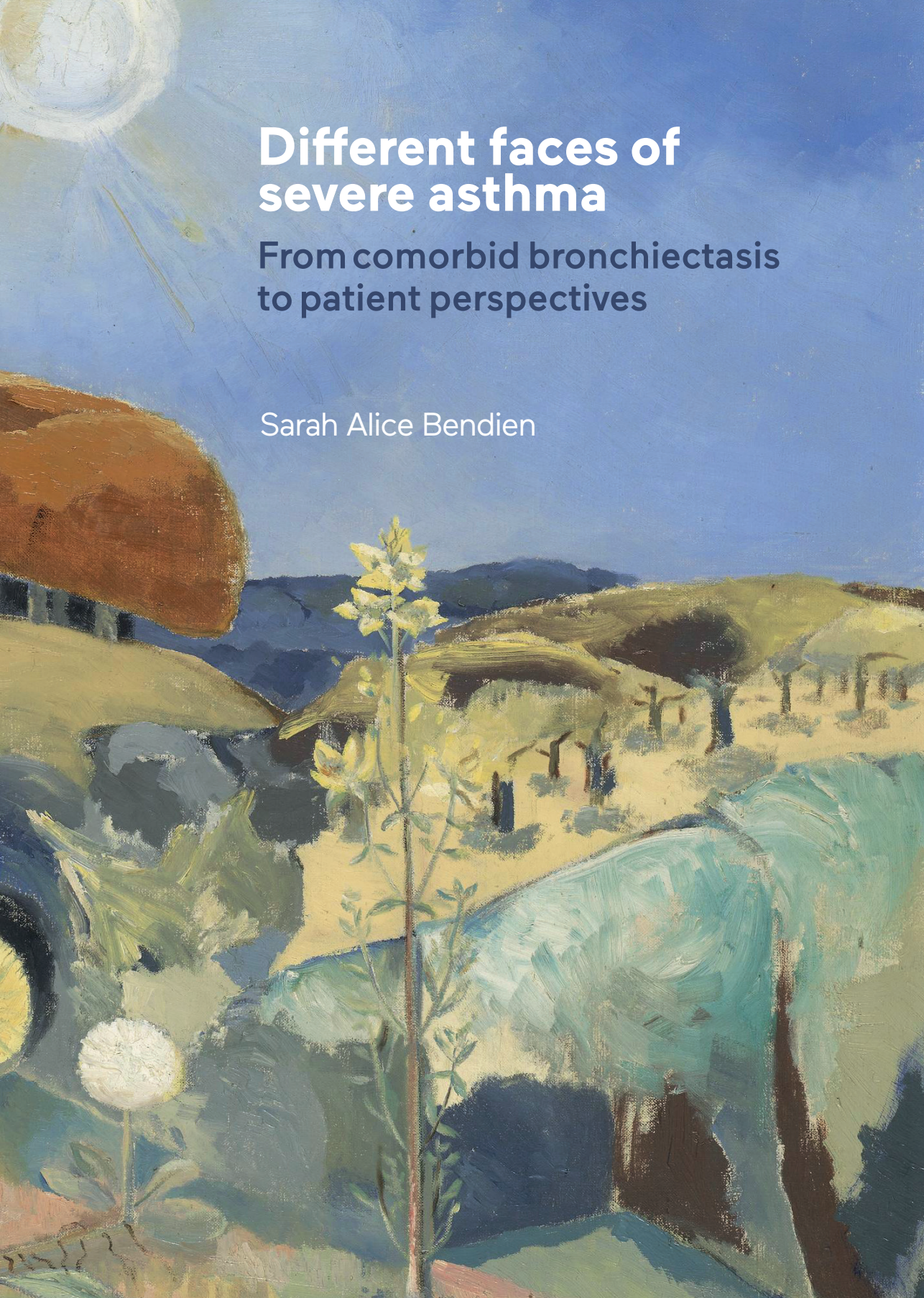
Different faces of severe asthma

From comorbid bronchiectasis to patient perspectives

Sarah Alice Bendien



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'Landscape of the summer solstice' Paul Nash, 1943

Born in London, Paul Nash grew up in an artistic family. He is considered one of Britain's most important modern artists and played a crucial role in the development of surrealist and abstract art in the first half of the 20th century.
Throughout his life, Paul Nash suffered from asthma, which severely affected his health and his artistic career. It is also possible that his illness contributed to the introspective and often melancholic tone of his work, as he spent a lot of time in rest and reflection. Nash's perseverance despite his asthma is testament to his dedication to art.

Paul Nash werd geboren in Londen en groeide op in een artistieke familie.
Hij wordt beschouwd als een van de belangrijkste moderne kunstenaars in Groot-Brittannië en speelde een cruciale rol in de ontwikkeling van de surrealistische en abstracte kunst in de eerste helft van de 20e eeuw.
Paul Nash leed zijn hele leven aan astma, wat een aanzienlijke invloed had op zijn gezondheid en zijn artistieke carrière. Het is ook mogelijk dat zijn ziekte bijdroeg aan de introspectieve en vaak melancholische sfeer in zijn werk, aangezien hij veel tijd doorbracht in rust en reflectie. Nash's doorzettingsvermogen ondanks zijn astma getuigt van zijn toewijding aan de kunst.

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Sponsoring: Stichting Gebroeders De Jong's Leen
Stichting Astma Bestrijding
Wetenschaps- en Onderzoeks Commissie (WOC) van het HagaZiekenhuis

ISBN: 9789464916881


Vormgeving en opmaak: Erik Elferink / Meneer E. illustratie en vormgeving


Organisatie: margreet@morganiseren.nl


Printing: Digiforce, Vianen

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op 7 november 2024, te 13.00 uur
door Sarah Alice Bendien
geboren te Groningen

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Appendices

CHAPTER 1

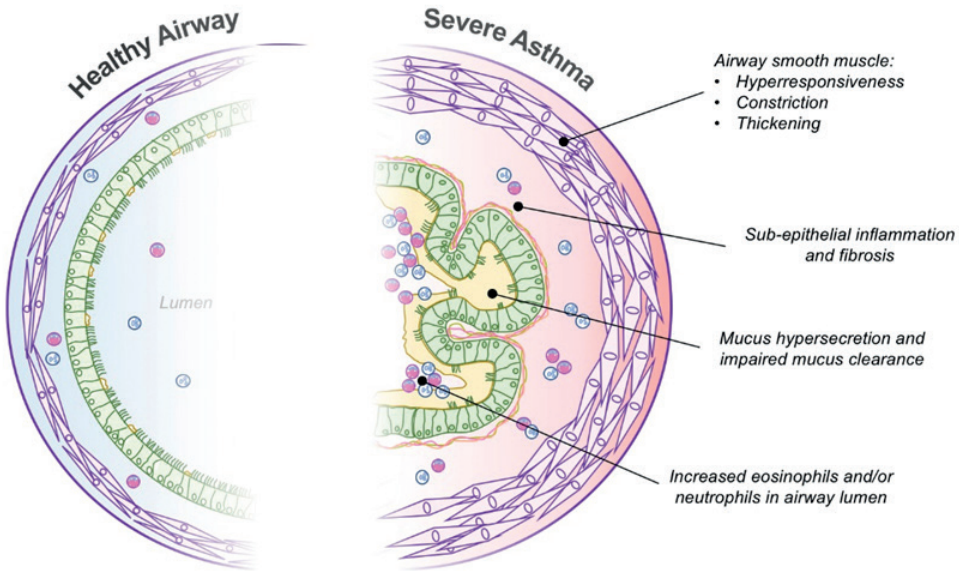
General introduction and research questions

GENERAL INTRODUCTION

SEVERE ASTHMA

Asthma is a chronic inflammatory airway disease, caused by both genetic and environmental factors, and characterized by reversible airflow limitation and airway hyper responsiveness (Figure 1.1). It is estimated that over 300 million people of all ages worldwide have asthma today and numbers are still increasing in many countries[1, 2]. Fortunately the majority of patients with asthma are well controlled and have minimal symptoms when treated with inhaled corticosteroids (ICS) and bronchodilator therapy. These patients are usually treated in primary care. A minority of these patients have difficult-to-treat asthma, defined as uncontrolled asthma despite treatment with medium- to high-dose inhaled ICS with a second controller (usually a long-acting beta-2 agonist (LABA)), or requires maintenance oral corticosteroids (OCS) to maintain well controlled asthma. In the Netherlands this is estimated to be the case in about 17-20% of all adult patients with asthma[3]. An even smaller subgroup of patients, about 5-10%[3, 4], has severe refractory asthma, where asthma remains uncontrolled despite adherence to high dose ICS and after optimizing inhaler technique, comorbid conditions and avoidance of triggers[5]. Due to frequent exacerbations, hospitalizations and work impairment, severe asthma is associated with significant impact on patients' lives and imposes a high burden on healthcare systems and society[6,7]. Patients with severe asthma are in need for more extensive assessment and personalized treatment approaches in specialist care.

Figure 1.1 Normal airway and airway with asthma



https://toolkit.severeasthma.org.au/

HETEROGENEITY OF ASTHMA

For a long time asthma has been considered to be the same disease for all patients. The main focus was on the largest group of patients with the 'classical' childhood onset allergic asthma and the most common distinction in asthma subtypes was based on allergy into allergic (extrinsic) or non-allergic (intrinsic) asthma. Only in the late fifties other observations of distinct types of asthma were made following different responses to OCS treatment in relation to eosinophilic airway inflammation[8]. In 1999, this insight was followed by Wenzel et al[9] who found evidence that severe asthma could be divided into two inflammatory subtypes based on the presence of airway eosinophils in endobronchial biopsies. These groups showed distinct physiologic and clinical characteristics. By the use of clinical, functional and inflammatory parameters, more different asthma phenotypes now have been identified.

The most relevant distinction in phenotypes with respect to targeted and personalized therapy is based on the type of inflammation. Two main inflammatory pathways are recognized: type 2-high and type 2-low inflammation. Type 2 (T2) high asthma is characterized by airway inflammation which is associated with blood or sputum eosinophilia, elevated levels of fractional exhaled nitric oxide (FeNO) or increased immunoglobulin E (IgE). T2 cytokines include interleukin (IL-)4, IL-5 and IL-13[10]. These cytokines are mainly produced by inflammatory cells such as T helper (Th)-2 cells, type 2 innate lymphoid cells and mast cells. T2 high asthma is present in approximately 60-90% of patients with severe asthma[9, 11, 12] and is considered to be steroid responsive [13, 14.]
T2-low asthma refers to a group of patients without evident type 2 inflammation. This inflammatory endotype is less well defined, and more difficult to recognize. As far as we know, T2-low asthma is characterized by neutrophilic or paucigranulocytic airway inflammation and may be associated with cytokines such as IL-17, IL-6, IL-12 and interferon-gamma (IFN-γ)[10 15]. To date, there are however no specific clinical applicable biomarkers for T2-low asthma. Response to treatment with corticosteroids is generally poor in patients with T2-low asthma[16].
In reality, the distinction in types of asthma inflammation is not as black and white as outlined here. For example, T2-low and T2-high inflammatory pathways may coexist in mixed granulocytic asthma (increase in both eosinophils and neutrophils)[17]. Overlap in phenotypes and inter-individual changing of the inflammatory endotype over time has also been observed[18]. Lastly, eosinophilic airway inflammation may be masked by the use of (inhalation-) corticosteroids and therefore misinterpreted as T2-low.

ASTHMA AND COMORBIDITIES

Not only is asthma a heterogeneous disease in itself but many patients also suffer from comorbid diseases, which can interfere with asthma, increase disease burden and even modulate the asthma phenotype and response to treatment. Comorbidity is common in difficult-to-treat and severe asthma[19] and contributes to uncontrolled disease. Not surprisingly, comorbidities in asthma are also associated with excessive costs, related to medication, health care utilization and hospitalizations[20]. Therefore, identification and appropriate management of comorbidities is a critical component of the systematic assessment of difficult-to-treat asthma.

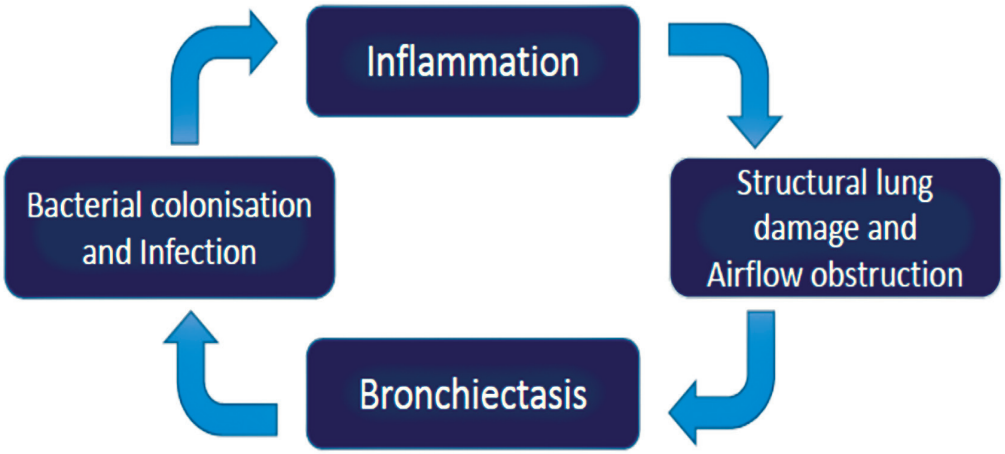
Comorbidities in asthma can be divided into pulmonary and extra-pulmonary comorbidities. Among the most frequently reported extra-pulmonary comorbidities in asthma are chronic rhinosinusitis (CRS) with or without nasal polyps (NP), obesity, gastroesophageal reflux disease (GERD) and psychological disorders. Chronic obstructive pulmonary disease (COPD), bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA) and vocal cord dysfunction are examples of well-known pulmonary comorbidities[21].

Bronchiectasis

Bronchiectasis is a common respiratory comorbidity in asthma with a prevalence varying among studies from <5% in overall asthma populations to 25–40% in uncontrolled or more severe asthma[22]. Bronchiectasis is diagnosed as the presence of irreversible airway dilatation and airway wall thickening on imaging by chest computed tomography (CT) scan in combination with clinical symptoms, particularly cough, sputum production and recurrent respiratory infections[23].
The etiology of bronchiectasis is often unknown but asthma and eosinophilic airway inflammation may contribute to the development of bronchiectasis (figure 1.2)[24].
Asthma and bronchiectasis often show similar clinical features, such as cough, mucus hypersecretion and dyspnea. Furthermore, as in asthma, bronchiectasis is a heterogeneous disease in which separate phenotypes have been recognized with different underlying inflammatory patterns[25]. Although bronchiectasis has traditionally been associated with neutrophilic airway inflammation, it is increasingly recognized that inflammation in bronchiectasis is heterogeneous, with a subset of patients having eosinophilic inflammation, suggesting a T2 inflammatory process[26]. Whether this 'eosinophilic bronchiectasis' is most frequently associated with comorbid asthma is not yet fully elucidated. It is therefore of interest to explore if a specific 'asthma-associated-bronchiectasis phenotype' can be identified and whether bronchiectasis is more common in a specific severe asthma phenotype. This could contribute to early identification and targeted treatment of patients with severe asthma and bronchiectasis.

Thus asthma and bronchiectasis are both heterogeneous diseases and often co-existing resulting in a high disease burden. So far, these patients have not been extensively characterized. A better understanding of the clinical, functional, radiological, inflammatory, and microbial characteristics associated with bronchiectasis in patients with severe asthma may contribute to early recognition and targeted treatment of this patient group.

Figure 1.2 Inflammation and bronchiectasis



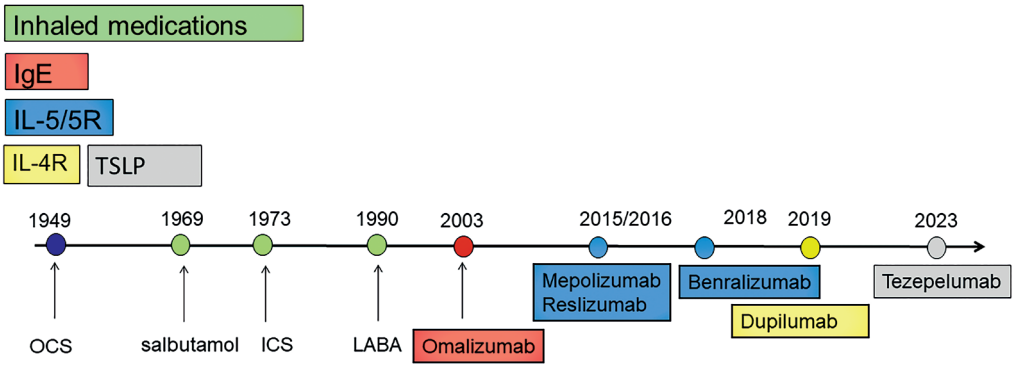
BIOLOGICS FOR SEVERE ASTHMA

Over the past decades, increased understanding of the heterogeneity of asthma has led to a refreshing vision on the management of asthma and the development of important new treatment strategies. One of the major breakthroughs for the treatment of severe asthma is the introduction of add-on therapy with monoclonal antibodies or biologics. This class of drugs was already introduced much earlier for other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The recognition of different inflammatory subtypes in asthma, also resulted in targeted therapy with biologics for severe asthma (figure 1.3). After the introduction of the first biologic for severe allergic asthma in 2003 (omalizumab) it took some time before new biologics for eosinophilic asthma followed. In 2015 the first IL-5 targeting biologic mepolizumab was registered for the treatment of severe eosinophilic asthma. Mepolizumab is administered subcutaneously in a fixed dose of 100 mg every 4 weeks.

Shortly after mepolizumab, in 2016, reslizumab was approved by the food and drug administration (FDA). Reslizumab has a similar mechanism of action to mepolizumab, but is administered intravenously rather than subcutaneously, in a weight-adjusted and not a fixed dose.
The third IL-5 targeting biologic, benralizumab, was introduced in 2018. Benralizumab is administered at a fixed dose as for mepolizumab, but after a loading dose the dosing interval of benralizumab is 8 weeks as opposed to 4 weeks for mepolizumab or reslizumab. Benralizumab distinguishes itself from previous biologics by targeting the IL-5 receptor on eosinophils, preventing IL-5 binding. In addition Benralizumab also targets eosinophils and basophils for antibody-dependent cell-mediated cytotoxicity, leading to depletion of blood eosinophils[27].

Thus, there are currently 3 anti-IL5/5Ra biologics available that target type -2-eosinophilic inflammation, making an important difference for patients with severe eosinophilic asthma, particularly those who are OCS-dependent or have high OCS exposure due to recurrent exacerbations. In phase 3 trials these anti-IL-5/5R therapies significantly reduced exacerbation frequency and OCS use in patients with severe eosinophilic asthma[28-30]. This treatment response, including long-term safety, has now been confirmed by several real-life studies[31-33].

Figure 1.3 Timeline asthma therapies



IL: interleukin; R: receptor; OCS: oral corticosteroids; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; TSLP: Thymic stromal lymphopoietin

In this thesis we focus mainly on anti-IL-5/5R biologics. However, in the meantime 2 additional biologics targeting type 2 inflammation became available. The first one is dupilumab, which targets IL-4 and IL-13 by blocking the shared IL-4 receptor alpha. Dupilumab was registered in 2019 for severe eosinophilic asthma with type 2 inflammation. Prior to this registration dupilumab was already approved for the treatment of severe atopic dermatitis. Following its success in asthma, dupilumab was approved a few months later that year for the treatment of CRS in adults whose disease is not otherwise controlled. The second new biologic is tezepelumab, which became available in the Netherlands at the end of 2023. Tezepelumab targets the 'upstream' cytokine (also called alarmin) thymic stromal lymphopoietin (TSLP). Tezepelumab appears to be a promising biologic in both T2-low and T2-high inflammation[34], although patients with more pronounced T2-inflammation undeniably show a better response[35].

Although, biologic therapy has led to major changes in a large group of patients with significant improvements in exacerbation rate, maintenance OCS use, asthma control and quality of life (QoL), not all patients with severe asthma benefit.
An important group of patients for whom effective biologics are not yet available, are

those with T2-low asthma. As outlined above, this asthma phenotype is less well defined and specific clinical inflammatory biomarkers are not available, which makes it more difficult to target therapy. Alternative treatments such as maintenance azithromycin and bronchial thermoplasty can be considered. However, therapeutic options and responses to therapy are not as successful, promising and rapidly emerging as those for patients with T2-high inflammation. This can be distressing for patients themselves, and challeng ing for clinicians seeking options to reduce the burden of disease in these patients.
Other subgroups of patients with severe asthma have been excluded from or are underrepresented in asthma biologic randomized controlled trials (RCTs)[36, 37], resulting in a lack of knowledge about the response to biologic therapy in these patients. This is particularly true for patients with comorbid diseases, including bronchiectasis. Some `phenotypic ` comorbidities, such as CRS with or without nasal polyps or allergic rhinitis, respond well to the biologics for asthma[38-40]. In bronchiectasis this is less well known and has not been studied extensively. clinicians are confronted with the high disease burden and complexity of these patients in daily practice, but are left with uncertainties about therapeutic needs and prognosis. Real-world data from registry databases could be an important source to answer these questions.

PATIENT - CENTRED CARE AND OUTCOME MEASURES IN BIOLOGICAL TRIALS IN SEVERE ASTHMA

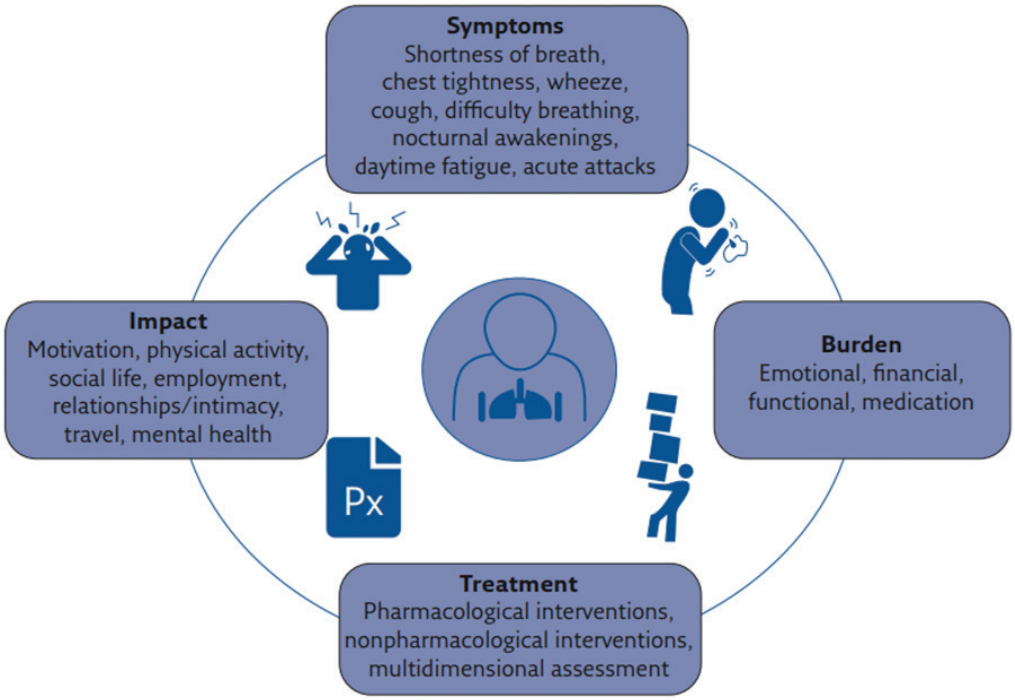
There are many ways to shape study outcomes for severe asthma research and to record treatment outcomes (e.g. to biological therapy) in clinical practice. It is well known that a broader view, including the perspectives and values of patients, is of utmost importance[41]. For example, a cross-sectional survey by Clark et al[42], showed that patients with severe asthma ranked QOL, breathlessness, cough and ability to perform physical activity as the most important treatment outcomes, along with exacerbation frequency and OCS use. These first four outcomes are currently not widely used in clinical asthma trials.
In recent decades, the healthcare system has moved from doctor-centred care to patient-centred care. This type of care implies that an individual's specific health needs and desired health outcomes are the key factor in making health care decisions and measuring quality. In this type of care the caregiver focuses on the whole person, including emotional, mental, spiritual, social, and financial perspectives[43]. Even though clinicians are becoming increasingly aware of the importance of patient-centred health care, it seems challenging to implement this in daily practice.

