVID-19 gerelateerde mortaliteit in patiënten met ernstig astma. Verder benoemden we in deze review de mogelijk beschermende effecten van type 2 inflammatie en ICS gebruik tijdens SARS-CoV-2 infectie, en het ontbreken van aanwijzingen voor veiligheidsissues gerelateerd aan het gebruik van astma biologicals tijdens de pandemie in de meerderheid van de studies. Tot slot bespraken we de resultaten van verschillende observationele studies die een opvallende afname van het aantal astma exacerbaties tijdens de pandemie rapporteerden, wat suggereert dat er ook enige positieve effecten van de pandemie zijn in deze specifieke patiëntenpopulatie.

In **hoofdstuk 8** onderzochten we de incidentie van (ernstig) COVID-19 in patiënten op biologicals geïncludeerd in het Nederlandse ernstig astma register 'RAPSODI' in vergelijking met de Nederlands populatie. De incidentie van COVID-19 was relatief hoog in deze RAPSODI patiënten, en de kans op COVID-19 gerelateerde ziekenhuisopname, intubatie en overlijden was respectievelijk 14, 41 en 5 maal verhoogd ten opzichte van de Nederlands populatie. Veel van de COVID-19 casus in RAPSODI hadden een of meerdere co-morbiditeiten die bekende risicofactoren zijn voor ernstig COVID-19. Op basis van deze studie was het niet mogelijk om te achterhalen welke factoren hadden bijgedragen aan ernstige COVID-19 ziekteprogressie in deze patiënten; ofwel factoren gerelateerd aan het ernstige astma, de behandeling met biologicals of co-

morbiditeiten. Andere register-gebaseerde studies toonden echter geen verhoogd risico op ernstig COVID-19 in hun populatie behandeld met astma biologicals, wat de vraag doet rijzen of er een rol was voor de biologicals in onze patiënten met een ernstig COVID-19 ziektebeloop. Ten slotte, consistent met bevindingen van andere studies, maar in tegenstelling tot bij andere virale infecties, lijkt SARS-CoV-2 geen belangrijke trigger voor astma exacerbaties.

In **hoofdstuk 9** presenteerden we de resultaten van een groot Europees onderzoek naar de impact van de COVID-19 pandemie op ernstig astma zorg vanuit het artsen- en patiëntenperspectief. De meerderheid van de artsen rapporteerden veranderingen in de organisatie van de ernstig astma zorg in hun centra, waarbij een switch naar video/bel consulten (45%) of een switch naar thuistoediening van biologicals (38%) frequent werden gerapporteerd. Dit waren ook de meest voorkomende veranderingen gerapporteerd door patiënten. Het niveau van tevredenheid van patiënten met deze veranderingen was hoog, en de impact op astma controle was laag. Daarnaast verwachten veel artsen dat het toepassen van zowel video/bel consulten als thuistoediening van biologicals zal worden voortgezet in toekomstige zorg. De bevindingen van deze studie impliceren daarom dat astma specialisten in heel Europa de ernstig astma zorg tijdens de COVID-19 pandemie adequaat hebben gereorganiseerd, en bovendien, dat de COVID-19 pandemie de zorg voor ernstig astma patiënten mogelijk voorgoed heeft veranderd.

Concluderend illustreert dit proefschrift hoe real-world studies ingezet kunnen worden om een breed scala aan onderzoeksvragen over de behandeling van ernstig astma te beantwoorden. Real-world studies slaan de brug tussen de sterk gecontroleerde setting van traditionele klinische trials en de heterogene omstandigheden van de dagelijkse klinische praktijk. Daarmee bieden ze het potentieel om artsen te ondersteunen bij klinische besluitvorming in hun real-world populatie. De opkomst van talrijke registers voor ernstige astma in de afgelopen jaren, en met name de samenwerking tussen deze registers, zijn belangrijke stappen voorwaarts in het genereren van grote hoeveelheden real-world data. Register-gebaseerde studies zullen naar verwachting belangrijke bijdragen leveren aan toekomstig real-world wetenschappelijk bewijs over ernstig astma behandeling.

Appendices

List of publications
Contribution of authors
PhD portfolio
Curriculum Vitae
Acknowledgements

List of publications

Eger K, Bel EH. The emergence of new biologics for severe asthma. Current Opinion in Pharmacology. 2019 Jun; 46:108-115.

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Contribution of authors

Chapter 2
Drafting of manuscript: Katrien Eger, Elisabeth Bel
Both authors revised and approved the final version of the manuscript.

Chapter 3
Conception and design: Elisabeth Bel (EB), Pieter Paul Hekking (PH), Marijke Amelink (MA), Cristina Longo (CL), Simone Hashimoto (SH)
Subject recruitment: PH, MA
Data collection: PH, MA
Statistical analysis and interpretation of data: Katrien Eger (KE), EB, PH, MA, CL, SH
Design of tables and figures: KE, EB, PH
Principle investigator and final responsibility: EB
Drafting of manuscript: KE, EB, SH
All authors revised and approved the final version of the manuscript.

Chapter 4
Conception and design: Katrien Eger (KE), Elisabeth Bel (EB), Anneke ten Brinke (AtB)
Data collection: KE, EB
Statistical analysis and interpretation of data: KE, EB, AB, Hans Kroes (HK)
Design of tables and figures: KE, EB, AtB, HK
Principle investigator and final responsibility: EB
Drafting of manuscript: KE, EB, AtB
All authors revised and approved the final version of the manuscript.