Patient-centred care and home treatment

Patients with severe asthma are known to experience a high burden of disease and treatment[44-46] (Figure 1.4). One component of the perceived treatment burden is the number of different medications used, and associated side effects, including concerns of potential (long-term) side effects[44]. Another relevant component may be the experienced burden of frequent hospital visits. These hospital visits may be due to visits to outpatient clinics and emergency departments, but also to day clinic visits for IV or SC administration of biologics. This may be particularly true for the group of patients who

are frequently and or chronically treated with IV drugs. In patients with severe asthma this is the case for patients treated with the anti-IL-5 biologic reslizumab, which is administered IV every four weeks. Studies on home administration in severe asthma are scare and focusing on self-administration of subcutaneous biologics[47, 48]. Under the right conditions, self-administration of subcutaneous asthma biologics seems successful and is increasingly implemented in daily practice [49]. No previous study has investigated the safety and feasibility of home administration of IV reslizumab. Studies in other disease areas show reassuring results about the safety of IV home treatment, but report that different types of patients have different preferences and needs concerning home-based therapy[50, 51]. Given that most people with severe asthma are confronted with their condition at an age when time can be scarce due to work and family commitments, it makes sense to make every effort to reduce the time spent in hospital. For the future, however, it will be important to consider individual patient preferences and the ability of the patient when deciding how to administer biologics.

Figure 1.4 Symptoms, impact, areas of burden and treatment options for people living with severe asthma (reproduced from Stubbs et al, Breathe 2019 [46])



Patient related outcome measures

To promote patient-centred care, patient related outcome measures (PROMs) have been developed. These PROMs measure patients' perceptions of their health and disease and can be used in routine clinical care as well as in research. The potential of PROMs for research purposes, has now been recognized by asthma researchers. For example, incorporating PROMs into clinical research may potentially help to better predict treatment outcomes of biological therapy for severe asthma. Severe asthma registries can play a role in collecting real-life data for this purpose.
Traditionally, the most commonly used outcome measures in studies of biologic therapy in severe asthma are exacerbation frequency, (maintenance-) OCS use and asthma symptom scores (ACQ). There is, however, no universally accepted agreement on the most appropriate set of core outcomes and as outlined above, patients may value certain outcomes differently from physicians or scientists. To fill in this gap, the Core Outcome Measures sets for pediatric and adult Severe Asthma (COMSA)-group performed a multi-step consensus approach to identify meaningful standardized patient-centered outcomes in patients who are treated with biologics[52]. This document emphasizes the importance of using existing (e.g ACQ) and newly developed PROMs (e.g severe asthma questionnaire (SAQ)[53] to understand the impact of asthma treatment on patient's QOL and their experience of biological therapy.

Narrative studies and the patient experience

Another way of gaining more understanding in the values and needs of patients are narrative studies. Narrative studies have the potential to shine a different light on patients experiences. Narrative studies can be defined as: collecting, analyzing and interpreting the stories people tell from their own personal experiences. Data are often collected by semi-structured interviews and or as 'life-histories'. In a previous study performed in Australia the use of semi-structured interviews enabled the authors to identify substantial overlooked needs in patients living with severe asthma[44]. This type of study design is relatively rare in the area of biological therapy for severe asthma, particularly in relation to patients' perceptions of treatment response and the increasing demands on patients to organise and coordinate their own care and to comply with complex treatment regimens . In-depth insight into the experience of severe asthma patients treated with biologics is therefore needed.

In conclusion, patient-centred care has become one of the core values of modern health care. This type of healthcare lends itself well to severe asthma management and may improve health outcomes. Meanwhile the patient experience is recognized as an independent dimension of healthcare quality, alongside clinical effectiveness and patient safety[54]. However, how patients experience 'living with severe asthma' and the treatment with biologics remains largely unknown. This includes the perceived burden of biologic treatment in general, but also to patients' perceptions of, for example, home treatment with intravenous biologics. As new biologics for severe asthma continue to emerge and given the changing healthcare landscape transferring care from the hospital to the home environment patient-centred care can help individual patients to make the

most appropriate choice. Lastly, by using this approach, including PROMs, in severe asthma research, hopefully, future study outcomes will be more in line with the needs and values of individual patients.

RESEARCH QUESTIONS OF THIS THESIS

As outlined above, there are still many unanswered questions about the needs and optimal treatment of patients with severe asthma.
The aim of the research presented in this thesis is to identify the characteristics of patients with severe asthma and comorbid bronchiectasis in more detail. In addition, we aim to gain more insight into the optimal treatment, experiences and preferences of individual patients with severe asthma treated with biologics. In particular, the effectiveness of biological therapy in patients with severe asthma and co-existing bronchiectasis is largely unknown.

This led to the following research questions for the present thesis:

1 What are the clinical, functional, radiologic, inflammatory, and microbial characteristics associated with bronchiectasis in patients with severe asthma and are bronchiectasis more common in a specific severe asthma phenotype? (Chapter 2)
2 What is the real-world effectiveness of anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis on exacerbation frequency and daily maintenance and cumulative oral corticosteroid dose? (Chapter 3)
3 What are the everyday experiences of patients living with severe asthma and using biologics and what is the burden of disease and the burden of treatment experienced by these patients? (Chapter 4)
4 What is the feasibility and safety of treatment with intravenous reslizumab via home administration in patients with severe eosinophilic asthma and are patients satisfied with home administration of this biological? (Chapter 5)
5 Finally, we reflected on core outcome measures for use in studies of biological therapies in patients with severe asthma, based on data from the 'Core Outcome Measures sets for paediatric and adult Severe Asthma' (COMSA). (Chapter 6)

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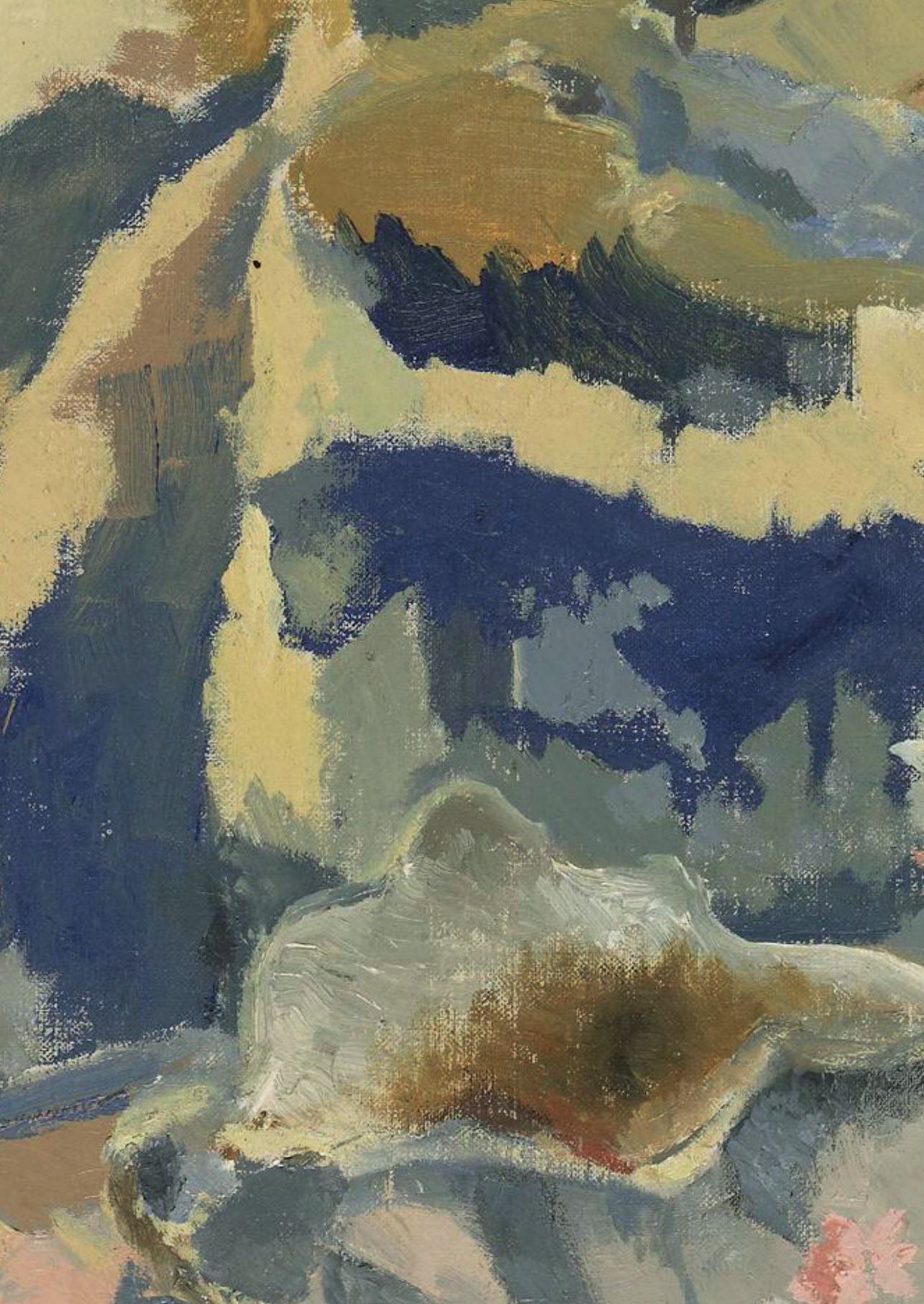

CHAPTER 2

Bronchiectasis in severe asthma, does it make a difference?

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Respiration 2020; Dec 15:1-9

ABSTRACT

Background

Asthma and bronchiectasis are 2 heterogeneous diseases that frequently coexist, particularly in severe asthma. Recognition of this co-diagnosis may importantly affect treatment decisions and outcome. Previous studies in asthma with bronchiectasis show inconsistent outcomes, probably due to the heterogeneity of the included asthma cohorts.

Objectives

We hypothesized that bronchiectasis contributes to asthma severity and that patients with severe asthma and bronchiectasis present with distinct characteristics resulting in different treatable traits. In addition, we explored whether bronchiectasis in severe asthma is more common in a specific phenotype.

Methods

This is a single-center study consecutively including patients with severe asthma from a tertiary referral center. Severe asthma was diagnosed according to the ATS/ERS guidelines. Asthma and infectious exacerbations were defined by the attending specialist as respiratory symptoms requiring treatment with systemic steroids or antibiotics, respectively. Two independentvblinded radiologists evaluated each CT.

Results

19% of patients with severe asthma showed bronchiectasis on CT. Patients with bronchiectasis had a lower FEV_1% predicted (p=0.02) and FEV_1/FVC (p = 0.004) and more infectious exacerbations (p = 0.003) compared to patients without bronchiectasis. Bronchiectasis is more common in patients with a longer duration of asthma, sensitization to *A. fumigatus* or a positive sputum culture. Sputum cultures of patients with severe asthma and bronchiectasis revealed more *P. aeruginosa*, *S. maltophilia*, *H. parainfluenzae,* and *A. fumigates* compared to the non-bronchiectasis group. The adult-onset, eosinophilic asthma phenotype showed the highest prevalence of bronchiectasis (29.4%).

Conclusions

Patients with severe asthma and coexisting bronchiectasis were found to represent a distinct group, in terms of disease severity, microbiology, and asthma phenotype. Performing (HR)CT and sputum culturescan help to identify these patients. These results can possibly contribute to early recognition and targeted treatment of this patient group.

INTRODUCTION

Only a small proportion of asthma patients (<4%) fulfil the criteria of severe asthma[1]. These patients are known to have a high risk of exacerbations, increased health-care utilization, and impaired quality of life[2]. One of the factors known to be associated with severe asthma is the existence of comorbidity[3]. Therefore, the workup of patients with uncontrolled asthma consists of optimal treatment of comorbidities before labelling asthma as severe and refractory.

Bronchiectasis (BE) is a common comorbidity in asthma. Currently, BE is often recognized late during disease in patients with severe asthma. However, treatment adjustments in severe asthma patients may be considered if BE is present, both for maintenance therapy as well asduring exacerbations[4–7]. Therefore, for optimal personalized treatment, early diagnosis of BE in severe asthma is important.

Actual numbers about prevalence of BE in asthma vary among studies from <5% in overall asthma populations to 25–40% in uncontrolled or more severe asthma[3,8–10]. This wide variability may be related to differences in study design or radiological methods used but probably is largely due to the heterogeneity of the included asthma cohorts. This heterogeneity may also underlie the different factors that are identified as associated with the BE coexistence in different asthma cohorts. Data on the presence of BE as comorbidity in truly refractory severe asthma and associated risk factors are scarce. Moreover, since some comorbidities may be more common in specific phenotypes of severe asthma[3], insight into the occurrence of BE in asthma phenotypes might be useful and might contribute to a better knowledge and characterization of BE in severe asthma.

Therefore, in the present study, we assessed the presence of BE in a well-defined group of patients with truly severe asthma and examined the clinical, functional, radiologic, inflammatory, and microbial characteristics associated with BE. In addition, we explored whether BE was more common in a specific severe asthma phenotype.

Materials and Methods

Patients

Patients (>18 years) with severe asthma were consecutively recruited from a tertiary severe asthma referral center in the Netherlands from 2008 to 2018. The diagnosis of asthma was objectively confirmed by a physician based on medical history and 1 or more of the following criteria: significant bronchodilator reversibility, defined as an increase in forced expiratory volume in 1 s (FEV_1) of ≥12% and ≥200 mL after bronchodilator therapy or a provocative concentration of methacholine or histamine causing a 20% fall in FEV_1 of ≤8 mg/mL or a worsening in FEV_1 ≥12% predicted and 200 mL after tapering of medication.

Severe asthma was confirmed, after a systematic assessment with a multidisciplinary team, using the American Thoracic Society (ATS) and European Respiratory Society (ERS) guideline criteria[2]. Patients with a smoking history of ≥15 pack-years were excluded.

Determination of asthma phenotype was based on clinical and inflammatory parameters. Patients were divided into non-eosinophilic, early-onset atopic, or late-onset eosinophilic asthma subphenotypes. The non-eosinophilic phenotype was defined as blood eosinophils <0.3 × 109 cells L-1 at baseline assessment. If patients had blood eosinophils ≥0.3 × 109 cells L-1 and an age of asthmaonset ≥18 years, they were considered a late-onset eosinophilic phenotype[11]. The early-onset atopic phenotype was defined as the start of asthma at age <18 years and a positive atopic status (defined as a score of >0.35 kU L-1 for at least one of the commonaeroallergens [non-aspergillus] tested). This study was performed in accordance with the Declaration of Helsinki, and ethics approval was waived by the Human Research Ethics Committee METC Zuidwest Holland (nr 18-058).

Design

In this single-center retrospective cohort study, all patients were seen by 1 of 2 asthma-specialized respiratory physicians and a respiratory nurse at first consultation. Data on demographics, medical history, comorbidity, health-care utilization, exacerbations, smoking history, and medication use were collected. The Charlson Comorbidity Index, a scoring system assessing presence of multiple comorbidities, was calculated for all patients[12].

The diagnosis of asthma exacerbations and infectious exacerbations was confirmed by the attending specialist. Asthma exacerbations were defined as episodes with worsening of asthma symptoms, requiring treatment with systemic steroids[13]. Infectious exacerbations were defined as respiratory symptoms requiring treatment with antibiotics.

Spirometry[14], fractional exhaled nitric oxide (FeNO) measurement[15], peripheral blood eosinophils, and allergy tests were performed during a stable state at the outpatient clinic. Peripheral blood counts were expressed as absolute numbers. Atopy was defined as a score of >0.35 kU/L for at least one of the specific aeroallergens tested. Specific IgE for Aspergillus was additionally tested. Allergic bronchopulmonary aspergillosis (ABPA) was diagnosed following diagnostic criteria proposed by the International Society for Human and Animal Mycology (ISHAM) working group for ABPA[16].

Criteria to select patients for performing a CT scan were set by the attending severe asthma specialist. Depending on symptoms and clinical presentation, additional diagnostic tests such as CT scan or sputum culture were performed. When diagnostic tests had already been performed by referring pulmonologists, these data were used in the assessment. If a patient had received multiple CT scans, the CT scan with the shortest time interval to primary assessment was chosen. However, patients with CT scans, showing BE, performed afterprimary assessment and during treatment with monoclonal antibodies were excluded (suppl. Fig. S2.1)

Table 2.1 Demographics of patients with severe asthma with and without bronchiectasis

	Total cohort $n = 91$	Severe asthma with BE $n = 17$ (18.7%)	Severe asthma without BE $n = 74$ (81.3%)	p value
Age at primary assessment, year	51.27±15.97	60.82±8.72	49.14±16.46	**<0.001**
Duration of asthma, year	28.83±18.77	39.12±18.62	26.38±18.22	**0.01**
Age of asthma onset, year	22.91±19.92	21.71±18.03	23.28±20.47	0.77
Gender, *n* (%)				
Female	62 (68.1)	12 (70.6)	50 (76.6)	0.81
Male	29 (31.9)	5 (29.4)	24 (32.4)	
Smoking status, *n* (%)				
Never	60 (65.9)	10 (58.8)	50 (67.6)	0.49
Active	5 (5.5)	1 (5.9)	4 (5.4)	
Past	26 (28.6)	6 (35.3)	20 (27)	
Ethnicity, *n* (%)				
Caucasian	74 (81.3)	15 (88.2)	59 (79.7)	0.66
Non-Caucasian	17 (18.7)	2 (11.8)	15 (20.3)	
BMI, kg/m^2	27.68±5.64	26.88±5.04	27.86±5.79	0.98
Charlson Comorbidity Index	0.00 [0.00–1.00]	1.00 [1.00–2.50]	0.00 [0.00–1.00]	**<0.001**

Data are presented as mean ± SD, median [interquartile range] or *n* (%). $p < 0.05$ was considered significant. BE, bronchiectasis; BMI, body mass index

Radiology

HRCT was performed on a multidetector computed tomography scanner at a slice thickness of 1 mm from the lung apex to the diaphragm using 1 mm of collimation. CT scans were viewed using Philips Intellispace PACS 4.4 software (Best, the Netherlands). Two independent radiologists blinded to the other research findings evaluated each CT scan. Criteria for BE were defined in accordance with the radiological criteria [9]. The extension of BE was assessed according to modified Reiff et al [17] criteria, resulting in a score between 0 and 18. When the Reiff scores were >2 points different, the cases were re-evaluated by both radiologists and a definite consensus score was given.

Statistical Analysis

Differences between patients with and without BE were analysed using unpaired Student's t test, $\chi 2$ tests, Fisher's exact tests, and nonparametric tests, where appropriate. Baseline characteristics of severe asthma patients without a chest CT were compared with patients with a CT scan performed without BE as a sensitivity analysis. Statistical analyses were carried out using SPSS software version 24 (IBM, Armonk, NY, USA). p values <0.05 were considered statistically significant.

RESULTS

Of the 127 consecutively recruited patients with severe asthma, 22 patients were excluded because of a smoking history of ≥15 pack-years. Of the remaining 105 patients, 14 patients did not have a CT scan at all (n = 12) or did not have an adequate timing

of the CT scan (n = 2) and were, therefore, excluded (suppl. Fig. S2.1). The mean time interval between CT scan and primary assessment was 1 ± 1.44 years. There was no difference in baseline characteristics between patients with no clinical suspicion of BE and no CT performed and those with a CT scan confirming the absence of BE.

Most of the 91 patients included in the analysis were female (Table 2.1). They all used high doses of inhalation corticosteroids (>1,000 µg fluticasone equivalent), and 30% of the patients were on daily oral corticosteroids. Seventeen out of these 91 (18.7%) patients showed BE with a mean total modified Reiff score of 6.88 ± 5.48. Most of the BE were localized in the left upper lobe (70.6% of patients), and most patients had bilateral BE (64.70%). Most BE were of the varicose type (59%). In 90% of the patients, the CT scan showed bronchial wall thickening (Table 2.2).

Table 2.2 Radiologic characteristics of 17 severe asthma patients with bronchiectasis

Location of BE		
Upper lobes	(*n* = 14)	82%
Lingula or middle lobule	(*n* = 11)	65%
Lower lobes	(*n* = 10)	59%
Bilateral	(*n* = 11)	65%
Quantity of lobes involved		
<3	(*n* = 8)	47%
≥3	(*n* = 9)	53%
Type of BE		
Cylindrical	(*n* = 7)	41.2%
Varicose	(*n* = 10)	58.8%
Cystic	(*n* = 6)	35.3%
Modified Reiff score; mean ± SD	6.88±5.48	

BE, bronchiectasis; BMI, body mass index

Table 2.3 Asthma severity parameters in severe asthma patients with and without bronchiectasis

	Severe asthma with BE *n* = 17 (18.7%)	Severe asthma without BE *n* = 74 (81.3%)	*p* value
Maintenance systemic corticosteroids at primary assessment, *n* (%)	6 (35.3)	22 (29.7)	0.68
Mean daily dose systemic corticosteroids, mg	8.33±2.58	9.32±6.08	0.71
Asthma exacerbations, courses of systemic steroids*,‡	3.00 [2.00–4.50]	3.00 [2.00–4.00]	0.46
Infectious exacerbations, antibiotic courses‡	2.00 [0.00–3.00]	0.00 [0.00–1.00]	**0.003**
Number of hospitalizations‡	1.00 [0.00–2.00]	0.00 [0.00–1.00]	0.16
Post-bronchodilator FEV1% pred	63.94±16.86	76.18±19.95	**0.02**
Post-bronchodilator FEV1/FVC ratio	57.22±10.29	66.29±11.81	**0.004**

Data are presented as mean ± SD, median [interquartile range] or *n* (%). $p < 0.05$ was considered significant. FEV_1, forced expiratory volume in 1 s; % pred, percentage of predicted value.
* Minimum of 5 days 30 mg. ‡ In the previous year.

Compared to patients without BE, severe asthma patients with BE were older at primary assessment 60.8 versus 49.1 years ($p < 0.001$), had a longer duration of asthma, 39.2 versus 26.4 years ($p = 0.01$), and reported more comorbidities (Table 2.1). Patients with BE showed more severe disease with more severe airway obstruction, more antibiotic cycles and a tendency to more hospitalizations compared to severe asthma patients without BE (Table 2.3).

Regarding the inflammatory biomarkers, high levels of blood eosinophil counts were found in both subgroups with significant higher levels in the BE group (0.80 vs. 0.40; $p = 0.028$) (Table 2.4). Severe asthma patients with BE were less frequently sensitized to the common aeroallergens tested, but showed a higher percentage of sensitization to A. fumigatus (53 vs. 20%). The diagnosis of ABPA was confirmed in 2/17 patients with BE and 3/74 patients without BE ($p = 0.23$).

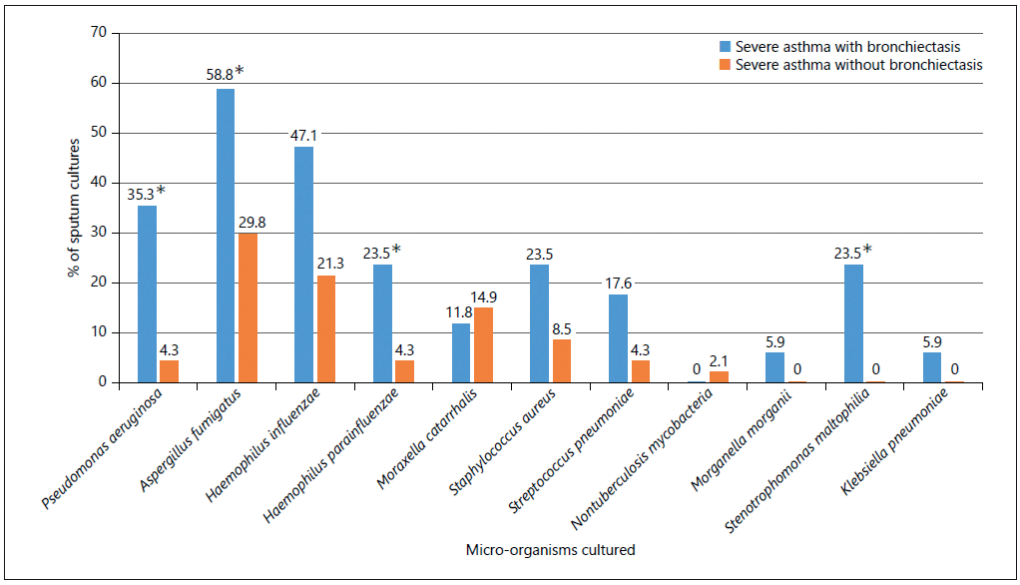
Table 2.4 Inflammatory parameters in severe asthma patients with and without bronchiectasis

	Severe asthma with BE $n = 17$ (18.7%)	Severe asthma without BE $n = 74$ (81.3%)	p value
Blood eosinophils, $\times 10^9$/L	0.80 [0.44–1.34]	0.40 [0.25–0.80]	**0.03**
Total IgE, kU/L	199 [47.5–434.5]	215 [65–677]	0.41
Positive atopic status, *n* (%)	6 (35.3)	50 (67.6)	**0.02**
Sensitized (serum IgE) to Asp. Fumigatus, *n* (%)	9 (52.9)	14 (20.3)	**0.01**

Data are presented as mean ± SD, median [interquartile range] or *n* (%). $p < 0.05$ was considered significant

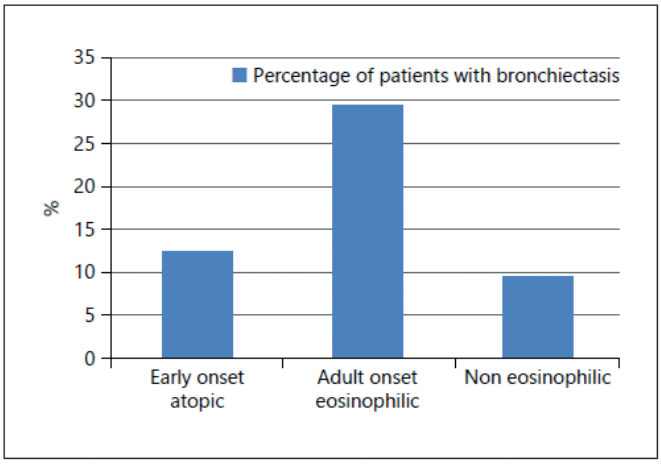
Sputum culture was performed in 47/74 (64%) patients without BE and 17/17 (100%) patients with BE. A total of 88.2% of the patients with severe asthma and BE had 1 or more positive sputum cultures compared to 57.4% of the patients without BE ($p = 0.035$). Sputum cultures of patients with severe asthma and BE revealed more P. aeruginosa, S. maltophilia, H. parainfluenzae, and A. fumigates as compared to the non-bronchiectasis group (Fig. 2.1). When grouping the patients according to their asthma phenotypes, adult-onset eosinophilic asthma was the phenotype with the highest prevalence of BE (29.4%) compared to a prevalence of 12.5% in patients with early-onset atopic asthma and 9.5% in non-eosinophilic asthma (Fig. 2.2). The difference in prevalence of BE between these 3 asthma phenotypes was not statistically significant ($p = 0.178$).

Figure 2.1 Micro-organisms cultured



Microorganisms isolated in sputum cultures of patients with severe asthma with and without bronchiectasis.
* Significant difference between patients with and without bronchiectasis.

Figure 2.2 Prevalence of bronchiectasis distributed by the different asthma phenotypes



Prevalence of bronchiectasis distributed by the different asthma phenotypes (p = 0.178). Phenotypes were defined as follows: eosinophilic: blood eosinophils ≥0.3 . 109/L; adult onset: age ≥18 years at diagnosis; atopy: specific IgE >0.35 kU. L-1 for at least one of the common aero allergens (non-aspergillus) tested. 1 patient not classified.

DISCUSSION

In an extensively characterized, well-defined severeasthma cohort, the presence of BE is more common in patients with a longer duration of asthma, older age at presentation, and sensitization to A. fumigatus. Coexistence of BE in severe asthma is associated with more airway obstruction and a higher amount of blood eosinophils. In addition, these patients show more infectious exacerbations and positive sputum cultures with different pathogens compared to patients with severe asthma without BE. Interestingly, this is the first study to suggest that BE might be more prevalent in a specific inflammatory phenotype of severe asthma, namely, late-onset eosinophilic asthma.

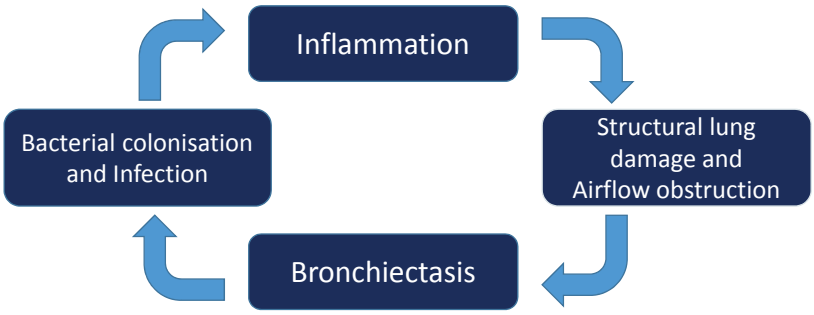
The association between asthma and BE has been studied before. However, previous studies in patients with asthma and BE have included less well-described populations with a less stringent or not up-to-date selection of severe asthma patients or have included past smokers [18–20]. Recently, a prospective study in 398 patients with uncontrolled asthma also found asthma severity to be one of the factors associated with the presence of BE[18]. Contrary to our study, only 60% of the patients in this study were classified to have severe asthma, and no ERS/ATS criteria for the diagnosis of severe asthma were applied. Notably, no difference in positive sputum cultures was found in this study. This contrasts with our study and what would be expected in patients with clinically relevant BE. In addition, only significant differences in absolute FEV_1 and FVC were found in this study and other comparable studies [18–19]. We demonstrated that patients with severe asthma and BE have more severe airway obstruction, defined by FEV_1 in percent of predicted and FEV_1 /FVC ratio, compared to patients without BE. This is an important finding as poor lung function is known to be associated with poor outcomes in asthma[21].

The prevalence of BE in severe asthma in the current study is 19%. This is lower than that reported in the existing literature (25–40%) [18–20, 22, 23]. One study describing qualitative analysis of HRCT findings in difficult- to-treat asthma found BE in 40% of the patients [24]. Another study found 47% of BE in severe asthma[19]. However, 50% of the patients in that study were smokers, and only 30% were treated according to Global Initiative for Asthma (GINA) step 5, which raises the question whether the inclusion of patients was based on truly severe asthma and COPD patients were excluded. This is important because the prevalence of BE in COPD is known to be higher than that in asthma[25–27]. CT scans performed in patients with BE in the current study showed no obvious signs of emphysema, which suggests COPD was adequately excluded. Differences in prevalence of BE in severe asthma and vice versa may also be country specific. Gao et al.[28] showed significant differences in riskfactors for developing BE in different geographical regions. Our study is the first study evaluating patients with severe asthma and BE in The Netherlands.

In the present study, 90% of the patients with severe asthma showed bronchial wall thickening on CT scan. The mean duration of asthma at presentation was 29 years. This is similar to results in previous studies[8, 24]and may imply that a long duration of

asthma and chronic inflammation finally will be accompanied by structural airway changes in nearly all patients with severe asthma (Fig. 2.3). In future diagnostic and treatment strategies for both asthma and COPD, radiologic imaging will be of increasing importance. CT scan in asthma and COPD can be applied not only for detection of coexistent BE but also for differential diagnosis, concomitant skeletal or cardiac diseases, and assessment of air trapping[29, 30]. In light of this, additional studies are needed to investigate if standard performance of CT scan and sputum cultures in patients with severe asthma is cost-effective or performing these tests should be considered on a case-by-case basis.

Figure 2.3 Airway inflammation and bronchiectasis



This study has some limitations. First, not all patients in this cohort underwent a CT scan and therefore had to be excluded. However, this was a small group (13%), and the baseline characteristics of this group did not differ substantially from patients that did not have BE. Therefore, a different outcome in this group is not expected.

Second, sputum culture was performed in 64% of the asthma patients without BE and 100% of the patients with severe asthma and BE. This can be explained by clinicians following current guidelines where sputum culture is part of the standard assessment of patients with BE, but not in patients with severe asthma. Nevertheless, this difference in sputum cultures performed makes it difficult to compare the microbiological data from both groups.

Finally, the difference in prevalence of BE between different asthma phenotypes was not statistically significant. Likely, this is a consequence of insufficient statistical power because of small sample size. Because our absolute percentages were highly suggestive, we suggest that analyzing the prevalence of BE by different asthma phenotypes in larger groups of patients, such as national or international (severe) asthma and BE registries, will be useful.

The strength of this study lies in the extensive characterization of patients, an objectively confirmed diagnosis of severe asthma and BE according to the current guidelines and

exclusion of patients with a smoking history. Furthermore, all CT scans were re-evaluated and scored by 2 independent radiologists.

In this study, BE was more prevalent among severe asthma patients with the late-onset eosinophilic phenotype, and patients with severe asthma and BE had significant higher blood eosinophil counts. This is surprising taking into account that according to current insights, BE patients mainly show neutrophilic inflammation[31].
Blood eosinophil counts can be affected by treatment with maintenance corticosteroids and may be increased in ABPA, which is a common comorbidity in patients with severe asthma and BE. In this study, we consider it unlikely that the use of maintenance corticosteroids was of influence on the results, mainly the difference in eosinophil counts found. This is supported by the fact that there was no difference in treatment with maintenance corticosteroids and coexisting ABPA between both groups.

Eosinophilic inflammation is an important predictor of responsiveness to steroids and new treatments for severe asthma with monoclonal antibodies[32]. Our finding raises the question whether eosinophilic inflammation in severe asthma with BE is the same phenomenon and has the same therapeutic consequences as in severe asthma without BE.

Regarding the fast progress in development of new therapies for severe asthma and the development of more and better biomarkers for phenotyping of disease and optimizing therapy[33, 34], it is relevant to better understand how these findings should be applied with respect to patients with overlap of chronic airway diseases. Future research is needed to evaluate the effect of coexisting BE on responses to biological and other add-on treatment in severe asthma. This applies not only to maintenance treatment but also treatment of exacerbations should be more personalized in this group of patients. This is illustrated by a recent study of Stefan et al.[7]. They reported that antibiotic treatment for patients hospitalized with an asthma exacerbation may be associated with adverse outcomes. To the contrary, antibiotics are the mainstay of treatment of infectious exacerbations in BE. Therefore, characterization of exacerbations in patients with both severe asthma and BE is important in guiding treatment.

The results of this study may have implications for clinical care of patients with severe asthma. Some factors we found to be associated with BE coexistence, like poor pulmonary function and positive sputum culture with pseudomonas and sensitization for A. fumigatus, are known to be associated with poor outcomes in severe asthma[21, 23, 35]. This makes early recognition relevant.Moreover, both severe asthma and BE are associated with a substantial financial burden[36, 37]. Early recognition and appropriate treatment of BE in severe asthma patients may reduce health-care costs.

The strong association of BE with positive sputum cultures and antibiotic consumption, found in this study, is consistent with clinically relevant BE. Data on sputum cultures are often missing in earlier studies [20, 24], whereas in current guidelines, clinically significant disease in BE is defined as radiologic abnormalities associated with symptoms of persistent or recurrent infections[35]. BE severity in general is nowadays expressed by one

of the available scoring systems[38, 39]. By the absence of Medical Research Council (MRC) dyspnoea scale results, we are not able to give exact severity scores; but based on the current results with respect to the extent of BE, microbiology, exacerbation frequency, and pulmonary function, a large percentage of our cohort appears to qualify as moderate or severe BE which importantly affects prognosis and morbidity.

Although the current guidelines stimulate analysis and reduction of comorbidities prior to making the diagnosis of severe asthma, HRCT and sputum cultures that could help to identify patients with BE as a comorbidity are not yet included in the standard assessment of severe asthma. Based on our results, performing sputum cultures and HRCT in every severe asthma patient during primary assessment could help in early recognition of BE.

In conclusion, patients with concurrent BE were found to represent a distinct group within patients with severe asthma, in terms of disease severity, asthma phenotype, and possible outcome. Increased awareness of this co-diagnosis may contribute to early recognition and targeted treatment of this patient group which will improve disease outcome.

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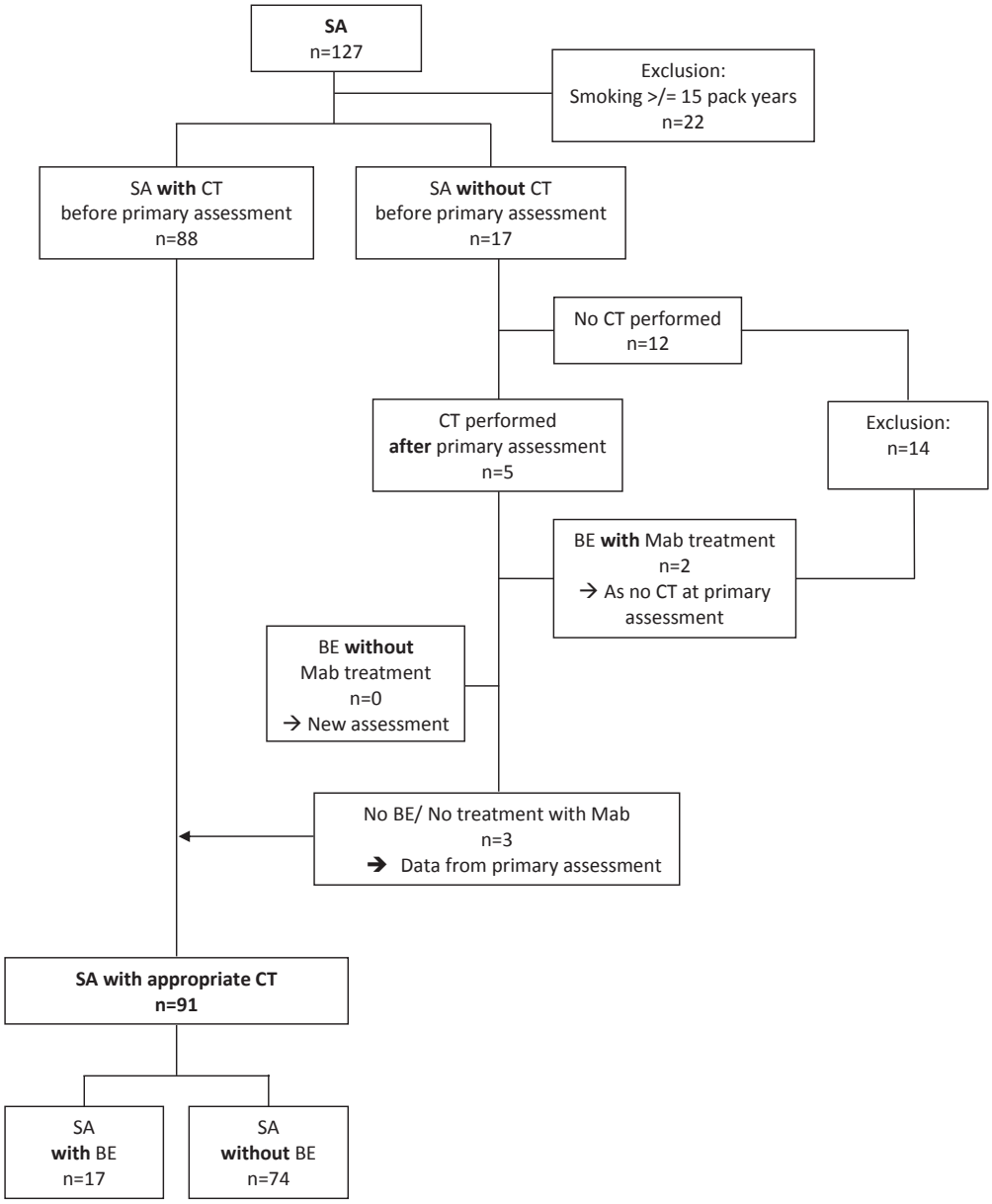
CHAPTER 2

Bronchiectasis in severe asthma, does it make a difference?

Supplementary Material

Figure S2.1



Flowchart showing number of included patients with severe 494 asthma with and without CT
BE: Bronchiectasis: CT: computed tomography; Mab: monoclonal Antibodies; SA: Severe Asthma

CHAPTER 3

Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis

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The Journal of Allergy and Clinical Immunology:In Practice 2023;11(9):2724-31 e2

BACKGROUND

Bronchiectasis is a common comorbidity in patients with asthma and is associated with increased disease severity. In patients with severe eosinophilic asthma, biologics targeting IL-5/5Ra have beneficial effects on oral corticosteroid (OCS) use and exacerbation frequency. However, how coexisting bronchiectasis affects the response to such treatments isunknown.

Objectives

To evaluate the real-world effectiveness of anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis on exacerbation frequency and daily maintenance and cumulative OCS dose.

Methods

This real-world study evaluated data from 97 adults with severe eosinophilic asthma and computed tomography-confirmed bronchiectasis from the Dutch Severe Asthma Registry, who initiated anti-IL5/5Ra biologics (mepolizumab, reslizumab, and benralizumab) and had follow-up data for 12 months or greater. The analysis was performed for the total population and subgroups with or without maintenance OCS use.

Results

Anti-IL-5/5Ra therapy significantly reduced exacerbation frequency in patients with maintenance OCS use as well as in those without it. In the year before biologic initiation, 74.5% of all patients had two or more exacerbations, which decreased to 22.1% in the follow-up year ($P < .001$). The proportion of patients on maintenance OCS decreased from 47% to30% ($P < .001$), and in the OCS-dependent patients ($n = 45$) maintenance OCS dose decreased from median (interquartile range) of 10.0 mg/d (5-15 mg/d) to 2.5 mg/d (0-5 mg/d) after 1 year ($P < .001$).

Conclusions

This real-world study shows that anti-IL-5/ 5Ra therapy reduces exacerbation frequency and daily maintenance as well as the cumulative OCS dose in patients with severe eosinophilic asthma and comorbid bronchiectasis. Although it is an exclusion criterion in phase 3 trials, comorbid bronchiectasis should not preclude anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma.

INTRODUCTION

Bronchiectasis is a common comorbidity in asthma. Actual numbers on the prevalence of bronchiectasis in asthma vary among studies at 5% to 40%, with a significantly higher prevalence in severe asthma compared with mild asthma[1-3]. In patients with severe asthma, concomitant bronchiectasis increases the risk for exacerbations and hospitalizations, decreases quality of life, and may worsen the prognosis[4-6]. In clinical practice, the severe asthma with bronchiectasis phenotype is often considered difficult to treat because it is more refractory to regular asthma treatment[7]. This poses a challenge to health care providers and is especially burdensome to affected patients.

Asthma and bronchiectasis are heterogeneous diseases in which separate phenotypes have been recognized[8,9] with different underlying inflammatory patterns, risk factors, and clinical outcomes. In severe asthma, most patients have a type 2-high subtype characterized by extensive eosinophilic airway inflammation, mediated by cytokines such as IL-4, IL-13, and especially IL-5. Although bronchiectasis has traditionally been associated with neutrophilic inflammation, recent studies show that inflammation in bronchiectasis is heterogeneous, in which a subset of patients exhibit eosinophilic inflammation, indicating a type 2 inflammatory process[10-12].

Until recently, many patients with severe eosinophilic asthma depended on repeated or daily use of oral corticosteroids (OCS) to control the disease,[13-15] which put them at high risk for serious long-term side effects. Studies showed that OCS-related side effects are dose-dependent and associated with cumulative OCS exposure rather than mean daily OCS dose[16,17]. In patients with severe eosinophilic asthma and comorbid bronchiectasis, the use of OCS may be even more detrimental because it may contribute to the suppression of host immunity and increase the risk for bacterial or fungal infections or colonization[18,19]. Thus, there is a great need for OCS-sparing treatment for these patients, possibly through biologics, particularly those targeting IL-5, the major cytokine responsible for the recruitment and activation of eosinophils.

For patients with severe eosinophilic asthma without bronchiectasis, the efficacy of biologics targeting IL-5 (mepolizumab and reslizumab) or IL-5Ra (benralizumab) has been demonstrated in multiple phase 3 randomized controlled trials (RCTs)[20-22] and real-world studies[23-25]. These studies show that IL-5/5Ra-targeted therapy reduces the exacerbation rate and OCS use and improves asthma control and quality of life in many patients with severe eosinophilic asthma[20-22,26]. However, data on the effectiveness of IL-5/5Ra-targeted biologics in patients with severe asthma with comorbid bronchiectasis are scarce and limited to pilot studies with a limited sample size,[27] case series,[28-30] or studies of patients with concomitant allergic bronchopulmonary aspergillosis (ABPA)[31-35].

Therefore, in the current nationwide study, we evaluated the real-world effectiveness of IL-5/5Ra-targeted biologic therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis on the asthma exacerbation frequency, daily and cumulative OCS dose, asthma control, and lung function. For analyses, we used real-world longitudinal patient data from the Dutch Registry of Adult Patients With Severe Asthma for Optimal Disease Management (RAPSODI).

METHODS

Study design and patient population

This was a real-world, nationwide, retrospective, observational, registry-based study. The study population consisted of all adult patients (aged 18 years and older) with severe asthma included in RAPSODI. Patients included in this registry have the diagnosis of severe asthma according to European Respiratory Society/American Thoracic Society criteria[36]. All are treated with high-dose inhaled corticosteroids combined with additional controller medication.