Chapter 5
Conception and design: Elisabeth Bel (EB), Katrien Eger (KE), Els Weersink (EW)
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Statistical analysis and interpretation of data: LP, KE, EB
Design of tables and figures: LP, KE, EB
Principle investigator and final responsibility: EB
Drafting of manuscript: KE, LP, EB
All authors revised and approved the final version of the manuscript.

Chapter 6
Drafting of manuscript: Katrien Eger, Elisabeth Bel
Both authors revised and approved the final version of the manuscript.

Chapter 7
Drafting of manuscript: Katrien Eger, Tessa Pletting
Both authors revised and approved the final version of the manuscript.

Chapter 8
Conception and design: Elisabeth Bel (EB), Els Weersink, Katrien Eger (KE), Simone Hashimoto (SH)
Subject recruitment and data collection: all authors contributed to recruitment and data collection.
Statistical analysis and interpretation of data: KE, SH, EB
Design of tables and figures: KE, EB
Principle investigator and final responsibility: EB
Drafting of manuscript: KE, EB, SH
All authors revised and approved the final version of the manuscript.

Chapter 9
Conception and design: Katrien Eger (KE), Michael Hyland (MH), Dora Paroczai (DP), Alison Bacon (AB), Elisabeth Bel (EB), Simone Hashimoto, Anneke ten Brinke, Ratko Djukanovic, Peter Howarth, Apostolos Bossios, Zsuzsanna Csoma, Sabina Skrgat, Hans Michael Haitchi, Ramesh Kurukulaaratchy, Olivia Fulton, Betty Frankemölle, Karen Needham, Emmanuelle Berret.
Subject recruitment: all authors who are physicians contributed to subject recruitment.
Data collection: all authors who are physicians contributed to data collection.
Statistical analysis and interpretation of data: AB, KE, DP, MH, EB
Design of tables and figures: KE, DP, AB, MH
Principle investigator and final responsibility: EB
Drafting of manuscript: KE, DP, MH, EB
All authors revised and approved the final version of the manuscript.

PhD portfolio

	Year	Workload (ECTS)
Courses		
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (eBROK)	2019	1.0
Practical Biostatistics – AMC Graduate School	2019	1.1
Randomized Controlled Trials – AMC Graduate School	2019	0.2
Seminars, workshops and master classes		
10th and 11th NRS Young Investigators Symposium	2018-2019	0.4
LUNG Amsterdam	2018-2019	0.2
Global Respiratory Leadership Young Investigators Forum Gothenburg	2018	2.0
6th Small Airways Symposium, UMCG	2019	0.1
TEVA mini LUNG symposium	2019	0.1
GSK Scientific workshop	2019-2020	0.2
Astra Zeneca Global Respiratory Leadership Forum 2019	2019	2.0
(Inter)national conferences		
European Respiratory Society Annual Congress - Madrid	2019	2.0
European Respiratory Society Annual Congress - Online edition	2020	2.0
Presentations		
Oral presentation ERS Annual Congress - Madrid	2019	1.0
Oral presentation 11th NRS Young Investigators Symposium	2019	0.2
Oral presentation ERS Annual Congress – Online edition	2020	1.0
Other scientific meetings		
Journal Club Respiratory Medicine AMC	2018-2020	2.4
Research Meeting Respiratory Medicine AMC	2018-2020	2.4
Project Coordination Meetings SHARP	2020-2021	0.4
Stakeholder Meetings RAPSODI	2019-2021	0.2
Teaching		
Supervising master student - project and paper writing	2020	1.0
Klinische les verpleging F5 short stay	2019	0.1
Onderwijs AIOS Longziekten	2019	0.1

Curriculum Vitae

Katrien Albertine Bedřiška Eger was born February 1st 1985 in Gouda. In 2003 she graduated from Emmauscollege in Rotterdam and moved to Leiden to study Medicine at Leiden University. In 2010 she graduated cum laude, and shortly afterwards she entered the pulmonology training program at the HAGA Teaching Hospital in The Hague. She has recently finished her residency, and will start working as a pulmonologist at the Antwerp University Hospital. Her scientific career began during her Medicine study, with a scientific internship at Newcastle University focused on the effects of lung-allograft derived primary bronchial epithelial cells on dendritic cell differentiation. Later she followed a research position at the Department of Respiratory Medicine and Parasitology at the Leiden University Medical Center, where she investigated the effects of microbial exposure on bronchial epithelial cells and dendritic cells. In 2018 she started a PhD project under supervision of prof. dr. Elisabeth Bel at the Amsterdam University Medical Center with the RESSAPEA study as the main project, which was a randomized placebo-controlled trial investigating the effects of the biologic reslizumab on small airway function in severe asthma patients. Additionally, she worked on real-world research projects focusing on severe asthma treatments, including studies of the Dutch severe asthma registry RAPSODI. While the RESSAPEA study was put on hold due to the COVID-19 pandemic, a multitude of new real-world issues arose as a result of the pandemic. Real-world research therefore became focus of the PhD project, resulting in this thesis entitled 'Real-world evaluation of severe asthma treatment – before and during the COVID-19 pandemic'.

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