For the current study, we selected all patients with bronchiectasis registered as a comorbidity by the attending specialist and confirmed by computed tomography (CT). We included patients who initiated anti-IL-5/5Ra therapy (mepolizumab, reslizumab, and benralizumab) between December 1, 2015 and September 1, 2020 with available follow-up data at 12 months after initiation (Figure 3.1). For the outcome measurements of exacerbation frequency and OCS use, patients needed data for over 1 year before beginning anti-IL-5/5Ra treatment.

According to the Dutch Severe Asthma Guidelines, the inhaled medication dose, inhalation technique, and adherence should be optimized, patients should be monitored for at least 6 months by an asthma specialist before initiating biologic treatment, and anti-IL-5/5Ra eligibility should be based on blood eosinophils of 0.3 x 10^9 cells/L or greater, or 0.15 x 10^9 cells/L or greater for patients using OCS maintenance treatment.

Because it was likely that OCS use and the exacerbation rate mutually influence each other, we distinguished two groups of patients in the analysis: patients who did and those who did not receive maintenance OCS at anti-IL-5/5Ra treatment initiation. Patients were excluded if they were lost to follow-up or no pharmacy data were available.

This study used a pre-post approach. We compared characteristics and outcomes at 12 months after anti-IL-5/5Ra treatment initiation with those for the same asthma patients at the time of anti-IL-5/5Ra treatment initiation. Informed consent for this study was collected at registry enrollment. The Medical Ethics Review Committee of Leiden, Den Haag, Delft, waived a formal approval from a medical ethics committee according to Dutch legislation (Reference No.G21.158).

Data source

We retrieved data on patients with severe asthma from 19 Dutch hospitals from the RAPSODI registry, which is based on two sources: annual electronic case report forms (135 CASTOR EDC platform, Amsterdam, the Netherlands), and 3-monthly electronic patient questionnaires (PatientCoach; Leids Universitait Medisch Centrum, Leiden)[23]. In addition, to assess cumulative OCS exposure, we requested the systemic corticosteroid dispensing data (ATCcode H02AB) for 12 months before and 12 months after anti-IL-5/ 5Ra initiation from each patient's pharmacy. We verified that the patient con-

sented to the Dutch National Exchange Point, to ensure that medication possibly dispensed at other pharmacies was captured[37].

Study variables and definitions

Study data included clinical characteristics (patient demographics, age at onset of asthma, smoking history, and atopic status), asthma control (assessed by the six-item Asthma Control Questionnaire (ACQ-6),[38] exacerbation rate, comorbidities (chronic rhinosinusitis with nasal polyps, gastroesophageal reflux disease, ABPA), inflammatory markers (leukocytes, eosinophils, neutrophils and total IgE in peripheral blood, and FeNO),[39] lung function measurements (prebronchodilator FEV_1 and FVC[40]), and data on treatment (receiving azithromycin or OCS maintenance treatment, OCS daily maintenance dose, and cumulative OCS dose).

Positive atopic status was defined as a score of greater than 0.35 kU/L for at least one of a set of specific aeroallergens tested. We also collected data on specific IgE for Aspergillus fumigatus. Blood tests for specific IgE for fungal agents other than A fumigatus are not part of the standard assessment in the Netherlands and therefore are unavailable in the registry.

Severe asthma exacerbations were defined by at least one of the following criteria: (1) the patient reported using OCS courses (if not receiving maintenance OCS), (2) the patient reported doubling the maintenance dose of OCS for at least 3 days, and (3) the patient reported unscheduled emergency visits or hospitalization for asthma. In RAPSODI, the number of exacerbations is categorically recorded. Therefore, the annualized exacerbation frequency was analyzed as the percentage of patients with an exacerbation frequency of none toone, two to five, or more than five exacerbations per year.

Daily maintenance OCS dose was defined as the prednisolone equivalent daily maintenance dose of OCS (milligrams per day).

Cumulative OCS dose was calculated as the sum of the amount of issued tablets multiplied by the strength (milligrams per tablet) in months 12 to 0 and months 0 to 12.

Study outcomes

Primary outcomes.

Co-primary study outcomes included (1) a change in categorized exacerbation frequency between 12 months before and 12 months after the start of anti-IL-5/5Ra therapy, and (2) a change in daily maintenance OCS dose (milligrams per day) after 12 months of therapy. In addition to the whole-group assessment, two subgroups were analyzed separately: patients who used maintenance OCS at anti-IL-5/5Ra initiation and those who did not.

Secondary outcomes.

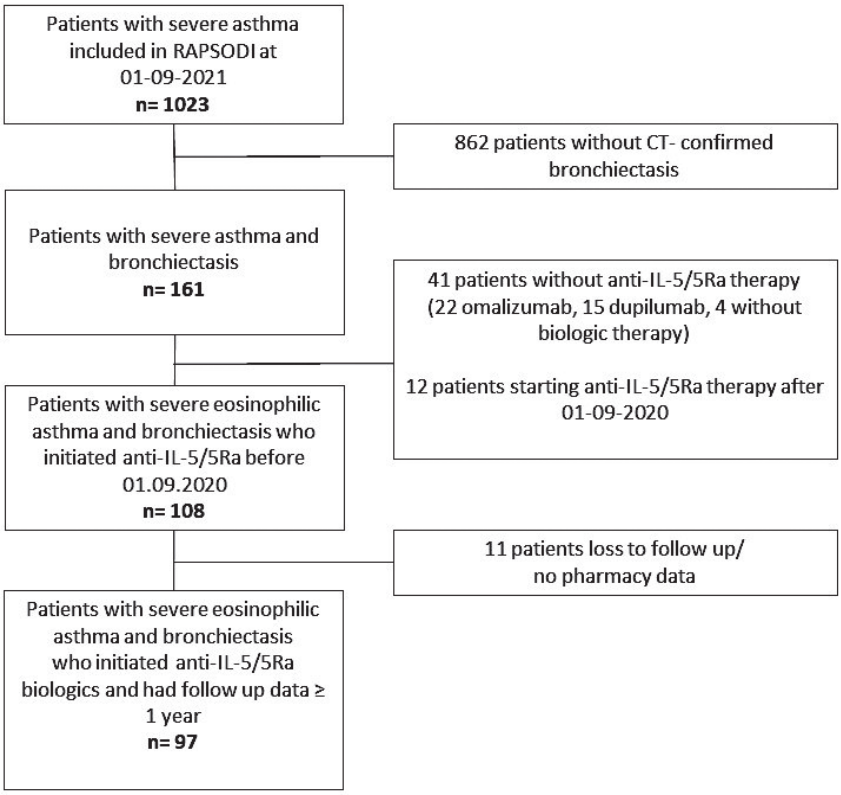
Secondary outcomes included the change in ACQ-6 and lung function parameters between baselineand 12 months after the initiation of anti-IL-5/5Ra therapy. In addition, we analyzed the change in cumulative OCS dose used 12 months before and 12 months after the start of anti-IL-5/5Ra therapy.

Statistical analysis

Patient and treatment characteristics are summarized using descriptive statistics. Continuous variables are expressed as mean (±SD) or median with interquartile range ([IQR], 25% to 75%). Differences in variables between 12 months before and 12 months after the initiation of anti-IL-5/5Ra therapy were analyzed using Wilcoxon signed-rank test or χ^2 test, when appropriate.

Because the results might be influenced by the concomitant presence of ABPA or by the effect of a non-IL-5/5Ra-targeted biologic treatment initiated within the follow-up year,

Figure 3.1 Patient selection



CT, computed tomography; RAPSODI, Dutch Registry of Adult Patients With Severe Asthma for Optimal Disease Management

we performed sensitivity analyses for the primary outcomes, first in the subgroup of patients after excluding those with known ABPA, and second after excluding patients who switched to a non-IL-5/5Ra-targeted biologic in the first year after anti-IL-5/5Ra initiation.

P less than .05 was considered statistically significant. All analyses were performed using SPSS software (version 24, IBM, Armonk, NY).

RESULTS

Patients

Of 1,023 patients with severe asthma included in the RAPSODI registry on September 1, 2021, 161 patients had comorbid bronchiectasis (16%), 97 of whom had initiated anti-IL-5/5Ra biologics before September 1, 2020 with available follow-up data over a 12-month period (range, 11-16 months) (Figure 3.1).

Table 3.I lists characteristics of the 97 included patients. Most patients were middle-aged, had adult-onset asthma, and were nonatopic. The majority of patients had two or more exacerbations per year, about half of them received maintenance OCS, and 21% of patients were treated with maintenance azithromycin. Whereas nasal polyposis was present in more than half of patients, only 8% received the diagnosis of ABPA.

Effect of anti-IL-5/5Ra therapy on exacerbation rate and OCS dose

Exacerbation frequency.

Within the total population, 75% of patients had two or more exacerbations in the year before anti-IL-5/5Ra biologic initiation, which decreased to 22% in the year after starting biologic therapy ($p < .001$). This beneficial effect was seen in both OCS-dependent and non-OCS dependent patients (Table 3.2 and Figure 3.2).

Oral corticosteroid use.

Within the total population of patients with severe eosinophilic asthma and bronchiectasis, 47.4% were receiving maintenance OCS before initiating anti- IL-5/5Ra therapy, which decreased to 29.5% after 12 months of follow-up (P < .001) (Table 3.2). In the OCS-dependent patients (n = 45), the daily maintenance OCS dose decreased from a median (IQR) of 10.0 [5-15] mg/d to 2.5 (0-5) mg/d after 12 months (P < .001). Of 45 patients with maintenance OCS at baseline, 35 (78%) showed a 50% or greater reduction in daily maintenance OCS dose after 1 year of anti-IL-5/5Ra therapy. Figure 3.3 and Table 3.2 show the cumulative OCS dose for 12 months before and 12 months after starting anti-IL-5/5Ra therapy; it was significantly reduced for the total population and both subgroups.

Table 3.1 Baseline characteristics of patients with severe asthma and comorbid bronchiectasis

Patient characteristic	Total group (n=97)
Age (y)#	62 (54-68)
Male sex, n (%)	54 (55.7)
Race *Caucasian*, n (%)	88 (91.7)
Never smokers, n (%)	62 (63.9)
Pack-years (y)#	13 (5-24)
BMI (kg/m^2) #	26.2 (23.3-28.8)
Age of asthma onset (y)#	43 (18-59)
Atopic asthma, n (%)	44 (45.4)
ACQ#	2.33 (1.50-3.0)
Exacerbation frequency, n (%)	
0 to 1 exacerbation / year	24 (25.5)
2 to 5 / year	48 (51.1)
>5 / year	22 (23.4)
Pulmonary function	
Pre-BD FEV_1 (% predicted)#	72 (56-90)
FEV_1/ FVC ratio, %#	63 (55-73)
Surrogate inflammatory parameters	
Blood eosinophils (x10^9 cells/L)#	0.38 (0.20-0.63)
Highest blood eosinophils ever (x10^9 cells/L)#	0.70 (0.47-1.20)
Total IgE (IU/ml)#	151 (55-358)
FeNO (ppb)#	43.5 (19.5-75)
Blood leukocytes (x10^9 cells/L)#	8.65 (7.40- 11)
Blood neutrophils (x10^9 cells/L)#	5.63 (3.84- 7.69)
Co-morbidity*	
ABPA, n (%)	8 (8.2)
CRSwNP, n (%)	55 (56.7)
Gastro-esophageal reflux, n (%)	13 (13.4)
Treatment	
OCS maintenance therapy, n (%)	45 (47.4)
Treatment with maintenance azithromycin, n (%)	21 (21.6)

Data are presented as n (%), mean ±SD or median (interquartile range)#, unless otherwise stated
*physician reported co-morbidity

BMI: body mass index; FEV1: forced expiratory volume in 1 s; % predicted: percentage of predicted value; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO: exhaled fraction of nitric oxide; ppb: parts per billion

Table 3.2 Effect of anti-IL-5/5Ra therapy on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis (n = 97)

	at baseline (anti-IL-5/5R initiation)	at 12-months follow-up	p-value
All patients, n= 97			
Exacerbation frequency, n (%)			<0.001
0 to 1 / year	24 (25.5)	74 (77.9)	
2 to 5 / year	48 (51.1)	21 (22.1)	
>5 / year	22 (23.4)	0 (0)	
Missing (n)	3	2	
OCS maintenance therapy*, n (%)	45 (47.4)	28 (29.5)	<0.001
Daily OCS maintenance dose, mg/day#	10 (5-15)	2.5 (0-5.0)	<0.001
OCS cumulative dose**, g/year#	1.61 (0.82-2.82)	0.51 (0.013-2.07)	<0.001
OCS-dependent*, n= 45**			
Exacerbation frequency, n (%)			<0.001
0 to 1 / year	15 (33.3)	31 (68.9)	
2 to 5 / year	17 (37.8)	14 (31.1)	
>5 / year	13 (28.9)	0 (0)	
Missing (n)	0	0	
OCS maintenance therapy, n (%)	45 (100)	28 (30)	<0.001
Daily OCS maintenance dose, mg/day#	10 (5-15)	2.5 (0-5.0)	<0.001
OCS cumulative dose, g#	2.63 (1.74-3.69)	2.02 (0.81-2.70)	<0.001
Non-OCS-dependent, n= 47			
Exacerbation frequency, n (%)			<0.001
0 to 1 / year	8 (18.2)	40 (88.9)	
2 to 5 / year	29 (65.9)	5 (11.1)	
>5 / year	7 (15.9)	0 (0)	
Missing (n)	3	2	
OCS cumulative dose, g#	1.0 (0.42-1.61)	0.067 (0-0.42)	<0.001

Data are presented as n (%) #median (interquartile range), OCS: oral corticosteroids
* valid n (5 patients missing data on OCS dependency), **Cumulative OCS dose; calculated as the sum of the amount of issued tablets multiplied by the strength (mg per tablet) in months -12 to 0 and months 0 to 12, ***OCS-dependent; defined as patients using maintenance OCS at anti-IL-5/5Ra initiation.

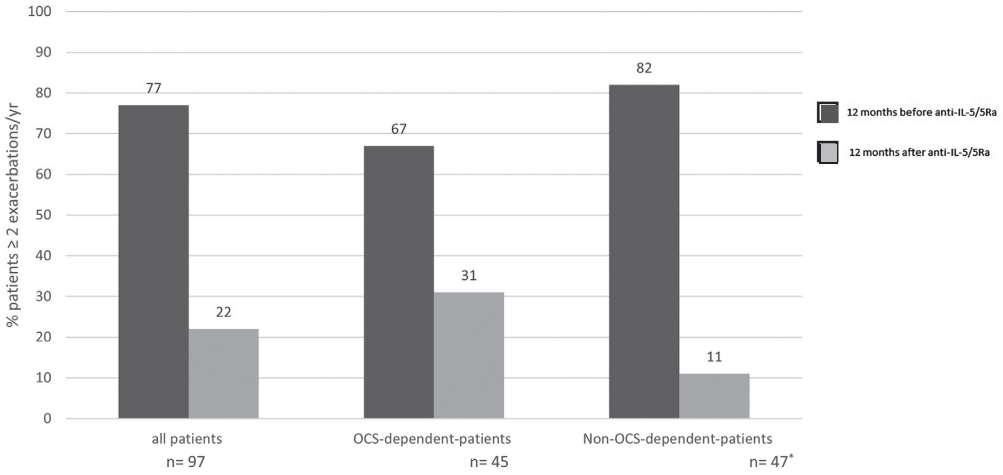
Similar significant effects in primary outcomes were found when we excluded patients with comorbid ABPA (n=8) (suppl. Table S3.1) or those who switched to a non-IL-5/5Ra-targeted biologic (n=2) (suppl. Table S3.2).

Effect of anti-IL-5/5Ra therapy on asthma control and lung function

Asthma control as assessed by ACQ-6 score significantly improved from 2.33 (1.50-3.0) at the start of biologic therapy to 1.29 (0.57-2.0) after 12 months of treatment ($P < .001$).

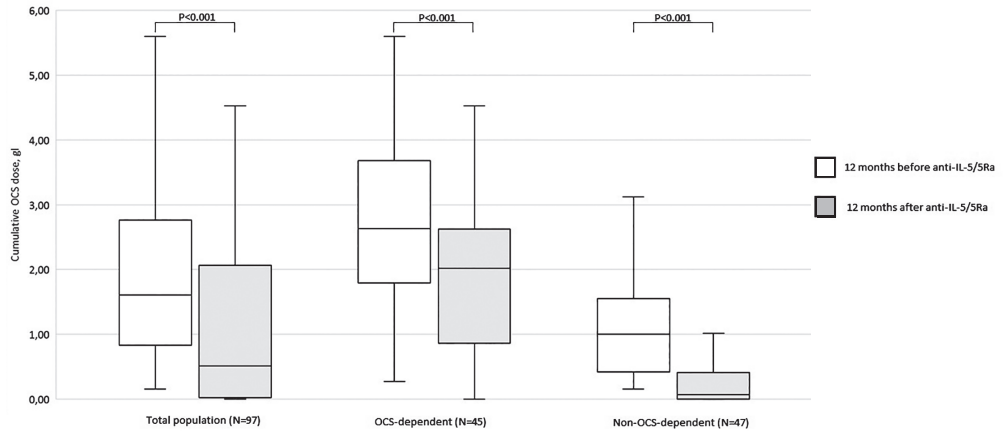
After 12 months of anti-IL-5/5Ra therapy, median (IQR) FEV_1 nonsignificantly ($P = .13$) increased from 72(56-90) percent predicted to 77 (61-94) percent predicted. Moreover, there was no significant change in FVC percent predicted and FEV_1/FVC 1 year after the start of anti-IL-5/5Ra therapy.

Figure 3.2 Effect of anti-IL-5/5Ra therapy on severe asthma exacerbations from 12 months before to 12 months after initiation.



OCS, oral corticosteroids. Valid n (five patients were missing data for OCS dependency).

Figure 3.3 Cumulative oral corticosteroids (OCS) dose from 12 months before to 12 months after initiation of anti-IL-5/5Ra therapy.



Valid n (five patients were missing data for OCS dependency).

DISCUSSION

This real-world study shows that treatment with IL-5/5Ra targeted biologics reduces exacerbation frequency and OCS use in patients with severe eosinophilic asthma and comorbid bronchiectasis. This applies to patients who did not use OCS daily, as well as patients on maintenance treatment with OCS, despite tapering the daily OCS dose in the majority of the latter patients. In addition, an important and clinically relevant improvement in ACQ-6 score was seen after 12 months of treatment with anti-IL-5/5Ra therapy, similar to results in previous phase 3 studies in severe asthma patients without comorbid bronchiectasis[20,21]. These results suggest that anti-IL-5/5Ra biologics should be considered as add-on therapy for patients with severe eosinophilic asthma and comorbid bronchiectasis. The demonstrated OCS-sparing effect may be particularly relevant in this patient group.

This is the first nationwide study evaluating the real-life response to anti-IL-5/5Ra therapy in a large cohort of patients with severe eosinophilic asthma and concomitant bronchiectasis. Because comorbid bronchiectasis was an exclusion criteria in phase 3 trials, evidence is scarce regarding the effectiveness of IL-5/5Ra-targeted biologics in this subset of patients with severe asthma. Two case series involving fewer than 10 patients with severe asthma and bronchiectasis reported significant improvements in the exacerbation rate and OCS use after 12 to 24 months of treatment with anti-IL-5/5Ra biologics[29,30]. Similar beneficial effects on the numbers of exacerbations and OCS dose were found in an Italian single-center study evaluating the effectiveness of mepolizumab in 16 patients with severe eosinophilic asthma patients who had bronchiectasis[27]. Our study in a larger cohort of patients with severe eosinophilic asthma and comorbid bronchiectasis confirms and extends these results by showing that anti-IL-5/5Ra biologics can significantly reduce frequent exacerbations and OCS exposure.

Our study had a number of important strengths, including the relatively large group of patients included and the nationwide, multicenter design that enhanced external validity. The large patient population allowed us to analyze patients separately with and without maintenance OCS use, mimicking the design of most phase 3 asthma trials on biologics. Moreover, our study provides good insight into the OCS-sparing effect of anti-IL-5/5Ra biologics in this population. We showed a reduction inpatients who were dependent on daily OCS, accompanied by a lower median daily OCS dose. Moreover, we were able to demonstrate the significant effect on the cumulative OCS dose over the year, which is a better predictor of OCS-related side effects than the daily dose at some point in the disease,[17] and may be particularly relevant in this patient group.

Our study had some limitations as well. First, the diagnosis of bronchiectasis was based on information entered in the registry by the attending physician, and it cannot be excluded that a standardized CT scan performed in all patients, with an assessment by an independent radiologist, would have led to different numbers. By requiring positive answers to two questions that regarded bronchiectasis listed as a comorbidity as well as demonstrated on a CT scan, we made the chance of a false bronchiectasis label as small as possible, but we cannot fully exclude this possibility. Furthermore, our severe asthma

registry provides no detailed information about the type, extent, and etiology of bronchiectasis, or the bronchiectasis severity index,[41] and sputum culture data are scarce. Therefore, we cannot analyze whether there is a relationship between these characteristics and the response to biologics. However, we found similar results when the analysis was repeated without the small group of patients with reported ABPA. Finally, as is the usual limitation inherent in the observational registry-based design of the study, we lacked a control group of patients with severe eosinophilic asthma and comorbid bronchiectasis who were not treated with anti-IL-5/5Ra, because patients without a biologic were less likely to be included in the registry. Aware of the reported effects in placebo arms of previous RCTs of biologics in severe asthma,[20-22] we realize the inherent risk of overestimating treatment effects in a study without a control group. We cannot exclude that other factors, such as improved compliance and inhalation technique, might also have influenced the better results, although in the Netherlands these factors need to be assessed and optimized in all patients before these patients are eligible for biologic therapy. Yet, even in the absence of such a control group, in our view, the degree of the observed effect justifies a recommendation to consider anti-IL-5/5Ra biologics as an add-on-therapy for patients with severe eosinophilic asthma and comorbid bronchiectasis.

The results of anti-IL-5/5Ra therapy in this population of patients with severe asthma and comorbid bronchiectasis are consistent with previous real-world studies evaluating the effectiveness of anti-IL-5/5Ra therapy in patients with severe eosinophilic asthma[23,42]. This suggests that there are no relevant differences in response to anti-IL-5/5Ra therapy between patients with and without comorbid bronchiectasis; however, future studies are needed to confirm this.

There is some evidence that patients with particularly severe asthma who have type 2 inflammation are likely to exhibit bronchiectasis[6]. A recent study suggested that type 2 inflammation can have a causative role in developing bronchiectasis[43]. Although the mechanism is not yet fully clarified, abundant eosinophilic bronchial inflammation and associated degranulation products are supposed to have a role in epithelial damage,[44] loss of the epithelial barrier, and consequently an increased susceptibility for upper and lower respiratory tract infections,[45,46] in addition to an impaired type 1 response to infections[46]. Future studies are needed to evaluate the long-term effect of type 2 directed biologics on modulating inflammatory and remodeling processes in patients with severe asthma who have bronchiectasis. In addition to IL5/5R-targeted biologics, it thus relevant to study the response to other biologics, such as anti-IL4/R or antithymic stromal lymphopoietin, especially considering patients with mucus hypersecretion.

In addition to these research recommendations, our study has important clinical implications. The favorable response to 12-month anti-IL-5/5Ra therapy observed in this study indicates that physicians should not worry that the effect of IL5/5Ra-targeted biologics in patients with severe eosinophilic asthma and comorbid bronchiectasis will be below expectations, even though comorbid bronchiectasis was an exclusion criterion in the RCTs. Moreover, by demonstrating the effect on the cumulative OCS dose, we highlighted the significant OCSsparing potential of IL5/5Ra-targeted biologics in

these patients. This should further encourage physicians to consider these biologics in patients with severe asthma complicated by bronchiectasis, for whom reducing OCS exposure appears to be crucial in view of the suppression of immunity and risk for infections.

This study demonstrates that patients with severe eosinophilic asthma and comorbid bronchiectasis have an excellent response in terms of a reduction in exacerbation frequency and OCS use when treated with anti-IL-5/5Ra biologics in real life. Therefore, these patients with a substantial burden of disease should not be excluded from biologic therapy.

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CHAPTER 3

Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis

Supplementary Material

Table S3.1 Effect of anti-IL-5/5Ra on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis after excluding patients with ABPA

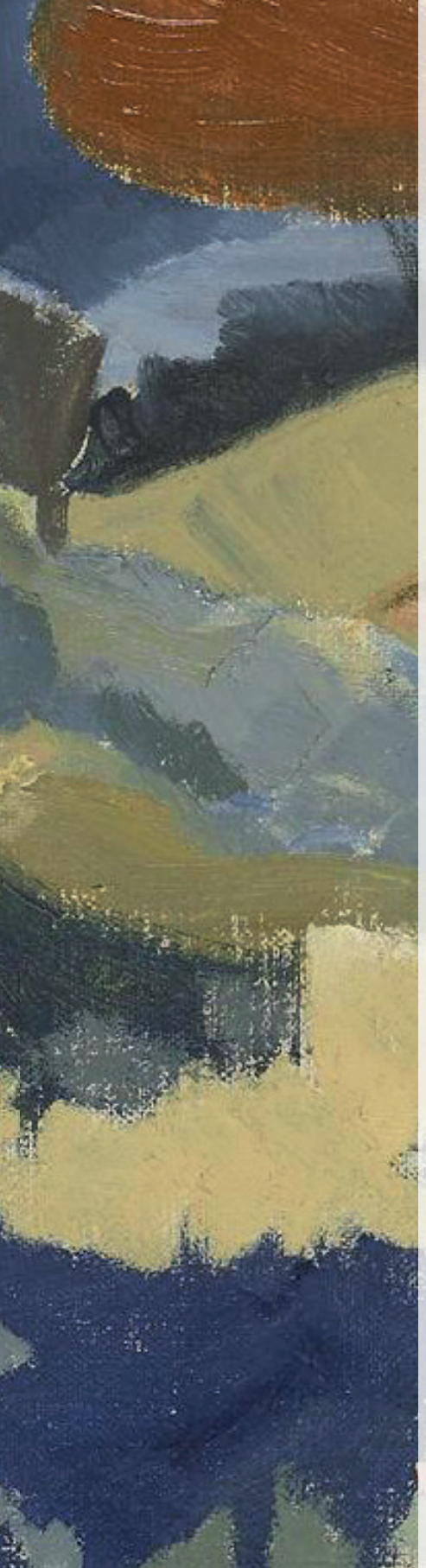
patients, n= 73*	at anti-IL-5/5Ra initiation	at 12 months follow-up	p-value
Annualized exacerbation frequency, n (%)			<0.001
0 to 1 exacerbation / year	19 (27.1)	58 (81.7)	
2 to 5 / year	37 (52.9)	13 (18.3)	
>5 / year	14 (20.0)	0 (0)	
Missing (n)	3	2	
OCS maintenance therapy, n (%)	31 (42.5)	20 (27.4)	<0.001
Daily OCS maintenance dose, mg/day#	10 (5-15)	5.0 (4.25-7.50)	<0.001
OCS cumulative dose, g#	1.56 (0.82-2.76)	0.48 (0.00-2.12)	<0.001

Data are presented as n (%) #median (interquartile range), OCS: oral corticosteroids, ABPA: allergic bronchopulmonary aspergillosis. * Valid n (missing value in 16 patients; no information on ABPA as comorbidity)

Table S3.2 Effect of anti-IL-5/5Ra on exacerbation frequency and OCS dose in patients with severe asthma and comorbid bronchiectasis after excluding patients who switched to a non-IL5/5Ra targeted biologic in the first year after anti-IL-5/5Ra initiation.

patients, n= 95	at anti-IL-5/5Ra initiation	at 12 months follow-up	p-value
Annualized exacerbation rate, n (%)			<0.001
0 to 1 exacerbation / year	24 (25.8)	72 (77.4)	
2 to 5 / year	47 (50.5)	21 (22.6)	
>5 / year	22 (23.7)	0 (0)	
Missing (n)	2	2	
OCS maintenance therapy, n (%)	45 (47.4)	28 (29.5)	<0.001
Daily OCS maintenance dose, mg/day#	10 (5-15)	5.0 (3.81-7.50)	<0.001
OCS cumulative dose, g#	1.56 (0.82-2.85)	0.51 (0.07-2.07)	<0.001

Both patients who switched to a non-IL-5/5Ra targeted biologic (n=2) switched to anti-IL-4R
#median (interquartile range)



CHAPTER 4

‘Like a fish on dry land’: an explorative qualitative study into severe asthma and the impact of biologicals on patients’ everyday life

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Journal of Asthma 2022; 59(5):980-8

ABSTRACT

Objective

In order to provide concrete context to research on biologicals for severe asthma we explore the everyday experiences of patients living with severe asthma and using biologicals.

Methods

We use a multi-method qualitative research-design including existing patient narratives, ten life-history interviews with patients using benralizumab (N = 8), dupilumab (N = 1), no biologicals (N = 1), and with healthcare professionals (N = 2) in the Netherlands. Our analysis focuses on patients' experiences with the burden of disease and the burden of treatment regarding severe asthma.

Results

Findings show how our respondents experience a high burden of disease (breathlessness, fatigue, exacerbations, loss of family, friends and employment) and treatment (oral corticosteroids' side-effects, dependency, life-style changes). Treatment with biologicals is relatively new for respondents. They mention to be cautious in their embrace of biologicals and in expressing hope for the future. Respondents who react to treatment with biologicals experience relief of both the burden of disease and treatment. They aim to regain their social life and societal participation, a contrast to those for whom biologicals prove ineffective. Biologicals' burden of treatment is experienced as low and minor side-effects are mentioned by three respondents. Respondents appear relatively unconcerned about the lack of knowledge concerning the long-term effects of biologicals.

Conclusions

Effective treatment with biologicals is generally experienced as a cautiously optimistic next step in a much longer and complex process of living with severe asthma. The practical lessons we draw point to managing patients' expectations and the need to pay attention to patients not eligible for treatment with biologicals.

INTRODUCTION

Over the past 15 years, the diagnosis of 'severe asthma' has evolved. According to the current universally accepted definition, severe asthma is: 'asthma which requires treatment with a high dose of inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy (1: p.344)[1]. Only about 3–5% of the total asthma population suffers from severe asthma. This relatively small subgroup uses about 60% of the resources for treatment. This is mainly due to their high use of medication[2]. Because of these differences, developing from medical and pathological differences, calls have emerged to distinguish severe asthma more explicitly from milder asthma[3].

From the early 2000s specific medicines for asthma called 'biologicals' have emerged [1]. Biologicals are monoclonal antibodies that influence the immune system directly by blocking a specific messenger protein, interleukin, that is involved in inflammation processes (biologicals work on immunoglobulin E (IgE interleukin-4 receptor (IL4) (R), interleukin-5 (receptor) (IL5(R)) and interleukin-13 (IL13). Anti-IL-5 reduces eosinophilic inflammation in asthma by inhibition of eosinophil maturation and survival[2]. Biologicals are add-on treatments such as omalizumab (Xolair®, 2003,IgE), mepolizumab (Nucala®, 2015), reslizumab (Cinquero®) (2016, IL-5), benralizumab (Fasenra®, 2017, IL-5R), and most recently dupilumab (Dupixent®, 2019, IL4R). Only about 50% of patients with severe asthma meet the criteria for treatment with these biologicals, as this depends on the type of inflammation and which interleukins are involved. For patients with severe eosinophilic, T helper type 2 cells (Th2) driven, asthma the addition of biologicals to their treatment has proven to be effective in order to regain control over the disease, such as reducing asthma exacerbations [4]. Clinical trials show biologicals having a 'relatively favorable safety profile' (5: p. 747, cf. 6,7). Novel approaches and therapies are needed for patients with severe non-eosinophilic asthma for whom currently available biologicals are not effective.

There is little research published that addresses patients' experiences of living with severe asthma, and to the best of our knowledge, no interpretive research has been executed that explores the use of biologicals for this group of patients[8]. Such an exploration is highly relevant in order to provide the necessary lived context to existing technical pharma-economical and epidemiological research on the use of biologicals for severe asthma. In this paper we focus on patients' experiences with biologicals. However, we also pay attention to the experience of living with severe asthma in general at the same time as the experiences with this type of drugs will be connected to patients' experiences with the disease in daily life life and past experiences with treatments.

The literature on the impact of living with chronic conditions, such as asthma, in daily life focuses on the burdens caused by these conditions. Firstly, this literature identifies a burden of disease; the burden of symptoms that patients experience. Secondly, it identifies a burden of treatment; the experience of patients 'new and growing demands to organize and coordinate their own care, to comply with complex treatment and self-monitoring regimes, and to meet a whole range of expectations of personal motivation,

expertise and self-care' (9: p0.2). The burden of treatment thus refers to the engagement of patients with their own (chronic) conditions that cannot be cured but rather must be managed.

From the few studies that have been done on experiences of patients we can distill that suffering from severe asthma shows high burdens of disease and treatment, although the experiences of patients are not conceptualized as such in these studies. Applying this conceptualization, we can conclude from these studies that burden of disease is high. Patients find themselves continually short of breath, fatigued, at risk of fearful exacerbations, unable to breathe, and in need of regular medication, while dealing with anxiety and depression[3,10]. Besides physical distress, patients report living in fear, experience loss of contact with friends and family, and are unable to work. The latter also causes financial burdens[8,11]. Burden of treatment for severe asthma is also high. It includes regular use of medication with (risks of) side-effects, especially oral corticosteroids (OCS), and large lifestyle changes such as weight management, exercise, smoking cessation, and avoiding triggers at work, home, and in everyday social life[8,12–14]. The burden of treatment also involves health care utilization, such as repeated hospital visits and stays. Moreover, calls for patient empowerment and self-management can be found in literature on patients with severe asthma[15]. As self-management shifts responsibilities to patients, it can further increase the burden of treatment.

This paper focuses on exploring the burden of disease and burden of treatment in patients with severe asthma and treated with biologicals. In doing so, we respond to the call for in-depth insight into the lived experience of severe asthma patients treated with biologicals[8] by reporting on a qualitative study from the Netherlands.

METHODS

Our qualitative exploratory research involved two steps: an analysis of patient experience stories and an interview-study with a life-history approach. Firstly, we analyzed existing Dutch written patient narratives. Eighteen books were selected from the collection of 5409 patient narratives at the library of the Erasmus University Rotterdam[a] using the theme 'asthma'. We excluded eleven books after a first reading of the material, selecting the seven books written by patients living with severe asthma[16–22]. We identified two further publications through our interview study[23,24]. None of the publications focused on the use of biologicals. However, they did provide us with the opportunity to gain in-depth insight into the experiences of living with the condition.

Secondly, building on the insights gained from the patient narratives, we interviewed patients (n = 10) and healthcare professionals (n = 2). The patient interviews were approached as "life-histories" in which we gave patients the opportunity to share their own experiences, in their native language (Dutch), without over-structuring the interview[25,26]. The researcher used open-ended topics to elicit spontaneous discussion on patient experience in patient's own words. Topics were, except for biologicals, derived from thepatient narratives and included: experiences in everyday life, finding a diagnosis, getting treatment. This approach enabled us in our aim to seek diversity in pa-

tients' own narratives on daily life with severe asthma and the impact of biologicals. The patient interviews were supplemented with two interviews with specialized health care personnel (respiratory nurse, pulmonologist). These interviews helped us to contextualize the patient interviews.

For the interviews we purposefully selected patients using a specific biological, benralizumab[b] and included patients who are currently using benralizumab successfully and those that have (recently) stopped. In order to develop a broader understanding of the themes related to the therapeutic area as a whole, we also included patients who use(d) other biologicals and one patient who had no experience with biologicals and was diagnosed with allergic severe asthma. Details on respondents can be found in Table 4.1.

Respondents were selected from four nonacademic Dutch hospitals with tertiary severe asthma referral centers spread out across the Netherlands. AstraZeneca provided assistance for the selection of hospitals, however the researchers remained fully independent in their decision to adopt or reject the input. Physicians informed patients of the study and the primary researcher contacted them when they expressed the wish to participate. Interviews were, in all cases except for one (P008), executed in the homes of the respondents and lasted between 43 min (P009) and 86 min (P003) with an average of 56 min. Respondents P004 and P005 were interviewed together, and respondent P010 requested his wife to be present during the interview. All respondents consented to have their interview audio recorded, no incentives were offered for participation. Recordings were subsequently transcribed verbatim to enable detailed analysis.

The written patient narratives and interviews were analyzed abductively through iterative thematic reading of the material; moving back and forth between the data and the literature[27,28]. The initial coding scheme (supplement 4.1) thematically categorized how respondents give meaning to the burden of severe asthma on their lives, the burden of care and the impact of biologicals. Atlas.ti software was used to aid the analysis. The analysis was jointly done by the first and third author.

This study was given positive ethical advice (MEC-U, W19.113/NWMO 19.05.023), following the guidelines from the Dutch Clinical Research Foundation (DCRF) for non-interventional studies, and was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

Table 4.1 Overview of respondents

Respondent	Gender	Year of birt	Education (Dutch level)	Biologicals (effect*)
P001	Woman	1965	Secondary vocational education (MBO)	benralizumab (responder)
P002	Woman	1972	Secondary vocational education (MBO)	omalizumab (non-responder), benralizumab (non-responder)
P003	Woman	1963	Secondary vocational education (MBO)	mepolizumab (non-responder), benralizumab (decreasing response)
P004	Man	1954	Higher professional education (HBO)	dupilumab (responder)
P005	Woman	1956	Higher professional education (HBO)	none (non- eosinophilic severe asthma)
P006	Woman	1968	PhD (Doctor)	benralizumab (responder)
P007	Man	1970	Higher professional education (HBO)	omalizumab (non-responder), benralizumab (responder)
P008	Woman	1968	Secondary vocational education (MBO)	benralizumab (responder)
P009	Woman	1952	Secondary vocational education (MBO)	benralizumab (responder)
P010	Man	1951	Primary education (Basisonderwijs)	benralizumab (responder)
A001	Pulmonologist			
A002	Pulmonary nurse-specialist			

*Effect as mentioned by the respondent during the interview

Table 4.2 Overview of the main findings

Themes	Findings
Burden of disease	Dealing with symptoms and their unpredictability, low-energy, large consequences for social life and societal participation, struggling with general incomprehension of society
Burden of treatment	Long process of diagnosis, 'muddling through' care, high dependency on medication, focus on self-management.
Biologicals	Learning about this treatment option through specialist, low burden of treatment including limited worries on long-term effects and dependencies. Decreasing burden of disease by regaining lost social life and societal participation when effective. Burdens potentially increase when not effective.

RESULTS

In this section, we first discuss the burden of disease and the burden of treatment of living with severe asthma before we comment on the lived experiences with using biologicals. Table 4.2 provides an overview of the main findings.

Burden of disease: dealing with symptoms

Our empirical results on patients' experiences of the burden of disease align with the existing literature. An important part of this burden consists of having trouble breathing:

`... like a fish on dry land, yes, that's how I feel. Hoping for air, everything in my whole body tries to just catch this tiny little breath of air' (19: p.206).[c]

Breathlessness and other symptoms like coughing can reach high severity and frequency. Patients refer to being identified by their symptoms:

'Also, in my work, they said: 'I do not know the name of that lady, but that is the lady who always coughs, So... yes, that's what they said of me. I am known as 'that lady who coughs so much' (Respondent P009).

Severe asthma can be complicated by severe exacerbations which are difficult for the respondents to control. They are described as intense and fearful experiences. Severe exacerbations and prolonged extreme breathlessness may require respondents to be hospitalized for weeks, sometimes leading to recurrent hospitalizations. Some respondents and authors have been hospitalized for more than 15 times. This is experienced as very frustrating, and the sheer frequency appears to influence care-seeking:

'I just want to be normal, just live... I refuse any admittance because I just don't want to let my health ruin another year, I want to stop worrying about my health!' (19: p.67).

To 'just live' is difficult for respondents. At the time of the interview, some respondents still had regular paid employment (P004, P006, P007), or have continued working until retirement, but most were not able to do so. The impact on other aspects of social life can also be large. With symptoms being unpredictable and energy-levels low, respondents shared many examples concerning the importance of controlling triggers in order to avoid exacerbations. Avoiding asthma triggers has strong consequences for respondents' social life and societal participation. Many respondents share the same emotional experience, like losing friends and family because of having to deal with triggers affecting their symptoms, such as the use of perfume or smoking tobacco. Respondents mention that they struggle with people's incomprehension of the severity of their asthma and, as a consequence, do not disclose their illness easily. P007 is adamant in his determination with which he states not to be open about his disease, he does not want to appear sick and weak:

People say: 'P007 is the klutz of the neighborhood, we will ask someone else to help' [...] so I just didn't say anything anymore, so I am staying involved and my life remains intact' (P007).

Burden of treatment: the diagnosis and managing treatment

Whereas respondents seek ways to regain control and autonomy in their everyday lives, treatment for severe asthma is often insufficient. Respondents (except for P005 and P010) share an experience in exhibiting symptoms of asthma throughout their lives but have only recently been diagnosed with 'severe eosinophilic asthma'. They tell stories that generally consist of patients and healthcare professionals 'muddling through' symptoms and exacerbations with prednisone, anti-biotics, etcetera – for most of our respondents, culminating in receiving benralizumab. Biologicals can play a part in this diagnostic process for patients:

'I have always accepted that I had asthma, okay, and I am very happy that now, in fact, it has the stamp of this is it and nothing else. You can say that the syringe [benralizumab] is effective for me, but first, see if it really works for me [...] after two injections I had something like, this oh yes this is it, finally' (P001).

The realization of P001 is the final step in a long diagnostic process. Nonetheless, respondents appear to have a strong sense of trust in their current healthcare professionals. Regular checkups, controls and advice are deemed important - even though such tests are found to be strenuous themselves. Respondents who appear more able and willing to navigate their own healthcare also often appear critical of care professionals. Especially issues in the communication between specialists and patients can be experienced as increasing the burden of treatment, for instance, when specialists such as P007's ENT specialist and pulmonologist do not consult one another.

In the stories of patients, regular use of different kinds of medication is another prominent part of the burden of treatment. Respondents mention always needing to have a stock of medication readily available and share feelings regarding dependency. Some respondents have a rather ambivalent relationship to their medications and treatments, whereas others seem to be more straightforwardly at ease with it. Oral corticosteroids (OCS), prednisone, are mentioned more explicitly either as something that kept them going despite all odds or as medicine to be avoided - mainly because of the side effect of feeling bloated. Respondents also mention treatment with a strong focus on self-management techniques, for example, by practicing breathing and inhaler-techniques or creating an exacerbation plan with the nurse (A002). Respondents mention learning such self-management principles, linked to a more holistic perspective of a patients' life, rather effectively in revalidation centers. This is also simultaneously experienced as a very intense step: removing oneself from existing routines in everyday life is an integral part of the treatment.

Respondents generally state to adhere to their prescribed treatment, while at the same time giving ample examples of moments in which they have taken matters into their own hands. This can consist of using complementary medicine, but it is also expressed as learning to feel your own body and predicting flares, to such an extent that respondents argue against the doctor if necessary:

'Yes, I had a fight with that new doctor who said: 'no, I am against prednisone'. Yes, I said you can be, but I have an agreement, [with her regular GP] I feel my own body. 'Well yes, I will give you antibiotics', the doctor said, and I said: 'You can do it but on the weekend, I'll call [my GP] immediately, so then I got [prednisone] anyway' (P001).

This new doctor made the self-management effort of this respondent more difficult. This shows how patients can struggle to engage healthcare professionals in meaningful ways, and how such management is very much interaction between different actors. Interestingly, our interviews where the spouse of the patient was present as well (P004/P005 and P009) show how 'self ' management is a shared rather than individual effort; P005 seems to follow his wife in her efforts, and P001 reasons with her family, and her daughters, all the time.

Living with biologicals: cautiously embracing the last straw

Our respondents talk about the use of biologicals in the context of their experiences regarding the burden of disease and treatment. They have generally just recently learned of the existence of biologicals, mostly through their specialist. Respondents with relevant education and experience (such as P006) do mention to have researched possible treatments on Google and Pubmed. Other patients also heard about this treatment option through the national patient organization for asthma (Longfonds) or the media, - such as reports on the 'magic drug' from Bennie Jolink [regional celebrity folksinger]. Most respondents appear hopeful but reasonably sober in their expectations about biologicals. Their emotions, hopes and expectations are also actively managed by healthcare professionals.

Most respondents have recently started using biologicals, sometimes in an experimental setting that requires quite some work from the respondents. However, respondents tend to be rather opaque about the actual use of biologicals; if it is about a shot, they must visit the hospital every now and then and extensive training is not required. This indicates a lower burden of treatment:

"The first time I got it I had to wait for two hours because you can get side effects and [...] then you get the medicine a month later again, because it is every month, and then you just see your lung values going up. Once you see more lung capacity without having increased my medication, I think: 'hey, that's funny stuff. It works!' (P007).

For some respondents, the monthly visits are also a comforting affair. It is nice to have tests and controls, and the meetings with the specialist or nurse can be encouraging. The relatively new concept for patients to inject themselves at home is accompanied by some worries about less frequent controls at the hospital. Hence, this next step in treatment, intended to alleviate the burden of treatment, might for some patients in fact increase it.

The respondents for whom benralizumab is working well are positive about the effects - it allows them to reboot their social life and societal participation. The main positive effect they mention is to be able to significantly reduce or stop the use of prednisone. According to respondents, that effect is usually achieved directly after the first injection. Interestingly, the common reaction is not elation when able to do something new, but instead, it is about regaining what has been lost. This experience is joyful to respondents, but also rather precarious; it is contextualized within their existing experiences of the burden of disease and treatment. Most respondents continue to need prednisone and inhalers and need to continue making lifestyle changes. In that sense, biologicals are really an 'add-on' treatment, an extra but important 'last straw' to be grasped with both hands (wife of P010). However, successful treatment with biologicals is not the case for all respondents. Respondent P002, for instance, mentions her frustration that the biologicals do not really seem to affect her:

'Inhalers and the other medication did not do much anymore, so then we searched for another possibility. [omalizumab] came into the picture, so for five years I had that, but I was admitted to the hospital quite a few times [...] And that was also the only biological so far because I have had five or six, which I think helped me [...] but good, in November I will start a new one' (P002).

P002 has been taking biologicals since becoming available, generally to no avail. Still, she does pin her hopes on the next and new biological (dupilumab). Perhaps because of this 'last straw' approach to the biologicals, only three respondents talk explicitly about side effects of biologicals such as heavy sweating (P008). Almost all respondents are aware of the lack of scientific understanding of the long-term effects of the use of biologicals. They do not seem to worry too much about them despite the potential life-long dependency, only the possibility that it negatively affects the immune system is mentioned. Instead, their focus is on the present: respondents mention for instance that they are simply happy to be able to go on a holiday (P003).

DISCUSSION

Little is written about the way patients with severe asthma experience the burden of disease and treatment, and even less is known about how these patients consider treatment with biologicals[8]. Our findings show that patients with severe asthma experience a high burden of disease. This burden moves beyond the boundaries of the experience regarding the symptoms (shortness of breath, coughing, fatigue, etc.) to difficulties with (intimate) social interaction and societal participation[13–15], and includes living with incomprehension and in fear [8,29]. The burden of treatment appears similarly high and to consist of the regular use of, and dependency on, medication with risks of side-effects combined with large lifestyle changes. Dependency on, and side effects of, OCS dominate how respondents discuss their treatment[6,12,13]. Treatment burden also includes many interactions with healthcare professionals and repeated (emergency) visits to hospitals and revalidation centers. Generally, our respondents show high trust in the professionals currently treating them and we have found relatively few moments of tension between lay and expert knowledge that might compound frustration and uncertainties - although comprehensive information is not accessible to all severe asthma patients[30–32]. A good relationship with professionals, partners and friends can alleviate burden of treatment. In cases where such relationships are harder to find respondents feel they have to take matters in their own hands. This potentially heightens the burden of disease.

Severe asthma patients' self-management is generally dominated by ideas of adherence and control derived from evidence-based clinical guidelines[33-35]. However, based on our results, we support the call to reconsider the nature of self-management, the asthma action plans that are meant to support it and to thoroughly value the patient's daily life experience. Intentions and initiatives from doctors and health care institutions, concerning shared decision-making, self-management, home treatment and monitoring by E-Health, may thus not always be in line with the patient's needs or wishes. This is especially important because the main impetus for patient self-management is to enhance autonomy in everyday life and gain control over their disease[15].

Biologicals are meant to serve as add-on medication and if they are effective, appear to significantly lighten the burden of treatment[8,13]. We indeed find that, when effective, the positive impact on both the burden of disease and treatment can be high. However, most of our respondents appear cautious in their embrace of biologicals and in expressing hope for the future. This may be related to their turbulent patient journeys. Respondents' tentative position to biologicals appears to be justified considering that for some respondents, biologicals do not seem to be effective or the effects diminish over time. These patients resume an everyday life dominated by severe asthma. To return to such a situation might even increase the experienced burdenof disease and treatment. This group of patients continues to be rather invisible to the broader public and to be at risk of social isolation. The efficacy of biologicals potentially further obscures this group as clinical attention is drawn to the success of these new treatment options. It seems important to ensure that a concrete focus on improving the burden of disease and treatment in the everyday lives of all patients, including patients with non-Th2 inflammation, suffering from severe asthma is maintained.

Limitations and future research

In this research we conducted an exploratory qualitative study with a small sample size. Such a design proves effective for exploring commonalities in patient's experience and narratives, but is limited in for instance, comparisons between different sub-groups of patients suffering from severe asthma. Future research should consider to detail differences between experiences of patients of different educational backgrounds or between responders and non-responders to biologicals as we could only provide indications of variation. Also, most of our respondents are using benralizumab and exhibit a positive response to treatment, our results may be biased on these issues and future research could consider more variation in terms of biologicals used and in terms of responders and non-responders. Other interesting comparisons would be to compare the perceptions of (the burden of) treatment between patients and healthcare professionals. This might bring to light more concrete information on how to further improve self-management and communication. Comparing the experiences of patients across healthcare systems would also be interesting. For example, our respondents did not mention the relative high costs of biologicals[5], which could be an effect of the Dutch healthcare system in which biologicals are insured without out-of-pocket costs for eligible patients. Another limitation of this study is that, although we have strived to discuss patients' experiences over time through our life-history interviews, we only collected data on one point in time. For future research it is important to gauge if and how patients' experiences of biologicals develop over time using a repeated longitudinal design.

CONCLUSIONS

Severe asthma poses a significant burden of disease and treatment on patients, families and healthcare systems. By performing this study, important lessons have been learned based on everyday experiences of patients living with severe asthma and receiving treatment with biologicals. These lessons can have implications for daily healthcare practice, see Table 4.3.

Table 4.3 Main takeaway message for healthcare practice

Themes	Findings
Burden of disease and treatment	Provide timely, accurate diagnosis and supportive communication; include patient's perspective on everyday life in care provision and in self-management support strategies.
Biologicals	Help to manage patients' expectations; give attention to severe asthma patients not eligible for treatment with biologicals

Lessons reported in this study include the importance of timely and accurate diagnosis of (severe) asthma, the availability of supportive communication with health care providers, the relevance of patients' perspective on everyday life with self-management strategies, and attention to the invisibility of severe asthma patients not eligible for treatment with biologicals. Most importantly, severe asthma generally still seems to be a rather 'invisible disease', and more attention could be paid to the burden of disease and treatment experienced by patients. It is important for clinicians, scientists, politicians and healthcare insurance companies to join forces to help all severe asthma patients deal with this 'hidden burden' of severe asthma.

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CHAPTER 4

‘Like a fish on dry land’: an explorative qualitative study into severe asthma and the impact of biologicals on patients’ everyday life.

Supplementary Material

NOTES

a See: https://www.eur.nl/library/collecties/collectie-patientervaringen

b Benralizumab is administered using a syringe, once every 8 weeks, with a loading dose in week 4, about 8-6x times a year - a much smallerfrequency than the daily medication patients with severe asthma are accustomed to. Tests by, amongst others, the pharmaceutical company show it to be a rather successful add-on treatment; 74% of patients report no exacerbations of severe asthma in their second year of taking it. Overall, biologicals' greatest clinical benefit lies in reducing severe asthma exacerbations, with modest effects on day-to-day symptoms and quality of life[1], thus diminishing the need for the use of oral corticosteroids, and prednisone, of which side-effects are relatively strong both physically (osteoporosis, cataract, blood pressure drops) and mentally (anxiety, irritability, depression).

c All quotes are translated from Dutch by the first author and edited for readability.

S4.1 QUALITy – Codeerschema

-Getting a diagnosis [burden of disease]
Symptoms; start of, current

Exacerbations, fear

GP, specialists (trust)

Finding/searching for diagnosis

Information/knowledge-gathering

-Doing treatment [burden of treatment]
Treatments (regular, alternative medicine)

Hospitalization

Prednisone and side-effects ()

'Doctoring' by patients (adherence)

-Everyday life [balancing burden of disease/burden of treatment]
Control, uncertainty, unpredictability – and low energy, being out of breath

Managing triggers

Social, intimate life
    Family, friends
Trouble understanding / 'stigma'

Societal activities
    Work (most stop)
    Volunteering

-Biologicals [hope, disappointment, just 'an add-on']

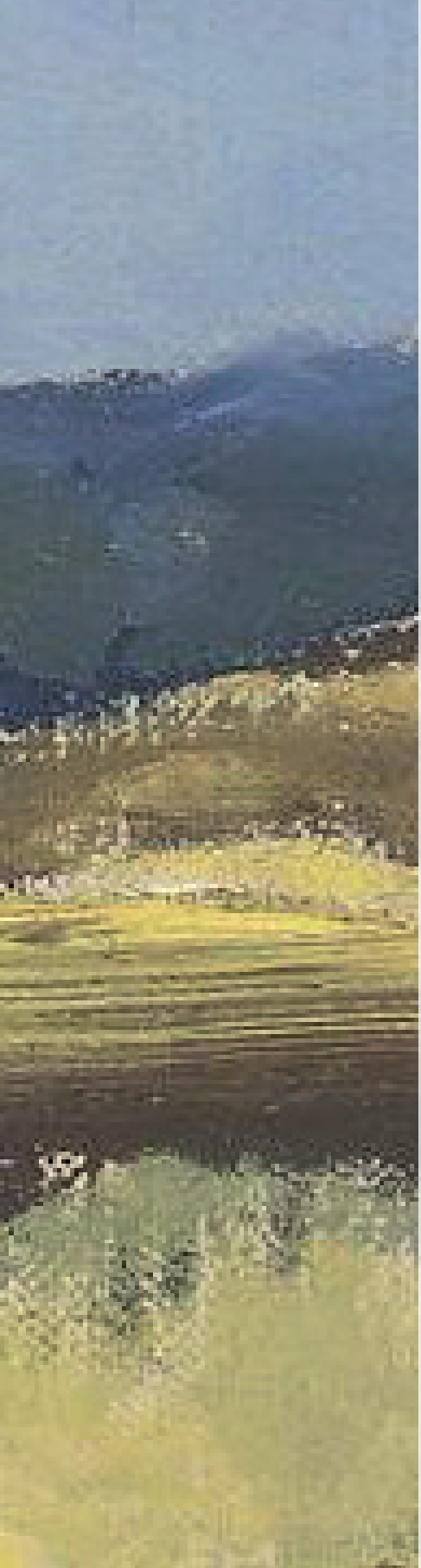
Learning about biologicals ['mabs', difficult, hard to tell apart, most patients are not fully aware]

Expectations raised – hope

Using biologicals (getting injections, going to hospital – looking forward to being able to do it at home)

Experiencing effects: great success, and great disappointment

Long-term worries? Unexpected consequences?



CHAPTER 5

Home-based intravenous treatment with reslizumab for severe asthma in the Netherlands - an evaluation

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Respiratory Medicine 2021; Apr;194:106776

ABSTRACT

The anti-IL-5 biologic reslizumab for the treatment of severe eosinophilic asthma is administered intravenously.

In the current study home administration of intravenous reslizumab was evaluated in 24 patients included between 2019 (July) and 2020 (July). This is the first study to show that intravenous reslizumab can be administered safely and successfully in an outpatient setting.
Notably, not all patients prefer home administration and severe asthma patients may have different needs when it comes to choosing treatment at home or in the hospital.

Highlights

- The worldwide COVID-19 pandemic urges us to speed up implementation of home treatment for chronic diseases such as severe asthma.
- Intravenous reslizumab can be administered safely and successfully in an outpatient setting.
- Patients with severe asthma have different needs when it comes to choosing in-hospital or home treatment with biologics.

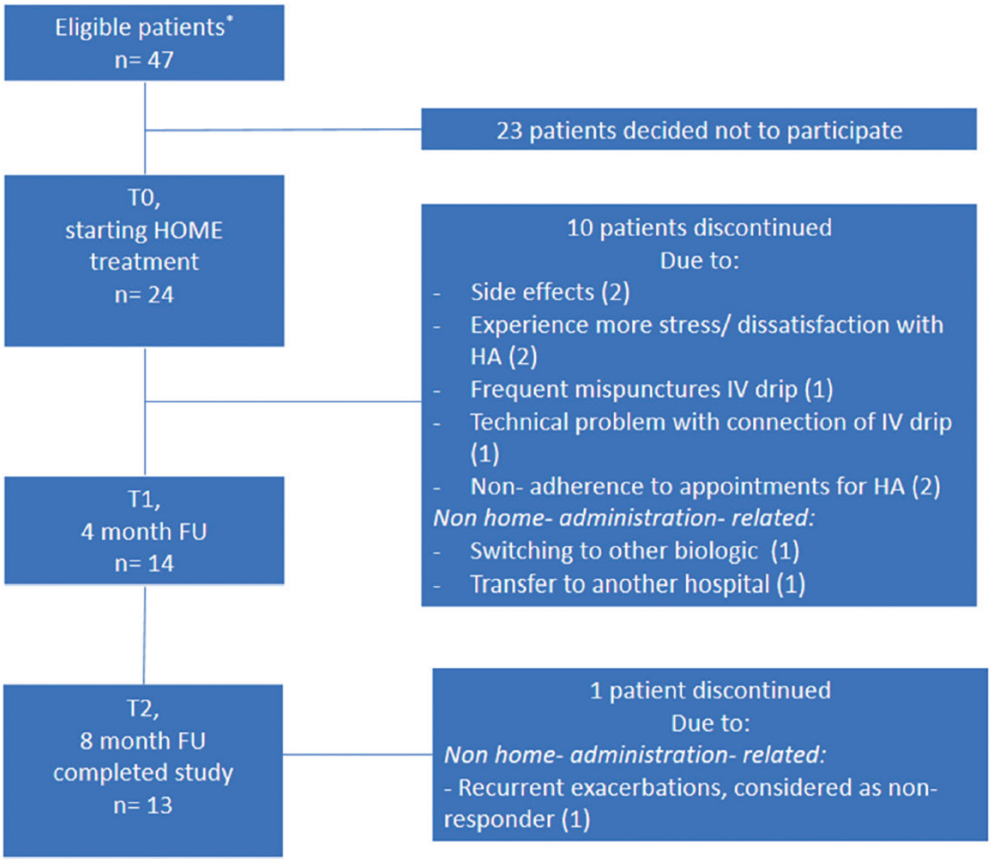
INTRODUCTION

Increasing numbers of patients with severe asthma (SA) are treatedwith biologics (anti-interleukin (IL)-5, anti-IL-5 receptor (5R), anti-IgE, anti-IL-4R). Recently, some of the subcutaneous (SC) biologics for severe refractory type 2 asthma were approved for home administration (HA)[1,2]. Although ideally biologics for SA should all be SC pre-filled auto injectors, the pharmacokinetic profiles of SC and intravenously (IV) formulations differ, which still makes IV formulations a valuable option in selected patients[3,4]. Due to the lack of head-to-head comparison between reslizumab and the other anti-IL-5/5R biologics, there is no clear statement about differences in efficacy. However, there are indications that the three drugs are not necessarily interchangeable and the lack of response to one anti-IL-5/5R drug does not rule out a response to another anti-IL-5/5R drug[5]. Reslizumab is the only IL-5-blocker that is administered IV, every 4 weeks, with a weight-adjusted dose. In patients with severe eosinophilic asthma (SEA), treatment with reslizumab resulted in decreased exacerbation frequency, improved lung function and asthma control[6]. Because of the IV administration route of reslizumab, it is still administered in the hospital. This results in increased use of healthcare resources and demand on hospital beds. Moreover, patients experience a high burden of disease and treatment due to frequent hospital visits[7]. Finally, the worldwide COVID-19 pandemic urges us to speed up implementation of HA and tele-medicine. Therefore, transferring care from the hospital to the home environment is much needed. In this single-armed before-and-after study we investigated patient satisfaction, feasibility and safety of HA of reslizumab in SEA patients.

PATIENTS AND METHODS

SEA patients, treated with reslizumab were prospectively enrolled from two hospitals in The Netherlands. Eligible patients were aged ≥18 years, diagnosed with SA according to the ERS/ATS criteria[8], which requires treatment with high-dose inhaled corticosteroids (≥1000 mcg fluticasone proprionate equivalent) plus a second controller (and/or systemic corticosteroids) to prevent the disease from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy. Both participating hospitals had mepolizumab, benralizumab and reslizumab available in the assortment of the hospital pharmacy. Selection of one of the 3 anti-IL-5/5R biologics was made by the attending asthma-specialized respiratory physician based on individual patient characteristics or response to previous treatment with biologics in the same patient (Table 5.1). All patients had to be treated with reslizumab fora minimum of 4 months without side-effects and considered as responder to reslizumab therapy at first evaluation. No exclusion criteria were defined. Patients were included in the analysis if at least one dose of reslizumab was administered at home. The study was approved by the regional Medical Ethical Review Committee. All patients provided written informed consent. Details on HA procedure and questionnaires used are provided (supplement). Outcomes such as patient satisfaction, symptom scores and asthma quality of life (AQLQ) were collected on T0 (after 4 months of hospital treatment, prior to first HA), T1 (after 4 months of HA by nurse) and T2 (after 8 months).

Figure 5.1 Flowchart; summary of screening, patient enrollment and reasons for discontinuation of home administration



* Eligible patients for the present study are: age ≥18 yr, diagnosed with severe asthma according to the ERS/ATS criteria, treated with reslizumab for a minimum of 4 months without side-effects and considered as responder to reslizumab therapy at first evaluation
FU; follow up, HA; home administration, IV; intravenous.

RESULTS

Out of 47 SEA patients treated with reslizumab, 24 patients agreed to participate (Fig. 5.1). Table S5.2 summarizes patients' rationale for declining HA. Patients included in the study had a mean age of 54.9 years and most of them (56.5%) were women. Most patients (61%) lived outside the region of the primary hospital with a mean driving time of 29 min to the hospital. The education level of the majority of patients was primary or secondary school and only 29% of patients reported to have a current employment (Table S5.3). The main reasons for discontinuation of HA were not related to HA, such as switching to anotherbiologic or transfer to another hospital. HA was discontinued in 8 patients (33%) due to HA related issues, like difficult peripheral intravenous access. Two patients reported dizziness or headache during reslizumab infusion, possibly due to a relatively 'short' running-in time (30 min). There was no difference in baseline characteristics and social economic status (in terms of education level and current employment status) between patients continuing and patients discontinuing HA (Table S5.4). A total of 128 administrations of reslizumab were given at home. No safety issues or significant complications occurred during these infusions. The frequency of follow up visits to the outpatient clinic was reduced during HA (Table 5.1). Three unscheduled emergency room visits (in 2 of 24 patients), related to asthma exacerbations, were reported during the period of 8 months HA. HA was reported as less burdensome, more personal and less stressful. AQLQ improved during HA. The perception of safety after 8 months of HA (T2) was similar to the perception of safety after ≥4 months in hospital treatment (T0)(Table 5.1). The respiratory physicians and clinical pharmacists involved in this study all judged positive about the implementation of HA and continued to include the option of HA in regular clinical care.

DISCUSSION

So far, this is the first study to evaluate the safety and feasibility of reslizumab via HA for SEA. HA of reslizumab for SEA was safe, relatively easy to implement and improved the perceived burden of treatment and satisfaction in the majority of patients. Patients' perception of safety increased while treated at home for a longer period (between 4 and 8 months). This may imply that it takes some time for patients to get used to and feel comfortable with home treatment. This was supported by the improvement in overall rating of HA and the increase in the proportion of patients experiencing HA as superior or similar to in hospital treatment between 4 and 8 months. Of interest is that this study also shows that patients preference for HA differs. 49% of patients who completed ≥4 months in hospital treatment, decided not to participate in HA, and 17% of patients deliberately discontinued HA during this study. This emphasizes that patient involvement through shared and informed decision making should be part of the consultation with patients offered HA. The level of health literacy, self-management skills and education may possibly affect the success of HA in the individual patient. The current study did however not show differences in education level between patients continuing and patients discontinuing HA (Table S5.4). Studies in other types of IV HA report that different types of patients have different needs concerning home-based therapy and personalpreferences are influenced by individual attitudes to health care[9,10].

Table 5.1 Main results and evaluation of HA

	N= 24	**N=24***	**N=13**
	T0 (baseline, after ≥ 4 months **in hospital** treatment)	T1 (4 months **home** treatment)	T2 (8 months **home** treatment)
Global rating of HA by patient (0-10)		8.25 ± 1.81	8.44± 1.01
Global rating of in hospital treatment by patient (0-10)	8.3 ± 1.5	-	-
Global rating of HA compared to in hospital treatment (%)			
HA superior		60 %	66.7%
HA similar		12.5%	33.3%
HA inferior		27.5%	0%
Patients' perception of safety during administration of reslizumab			
Do you feel safe during reslizumab administration?			
Sometimes (%)	8.7	20	0
Mostly (%)	17.4	33.3	22.2
Always (%)	73.9	46.7	77.8
Patients' perception of safety during HA compared to in hospital treatment			
HA feels as safe as in hospital treatment	-	53%	89%
HA feels less safe as in hospital treatment	-	20%	0%
HA feels safer than in hospital treatment	-	27%	11%
Perceived burden of treatment			
Low (%)	39.1	46.7	77.8
Moderate (%)	34.8	40.0	22.2
High (%)	26.1	13.3	0
Side effects reported (n, %)	0 (0%)	2 (8.33%)	0 (0%)
Min-AQLQ	4.53 (3.80-5.93)	5.73 (4.07-6.47)	5.07 (3.97-6.00)
ACQ	1.17 (0.83-1.87)	1.42 (0.79-1.96)	1.17 (0.83-1.83)
Hospital visits to outpatient clinic respiratory medicine in previous 4 months (%)			
0			
1	17.5%	46.6%	66.7%
≥ 2	65%	46.7%	33.3%
	17.5%	6.7%	0%

Table 5.1 Main results and evaluation of HA (continued)

	N= 24	**N=24***	**N=13**
	T0 (baseline, after ≥ 4 months **in hospital** treatment)	T1 (4 months **home** treatment)	T2 (8 months **home** treatment)
Previous treatment with biologics			
No (reslizumab first biologic)	54.2%	-	
Omalizumab	8.3%		
Mepolizumab	33.3%		
Mepolizumab and benralizumab	4.2%		
Dupilumab	0%		

Data are presented as mean ± SD (standard deviation) or median IQR (interquartile range), unless otherwise stated. *Results on T1 are evaluated for all patients starting with HA, including 10 patients who discontinued HA.

Additional studies in larger patient groups may help to identify a subgroup of patients most suitable for HA of biologics for SA. This study has several limitations. First, the sample size is relatively small as most SEA patients are currently on SC anti-IL-5/5R treatment. Unfortunately, a recent study investigating fixed-dose SC administration of reslizumab for SEA failed[11]. Therefore, we expect that reslizumab IV will still be around the upcoming years. Second, the organization of health care may differ between countries and hospitals. Although in the current study, participating hospital and outpatient pharmacies already gained experience with HA for other diseases such as cystic fibrosis, the multicentre aspect increases the external validity. Finally, we only included patients who were willing to participate in HA, although no difference in baseline characteristics was found between patients who did versus who did not agree to participate (Table S5.5). Similar to our study, several other studies show that most patients prefer HA to hospital treatment[12,13]. On the contrary, Lombardi et al.[14] identified some concerns in patients self-administrating asthma biologics at home, including difficulties in verifying adherence to treatment and lack of regular personal contact of patients with healthcare providers. Interestingly, these disadvantages do not seem to apply for IV HA by a specialized nurse. In conclusion, our results show that IV reslizumab can be administered safely and successfully in an outpatient setting. The results of this study will hopefully stimulate broader implementation of home administration of reslizumab as well as other IV therapies and help to tailor HA to the needs of the individual patient and decrease pressure on hospital capacity.

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CHAPTER 5

Home-based intravenous treatment with reslizumab for severe asthma in the Netherlands - an evaluation

Supplementary Material

Objectives

Primary endpoint:
- Patient satisfaction and experience (burden of treatment, perceived safety) with the provided HA

Secondary endpoints

- Safety of HA
- Asthma control (as measured by Asthma Control Questionnaire (ACQ-6) scores) [2]
- Asthma related quality of life (assessed by asthma quality of life questionnaire (AQLQ)) [3]
- Number of asthma-related outpatient clinic visits

Detailed methods

The Medical Ethical Review Committee (METC) grant sed a waiver of informed consent (nr 19-030). The researchproject was approved by the Board of Directors of the Haga Teaching Hospital and the FGV hospital. The study was registered at ClinicalTrials.gov.

Inclusion criteria

Eligible patients for the present study are: age ≥ 18 yr, diagnosed with severe asthma according to the ERS/ATS criteria[4], treated with reslizumab for a minimum of 4 months without side-effects and considered as responder to reslizumab therapy at first evaluation. No exclusion criteria were defined. Patients were included in the analysis if at least one dose of reslizumab was administered at home.

Study procedures

Education of the study-team

Before starting this project a multidisciplinary working group consisting of a pharmacist, respiratory physician, respiratory nurses, participating investigator and a project leader had different meetings to discuss and create the most optimal setting for home administration. Thematic sessions were organized to educate the team about; technical aspects of iv treatment, pathophysiology of severe asthma and working mechanism of biologicals.

Legal aspects

For legal aspects the hospital jurist and information security officer (ISO) were consulted.

Process of preparing and administering reslizumab at patients' homes

The first four doses of reslizumab were always administered in the hospital with frequent monitoring of vital parameters and possible side effects (and a small risk of anaphylaxis). Reslizumab was administered at patients' home by trained respiratory nurses from the treating hospital. All study participants received a new intravenous drip before each administration of reslizumab. The specialized nurses had gained sufficient experience with the technique of parenteral drug administration during clinical work. When visiting patients' home the nurses were supplied by a 'backpack trolley' with infusion pump, thermometer, oxygen saturation and blood pressure monitor.
Reslizumab had to be transported refrigerated and prepared at home because of the short preservability in combination with variable dosing. Prior to each administration a standardized checklist was filled out (including questions about recent vaccinations, fever etc.). Reslizumab was administered every four weeks with a running-in time of 20-50 minutes (mean time 30 minutes). Subsequently the IV administration set was flushed for 15 minutes with 0.9% sodium chloride solution. Double check of the right dose and drug before administration was performed by a pharmacist in the hospital by a secure app on the mobile phone.

Data collection and administrative procedures in the electronic patient file

The Electronic patient file (HIX®) was used to report the findings concerning the reslizumab administration at home directly in the digital patient file. The data management system castor® was used for collection of study data. Symptom scores like ACQ could be provided by patients themselves by castor questionnaires (send by a personal email to patients) or ` patient portal' (an online component of the electronic patient file).
The planning for upcoming visits was made by the specialized nurse visiting patients at home. These appointments were also registered in 'patient portal' which enabled patients to check the appointments themselves.

Design and Analysis

Statistical analyses were carried out using SPSS software version 24 (IBM, Armonk, NY, USA). In the absence of a control population we designed this study as a before-and- after study. The same outcomes were evaluated before and after introducing home administration in the same group. Patient and reslizumab treatment characteristics were summarized using descriptive statistics. Continuous variables are described using mean ± SD (standard deviation) or median IQR (interquartile range) where appropriate. Categorical variables are described using the count and percentage for each level. Differences between patients who continued HA and patients who discontinued HA were analyzed using unpaired Students' t-test, chi- square tests, Fisher's exact tests and non-parametric tests, where appropriate. P less than .05 is considered statistically significant.

Table S5.1 Summary of Questionnaires

Questionnaires	Outcome	Nr of questions	Frequency	Score	Source
PAZEA *	Patient satisfaction	6 out of 28	3x (T0,T1,T2) CASTOR	scale 0-10, 10 being best	Nivel CQI index asthma /Long alliantie NL (LAN)/ Thesis MHBA, Erasmus Centrum voor Zorgbestuur [1]
Logistic items	Time investment Complications of home administration	6	Following each administration(4w)		HagaZiekenhuis/ FGV
Questionnaires regular health care					
ACQ(6)	Astma control Questionnaire	6	1x/ 2 months CASTOR	item 1+2+3+4+ 5+6/ 6	[2]
Mini-AQLQ	Asthma Quality Of Life Questionnaire	15	3x/year CASTOR	all items/15	[3]

*PAZEA (Patientervaring Aangeboden Zorg Ernstig Astma, patient experience related to severe asthma care) CASTOR; data management system, with automatically generated questionnaires send to the patient by email, FGV; Franciscus Gasthuis & Vlietland

Table S5.2 Reasons for refusal to participate in home administration

Preferred in hospital treatment, rationale
· Switching to different biological in short time
· Frequent mispunctures of intravenous drip during treatment in the hospital
· Poor health status, frailty
· Limited flexibility in offered time slots and days for home administration
· Side effects with short (≤ 30 min) running in time during the first 4 months of in hospital treatment (longer running in time of reslizumab not feasable during HA)
· Opinion of treating physician

Table S5.3 Baseline characteristics and demographics of participants

	n= 24
Age (years)	54.9 ± 13.7
Gender	
Female	56.5%
Male	43.5%
Age of asthma onset (years)	27.7 ± 20.6
Weight (kg)	87.8 ± 22.2
BMI (kg/m2)	29.79 ± 6.2
Reslizumab dose (mg)	256 ± 62
Living outside the region of primary hospital (n, %)	14 (61%)
Time driving by car from home to hospital (minutes)	29 ± 20
Education	
No or primary education	46%
Lower or upper secondary education	41.5%
Bachelor or master or equivalent	12.5%
Present employment	
Yes	29.2%
No	62.5%
Disabled	8.3%
Living condition	
Alone	29.2%
Living together	25.0%
Living together with children	37.5%
other	8.3%

Table S5.4 Difference in baseline characteristics between patients continuing and patients discontinuing HA

	Total group n= 24	**Continuation of HA* n= 13**	**Discontinuation of HA* n=11**
Age (years)	54.9 ± 13.7	56 ± 12.9	53 ± 15.7
Gender			
Female	56.5%	46%	70%
Male	43.5%	54%	30%
Age of asthma onset (years)	27.7 ± 20.6	29.7 ± 20.0	25.0 ± 21.9
Living outside the region of primary hospital (n, %)	61%	61%	54%
Education			
No or primary education	46%	15%	30%
Lower or upper secondary education	41.5%	85%	40%
Bachelor or master or equivalent	12.5%	0%	30%
Present employment			
Yes	29.2%	31%	18%
No	62.5%	54%	82%
Disabled	8.3%	15%	0
Living condition			
Alone	29.2%	23%	40%
Living together	25.0%	31%	20%
Living together with children	37.5%	38%	30%
other	8.3%	6%	10%

No significant difference was found in baseline characteristics between patients continuing and patients discontinuing HA

Table S5.5 Baseline characteristics of patients who did versus who did not agree to participate

	Agreed to participate** n= 24	**Did not agree to participate**** n= 10*
Age (years)	54.9 ± 13.7	58 ± 11.31
Gender		
Female	56%	70%
Male	44%	30%
Education		
No or primary education	46%	40%
Lower or upper secondary education	41.5%	20%
Bachelor or master or equivalent	12.5%	40%
Present employment		
Yes	29.2%	56%
No	62.5%	22%
Disabled	8.3%	22%
Living condition		
Alone	29.2%	10%
Living together	25.0%	70%
Living together with children	37.5%	20%
other	8.3%	0%
Living outside the region of primary hospital (n, %)	61%	30%
Duration of treatment with reslizumab at screening or inclusion (months)	13 ± 7	22 ± 7

*The analysis was restricted to patients with data available (10 out of 23 patients who decided not to participate)** No significant differences were found between patients who did versus who did not agree to participate

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CHAPTER 6

Defining the questions to be asked in severe asthma trials: data from the COMSA working group

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European Respiratory Journal 2023; 61 (4)

Patients with severe asthma often do not experience sufficient disease control or, if they do, only at the expense of significant side-effects related to high oral corticosteroid (OCS) use. Biologics have changed the management of severe asthma by offering multiple therapeutic options targeting IgE, interleukin (IL)-4Ra/IL-13, IL-5/5Ra, thymic stromal lymphopoietin (TSLP) and related pathways. Soon, more (upstream) biologics are expected to follow. However, these opportunities also pose new challenges for physicians and the healthcare system. Considerable costs demand that treatment response in patients with severe asthma is well defined by accepted Core Outcome Measures (COM).

In this issue of European Respiratory Journal, the Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA) group addresses one of these questions by performing a multi-step consensus approach to identify meaningful standardised outcomes in patients who are treated with biologics[1]. Their process involved four stakeholder groups (patients, caregivers, healthcare regulators and pharmaceutical representatives). It is based on a systematic review published separately[2], with seven studies meeting the inclusion criteria. They conclude forced expiratory volume in 1 s (FEV_1) (z-score), the annual frequency of severe exacerbations and maintenance use of oral corticosteroids (mOCS) are core outcome measures for children (6–17 years) and adults. In children, the Pediatric Asthma Quality of Life Questionnaire, Asthma Control Test (ACT) or Childhood-ACT are added. In adults, they suggest the Severe Asthma Questionnaire and the Asthma Control Questionnaire-6 (ACQ-6) for inclusion. The authors claim that this combination implements an established objective lung function parameter, and quality of life, clinical control and healthcare utilisation parameters, which are also backed up by an abundance of clinical and research expertise of the co-authors. COMSA represent a "minimum set", as the authors acknowledge. Nevertheless, this document is an essential step towards the harmonisation of core outcomes in a group of patients which is paramount for respiratory research.

An important outcome of the COMSA manuscript is certainly the documentation and uncovering of the limits and gaps of evidence on patient-centred outcomes. These gaps include a lack of knowledge regarding long term remission, disease modification and the optimal duration of biological treatment. In addition, more accurate quality of life outcomes in children cannot be stressed enough. This also implies comparability across age groups. The lack of validation of most of these variables cannot be justified by monetary constraints of global phase III trials. Outcome parameters involving the individual burden of side-effects are another issue. Conventional systematic reviews such as the European Academy of Allergy and Clinical Immunology guidelines on biologics for severe asthma and T2 asthma[3–6] may not be able to detect such subtle changes.

Another critical gap in our current knowledge relates to the need for reliable endotyping, which could help to choose the most accurate treatment and predict treatment responses, and decrease patient burden and costs. Currently, these tools are not available. In the light of emerging evidence on the importance of auto-immune phenomena to promote clinical non-response, meticulous investigations on biomarkers of treatment response are also an integral part of patient-centred outcomes[7, 8]. An evolution and

constant update of the herein-described COM sets for severe asthma is a prerequisite for maintaining their impact. It is safe to assume that core criteria defining the response to biological therapy in clinical asthma trials will change more than they did throughout the past decade due to novel approaches and technical advances[9–11]. The gaps described above need to be filled and other (new) relevant outcome measures should be implemented.

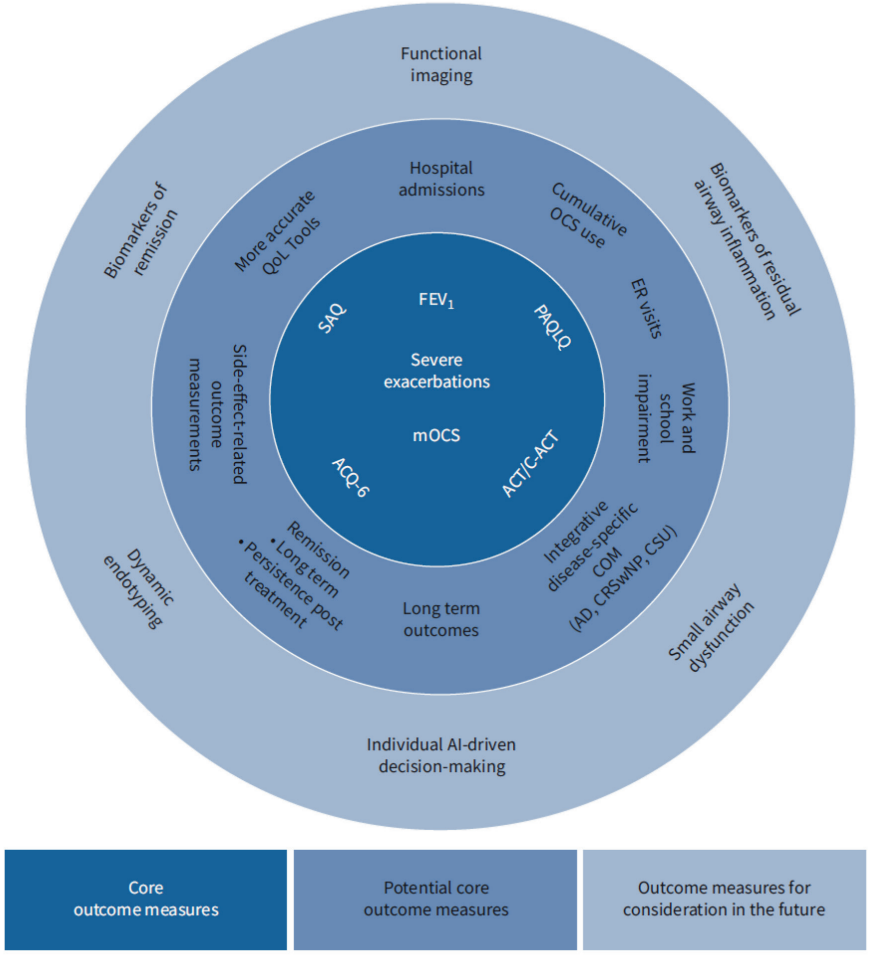
Comorbidities that add to disease burden may be targeted by the same biologics.The effect of biologicsused for asthma control on other diseases such as atopic dermatitis or chronic sinusitis (CRS) with or without nasal polyps (NP) is very difficult to assess in such a structured approach. Particularly in adult severe asthma patients, concurrent CRSwNP is common and reported in about 50% of patients[12]. Incorporation of other disease-specific COM sets (figure 6.1), as in CRSwNP[13], may better reflect the treatment response in the patient as a whole person and thereby help to better understand underlying immunological pathways targeted by these biologics. In the light of the high costs of biologics[14], this approach may also be more suitable to estimate cost-effectiveness of this type of treatment. Additional outcome measures to consider are cumulative OCS dose, mucus hypersecretion[15], functional imaging [16, 17], missed school days[18], productivity and work impairment[19], and lung function measures of small airway dysfunction (SAD) (figure 6.1).

A major difference to the previous coreASTHMA project[9] is the prominent role of FEV_1 in this COMSA document, even though the available biologics show inconsistent effects on lung function[20]. The decision to select FEV_1 as a key measure illustrates the importance of well-known metrics for physicians and patients who also ranked FEV_1 remarkably high[1]. Other measures, particularly for SAD [21, 22], may need to be added in the future. This also includes novel imaging approaches (computed tomography, magnetic resonance imaging, positron emission tomography and single photon emission computed tomography)[17], which are increasingly recognised as alternative measurements for evaluation of SAD.

Among the selected minimum set of COM sets, decreasing OCS-related side-effects was notably one of the treatment priorities identified by patients and caregivers[23]. Previous studies suggest that OCS-associated side-effects correlate with the cumulative OCS dose rather than with mOCS use[24, 25]. Thus, the cumulative OCS dose as a more accurate outcome measurement than mOCS dose needs further consideration and could help to overcome the inconsistency in the currently applied definitions for OCS bursts for asthma exacerbations[26, 27]. The usefulness of this outcome in real-life biological studies seems promising[28]. In line with this argument, the pan-European questionnaire and a narrative review on patients' perceptions, which also included grey literature, also published recently in the European Respiratory Journal[23], highlighted the following patient needs: the reduction of exacerbation frequency, ability to participate in everyday and family activities, and a reduction in medication, particularly OCS use.

With novel therapeutic options the relatively new concept of having asthma remission as an outcome measure emerges[29]. Proposed measures for clinical asthma remission

Figure 6.1 Proposed core outcome measures (COM) for pediatric and adult severe asthma trials on biologics



The innermost cycle denotes the "minimum COM set" defined by the COMSA group. AD: atopic dermatitis; CRSwNP: chronic sinusitis with nasal polyps; CSU: chronic spontaneous urticaria; AI: artificial intelligence; ER: emergency room; FEV_1: forced expiratory volume in 1 s; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; SAQ: Severe Asthma Questionnaire; (C-)ACT: (Childhood) Asthma Control Test; ACQ-6: Asthma Control Questionnaire-6; OCS: oral corticosteroid; mOCS: maintenance OCS use; QoL: quality of life.

are ACQ, exacerbation frequency and FEV_1, as suggested by THOMAS et al.[29], complemented by "no need for systemic corticosteroids for the treatment of asthma", as proposed by LOMMATZSCH et al.[30]. These four items are also part of the COM sets of the COMSA working group.

This structured approach to defining outcomes is novel for severe asthma and may facilitate future consensus approaches to create more unified and patient-centred outcomes. However, it also has some limitations, which are inherent to such a methodology, that demand careful consideration before being implemented in guidelines. First, patients' opinions are based on a pan-European questionnaire with good overall numbers which may still be insufficient to draw representative conclusions. Given the heterogeneity of patients' values in different societies and countries that need to be covered, future, more extensive evaluations are required. This is complemented by representatives who are limited in numbers (round 1: n=11; round 2: n=11; round 3: n=14). Second, children's and adolescents' views are very different, and a more granular assessment of patient outcomes in these age groups would be desirable. Third, clinicians from North America are missing. Interestingly, some patient representatives from North America are included. This is relevant since many, if not the majority, of phase three trials have been led by principal investigators from North America. On the other hand, UK-based physicians are overrepresented (40-46% of all clinicians and researchers) and are primarily of the male gender (61–73%). Fourth, pharmaceutical representatives are restricted to the four companies that are part of the 3TR project. Moreover, the systematic review "did not identify any validation data for the priority clinical and healthcare use measures for severe asthma". Thus, the current minimal tool set is the result of a highly standardised yet still very expert-driven consensus. This is supported by the fact that despite the apparent desire of patients to include hospitalisation, given the associated emotional burden and disruption of daily life, technical considerations on different referral behaviours across Europe prompted the experts to remove this outcome.

In conclusion, the COMSA consensus document is a big step forward to serve the need for harmonised patient-centred COM sets for severe asthma. An important strength of this COMSA document is that all relevant stakeholders are involved. To acknowledge the values of these COM sets as a core principle of future trials lies in the hands of these stakeholders. Meanwhile, these COM should be advanced in a step-by-step approach via a prospective comparison with novel, more sophisticated tools to assess treatment responses in patients with severe asthma.

ABSTRACT

The COMSA consensus document is a big step forward to serve the demand for harmonised patient-centred COM sets for severe asthma treatment by including all relevant stakeholders.

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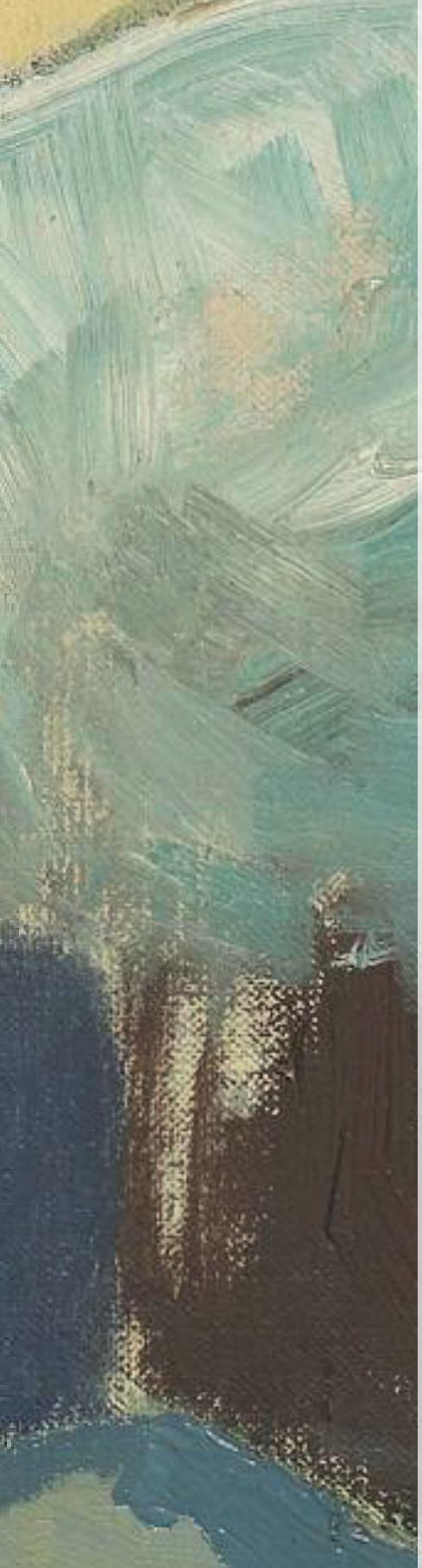


CHAPTER 7

General discussion and future perspectives

TOPIC OF THIS THESIS

It is widely acknowledged that asthma is a heterogeneous disease with different phenotypes, that require tailored therapeutic approaches. The last 20 years have been characterized by a series of developments and new insights in the field of severe asthma. This includes more diagnostic tools to phenotype and endotype patients, proper identification and treatment of relevant comorbidities and new therapeutic options, particularly biologics[1, 2]. Bronchiectasis is increasingly recognized as a common and clinically relevant comorbidity in severe asthma[3-6]. The combination of both diseases, with respect to early recognition, treatable traits and response to biological therapy, needs further consideration. While the emergence of biologics have brought us significant advances in the treatment of severe asthma, there remains a strong need to learn more about patients' perspectives and experiences regarding treatment with biologics. This also applies to patients treated in their home environment instead of in the outpatient clinic. Lastly, to promote personalized management and to allow better comparison between future biologic studies, there is a need for a more patient-centred and standardised definition of core outcome measures in severe asthma biologic trials.

The three main topics within the scope of this thesis are; severe asthma and bronchiectasis (the clinical, functional, radiologic, inflammatory, and microbial characteristics associated with bronchiectasis in patients with severe asthma and the response to anti-IL-5/5Ra therapy) (Chapter 2 and 3), the perceptions and experiences of patients with severe asthma on treatment with biologics in general and on home treatment with intravenous biologics (Chapter 4 and 5), and lastly a reflection on core outcome measurements in severe asthma biological trials, incorporating patient related outcomes (Chapter 6).

Here, we will present the main findings and implications, describe the methodological challenges and discuss future perspectives.

MAIN FINDINGS AND CLINICAL IMPLICATIONS

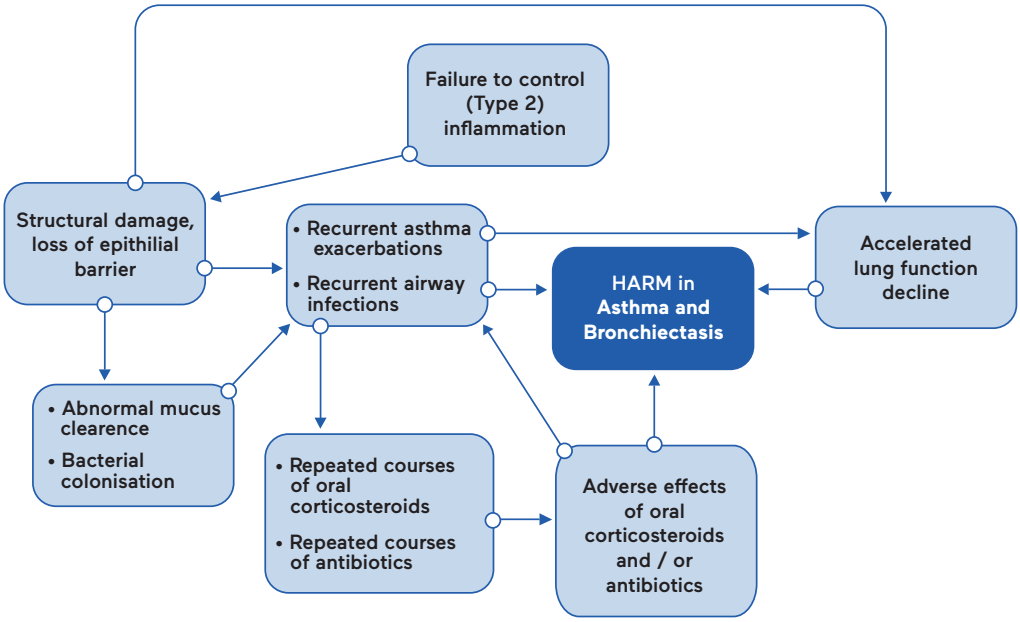
Main findings and implications regarding asthma and comorbid bronchiectasis (Radiology, Microbiology, Inflammation)

Over the past years there has been increasing interest in the link between asthma and bronchiectasis[3, 7], both part of chronic airway diseases. Bronchiectasis are common in asthma, and even more common in severe asthma[3]. Although several previous studies identified certain clinical features associated with the co-existence of bronchiectasis in asthma[8, 9], a detailed characterization in a well-defined population with truly severe asthma was lacking. **In chapter 1** we describe that the presence of bronchiectasis in patients with severe asthma is more common in patients with a longer duration of asthma, older age at presentation, and sensitization to *Aspergillus fumigatus*[10]. Compared with patients with severe asthma without bronchiectasis, patients with co-existing bronchiectasis had a lower lung function, a higher blood eosinophil count, more positive sputum cultures and more infectious exacerbations. Based on a combination of

inflammatory biomarkers and clinical characteristics (atopy, age of asthma onset) in our study population, we also suggested that bronchiectasis might be more prevalent in a subgroup of patients with severe asthma, namely the 'late-onset eosinophilic' asthma phenotype.

The features found in this study may help to alert the clinician to be aware of bronchiectasis as a potential comorbidity in patients with severe asthma. Early recognition of bronchiectasis is important because patients with severe asthma and co-existing bronchiectasis can have a high disease burden despite asthma treatment[1, 2]. Unrecognized this may be a struggle for both the clinician and the patient because asthma may remain uncontrolled despite optimal therapy. This can also lead to unnecessary discontinuation or switching of biologics without the expected improvement in clinical outcomes[11]. Lastly, early detection of bronchiectasis in patients with severe asthma, and subsequent personalized treatment, has the potential to prevent further harm from irreversible damage and remodelling (Figure 7.1). Early detection could be achieved by incorporating imaging timely into the systematic evaluation of patients with severe asthma.

Figure 7.1 Vicious cycle hypothesis in (T2 high-severe) asthma and bronchiectasis



Radiology

In recent years, the use of computed tomography (CT)- scans [12, 13] and functional imaging (i.e. by magnetic resonance imaging (MRI) (14)) has become more relevant and common in the evaluation of severe asthma. When bronchiectasis are suspected, performing a high-resolution CT (HRCT) scan is the gold standard. This type of scan has a relatively

low radiation exposure and no need for intravenous contrast. Although the prevalence of bronchiectasis in severe asthma was not an outcome measure in our studies[10, 15], the difference in prevalence between our studies (19% **(chapter 2)**, 16% **(chapter 3)**) and other comparative studies, such as the Italian severe asthma registry (47% in a subgroup of patients with severe eosinophilic asthma[16]) and a Danish severe asthma cohort (31%)[17] are remarkable. These differences in prevalence of bronchiectasis in asthma have been described previously, and are mainly attributed to radiologic over- and under- diagnosis of bronchiectasis due to no differentiation in radiologic extent of bronchiectasis, type of bronchiectasis or number of affected lobes (e.g. including patients with small isolated bronchiectasis in one lung segment)[3]. In addition to diagnosis, HRCT is also required for the classification of bronchiectasis[18] and the calculation of the bronchiectasis severity index (BSI)[19]. As shown in our study in **chapter 2**, the radiological characteristics and severity scores of bronchiectasis can vary significantly between patients.
Earlier studies, in patients with non-cystic fibrosis (CF)-bronchiectasis, already indicated that radiological severity scores are associated with bronchiectasis exacerbations , hospital admissions, and lung function[20, 21] and can predict disease severity[21]. It is not jet clear if the use of these radiological- and clinical bronchiectasis scores have the same predictive potential in patients with both asthma and bronchiectasis. A recent study in 268 patients with asthma and bronchiectasis in China[22], did in fact, show a positive correlation between severe asthma exacerbations and BSI-scores[19]. The study population in our study[10] was too small to investigate correlations between the radiological severity of bronchiectasis (as measured by the modified Reiff score[18]) and clinical outcomes, such as exacerbation frequency and hospitalizations. Further validation of radiological and clinical bronchiectasis scores in larger groups of patients with severe asthma and comorbid bronchiectasis is needed. The results of our study add to the above mentioned arguments for the inclusion of chest CT imaging in the early systematic evaluation of patients with severe asthma.

Microbiology

Sputum cultures play a crucial role in the management of bronchiectasis. Sputum cultures help to identify specific pathogens and help healthcare providers to choose appropriate antibiotics for short or long-term treatment. In addition, identification of *Pseudomonas aeruginosa* is one of the components of the bronchiectasis severity index[19] as it is associated with an increased burden of disease, a higher exacerbation rate and increased mortality[23]. Also in patients with asthma sputum cultures can have an important role in the diagnostic workup and identification of treatable traits (Figure 7.2). In our study **(chapter 2)** in a cohort of patients with severe asthma in a tertiary referral centre in the Netherlands[10], we found that sputum cultures were performed in the majority of patients, with a higher proportion in patients with comorbid bronchiectasis (100%) than without (64%). The most common cultured pathogens were: *Aspergillus fumigatus, haemophilus influenza and pseudomonas aeruginosa*. *H. influenzae* was the second most frequently cultured microorganism in our study. This is similar to findings from other studies in patients with severe asthma[24, 25]. Identification of *H. influenzae* in patients with severe asthma may have therapeutic consequences. In a post hoc analysis of the AMAZES (Long-term azithromycin treatment in adults with persistent symptomatic asthma) trial,

Taylor et al.[26] revealed that patients colonized with *H. influenza* showed the largest treatment effect in reduction of exacerbations. Azithromycin maintenance therapy is thus an important therapeutic option in patients with severe asthma and recurrent exacerbations, particularly in patients not eligible for biologics. Although *H. influenza* was more often cultured in patients with severe asthma and comorbid bronchiectasis, our study didn't reveal a significant difference compaired to patients with severe asthma without bronchiectasis. Nevertheless we have to interpret the microbiologic findings of our study with caution, because we included a relatively small group of patients, from a single centre and country. A recent analysis from the 'European Multicentre Bronchiectasis Audit and Research Collaboration' (EMBARC) registry among 28 countries showed marked differences in microbiology between countries, with a higher frequency of *P. aeruginosa* and lower *H. influenzae* frequency in southern Europe, compared with higher *H influenzae* frequency in the UK and northern and western Europe[27].
Measurement of specific micro- organisms in sputum cultures of patients with severe asthma can help the clinician to identify treatable traits and target treatment. Sputum culture is relatively inexpensive, but not all patients are able to produce good quality sputum.

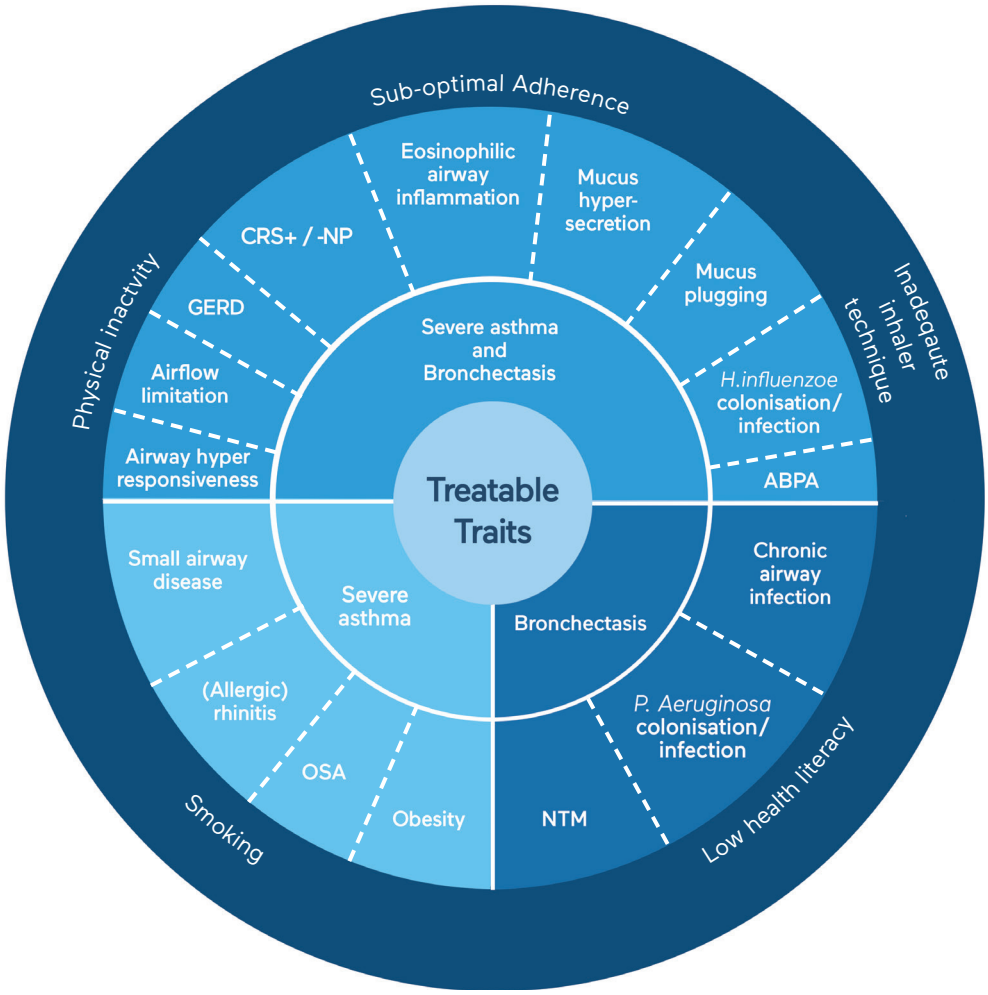
Role of eosinophilic inflammation in patients with asthma and comorbid bronchiectasis

Our tentative suggestion that bronchiectasis may be more common in a specific asthma phenotype[10], namely 'late onset eosinophilic asthma', was quite new at the time of publication of our study. Before our study, other studies had already shown a new and growing interest in the existence of 'eosinophilic bronchiectasis'[5, 28], most commonly defined by an elevated blood eosinophil count (>300cells/ul). Although historically bronchiectasis has been associated with infection and neutrophilic inflammation[29, 30)], eosinophilic bronchiectasis is nowadays recognized as a common entity[5, 28]. Apart from the co-existence of other type 2 respiratory diseases, like asthma, allergic bronchopulmonary aspergillosis (ABPA), or chronic rhinosinusitis +/- nasal polyps, approximately 20% of patients with 'pure' bronchiectasis show eosinophilic inflammation[5, 31].

In chapter 2 we grouped the included 91 patients according to their asthma phenotypes. This resulted in the observation that adult-onset eosinophilic asthma was the phenotype with the highest prevalence of bronchiectasis (29.4%) compared with a prevalence of 12.5% in patients with early-onset atopic asthma and 9.5% in non-eosinophilic asthma. Following our study, a Danish group[17] studied the same hypothesis, but included sputum eosinophilia as an inflammatory biomarker. In their cohort of 108 patients with severe asthma, they found comorbid bronchiectasis in 31% of all patients. Bronchiectasis in this study were significantly associated with eosinophil airway inflammation and activation (in induced sputum). These results support the finding of our study, implying that bronchiectasis in severe asthma might be more common in patients with eosinophilic airway inflammation. The authors of the Danish study[17] even postulate that, based on the airway inflammometry they applied, eosinophilic airway inflammation is the cause of bronchiectasis. This is thought to be related to an increased activation of airway eosinophils, with degranulation, release of cytotoxic enzymes and epithelial damage.

The still widely accepted 'vicious circle' hypothesis of 'structural airway damage, impaired mucus clearance and acquisition of respiratory pathogens', proposed by P.T. Cole in 1986[32], already stated that airway inflammation plays a central role in bronchiectasis (Figure 7.1). More recent studies that have focused on different types of airway inflammation, have seen this relationship specifically with eosinophilic airway inflammation[33, 34]. This makes the group of patients with severe asthma and co-existent bronchiectasis characterized by eosinophilic airway inflammation of particular interest, as these patients may benefit from anti/IL5-5Ra biologics.

Figure 7.2 Treatable traits in patients with severe asthma, bronchiectasis and patients with severe asthma and comorbid bronchiectasis



The outermost circle represents the behavioural domain
GERD: gastroesophageal reflux disease; **CRS:** chronic rhino sinusitis, with or without NP: nasal polyps; **OSA:** obstructive sleep apnea; **ABPA:** allergic bronchopulmonary aspergillosis; **NTM:** nontuberculous mycobacteria

Main findings and implications regarding biological therapy in patients with severe eosinophilic asthma and comorbid bronchiectasis

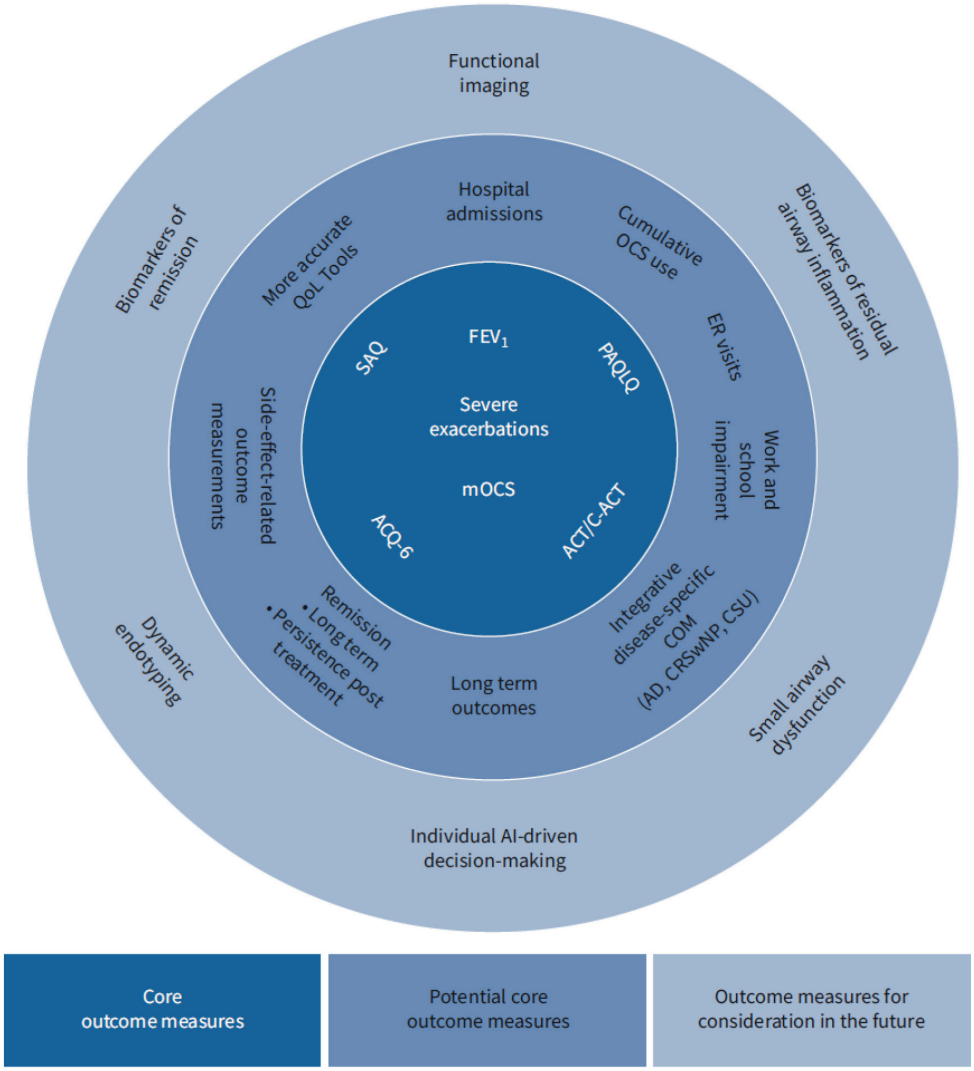
In chapter 3, we describe the real-world effectiveness of anti-IL-5/Ra biologics in patients with severe asthma and comorbid bronchiectasis[15]. The Dutch severe asthma registry enabled us to evaluate a large group of patients with severe asthma and comorbid bronchiectasis. After 1 year of anti-IL-5/5Ra therapy, the number of patients with ≥2 exacerbations per year, decreased from 75% to 22% and in the OCS-dependent patients the maintenance OCS dose decreased from median of 10.0 mg/d to 2.5 mg/d. The good treatment response demonstrated by our study, tells us not to be reluctant with starting anti-IL-5/5Ra biologics in this patient group. Even despite the exclusion of patients with comorbid bronchiectasis from previous randomized controlled trials (RCTs).

Shortly after our study, the Italian severe asthma group SANI, confirmed our findings [16]. They evaluated the 12 month-response to benralizumab in a real life population with data from the Italian severe asthma registry. Overall they found a significant reduction in exacerbations and daily oral corticosteroid (OCS) maintenance dose. However patients with severe asthma and comorbid bronchiectasis (n=35) achieved a lower OCS- sparing effect and less lung function improvement compared to severe eosinophilic asthma patients without bronchiectasis (n=37). In our study we did not find any improvement in lung function at all (FEV_1 and FVC) after 12 months of anti-IL-5/5Ra therapy. The lack of improvement in lung function in our study is on the one hand not so surprising, as the first RCTs with anti-IL5/5Ra biologics (as opposed to anti-IL4R) showed only small or moderate effect on FEV_1, in contrast to the large effects on exacerbation rate and OCS use[35, 36]. On the other hand, this is a remarkable difference compared to the results of Campisi et al. A possible explanation for this difference could be a difference in treatment response between benralizumab and mepolizumab in patients with severe asthma and comorbid bronchiectasis. Where Campisi only included patients treated with benralizumab, the majority of patients in our study used mepolizumab. There is evidence that the three available anti-IL5/5Ra biologics are not necessarily interchangeable[37, 38], and a lack of response in mepolizumab-treated patients could be a result of residual eosinophilic airway inflammation or eosinophilic driven mucus plugs[39, 40]. However, due to limitations in both the size and comparability of the patients included in both studies, no firm conclusions can be drawn.

Following the Italian study, Garcia-Rivero [41] revealed a post-hoc analysis of the Real world Effectiveness and Safety of Mepolizumab (REDES) RCT in a Spanish cohort of patients with severe asthma and concomitant bronchiectasis. Similar to the SANI study, their preliminary results suggest a lower OCS-sparing effect (in terms of daily OCS dose) in patients with asthma and comorbid bronchiectasis compared to patients without. In contrast to our study, both the Italian and the Spanish real-world studies on anti-IL5/5Ra treatment in patients with severe asthma and comorbid bronchiectasis, did not use 'cumulative OCS include' as outcome measurement. The use of data on cumulative OCS use in real-world studies or severe asthma biologic trials has not yet been widely accepted, but seems promising (Figure 7.3)[42, 43]. Previous studies have suggested

that the side effects associated with OCS correlate with the cumulative dose of OCS rather than with the use of OCS maintenance dose[44, 45]. The reduction of OCS-related side effects was notably also one of the treatment priorities identified by patients and caregivers in the recent narrative review by Coleman et al.[46]

Figure 7.3 Proposed core outcome measures for severe asthma trials on biologics



The innermost cycle denotes the "minimum COM set" defined by the COMSA group. AD: atopic dermatitis; CRSwNP: chronic sinusitis with nasal polyps; CSU: chronic spontaneous urticaria; AI: artificial intelligence; ER: emergency room; FEV_1: forced expiratory volume in 1 s; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; SAQ: Severe Asthma Questionnaire; (C-)ACT: (Childhood) Asthma Control Test; ACQ-6: Asthma Control Questionnaire-6; OCS: oral corticosteroid; mOCS: maintenance OCS use; QoL: quality of life.

One of the essential goals in the treatment of asthma is indeed to prevent harm to our patients. Two of the most important aspects that may cause this harm are: firstly, the failure to control inflammation[47, 48] and, secondly, the potential side effects of OCS[45] (Figure 7.1). As side effects of OCS appear to be particularly relevant in the group of patients with co-morbid bronchiectasis[49-52] because of the potential risk of increased susceptibility for infections, the significant effect on cumulative OCS exposure by anti-IL-5/5Ra therapy shown in our cohort of patients, (a significant reduction for the total population from 1.61 to 0.51 g/year) is an important 'harm reducing outcome' and extends the results of the studies by Campisi[16] and Garcia-Rivero[41].

What we can learn from our study in **chapter 3**, complemented by the data from the above mentioned studies, is that anti-IL5/5Ra biologics should be considered as add-on therapy for patients with severe eosinophilic asthma, regardless of comorbid bronchiectasis. Further research is needed to assess what is the best time to introduce this therapy and whether earlier intervention with biological therapy in this group of patients can preserve lung function and prevent progression of comorbid bronchiectasis.

Main findings and implications regarding patients' perceptions and experiences of living with severe asthma and using biologics, including home treatment

Despite the significant improvement in treatment outcomes following the introduction of biologic therapy for severe asthma, the burden of disease and treatment experienced by patients requires continued attention. **Chapter 4** focuses on every day experiences of patients living with severe asthma and treated with biologics, including the burden of treatment and the impact of non-response to biologics[53]. The results of this study show how patients with severe asthma experience a high disease burden (breathlessness, fatigue, exacerbations, loss of contact with family and friends due to reduced social participation and loss of work) and treatment burden (OCS- side-effects and medication dependency). Patients who showed a good response to treatment with biological therapy, experienced relieve of both the burden of disease and treatment. This was in contrast to those for whom biologicals proved ineffective.

This kind of an explorative narrative study is a relatively new field of interest in asthma research and fortunately the importance of this type of studies is increasingly recognized. This is nicely illustrated by Coleman et al[46], who included the results of our narrative study in a large narrative review. In this review, the authors aimed to capture 'patients' perceptions of non-response and response to biological therapy for severe asthma'. Based on a subtraction of the experiences from 78 adult patients (reported in three papers and one individual patient interview), increased participation in life, reduced exacerbations and reduced OCS exposure were all valued as important treatment outcomes. Ongoing steroid exposure and hospitalisations were important issues identified by non-responders to biological therapy. These findings are consistent with the in-depth interviews from our study and may help to define relevant topics that clinicians need to discuss with their patients in daily practice. During consultation in daily clinical practice, it is important to remember that the perspectives and priorities of patients and clinicians can diverge, as illustrated by a recent study from Ainsworth et al.[54] among

126 patients with severe asthma across 7 countries (including The Netherlands). They identified different perspectives and priorities between patients and clinicians, with clinicians focusing more on physical issues and patients caring more about holistic aspects such as the possibility of self-management. The insights of the above mentioned studies may also be of value to integrate patients perspectives and experiences in identifying the most appropriate outcome measures for future biological trials in asthma **(chapter 6)**. This was indeed conducted by the COMSA (Core Outcome Measures sets for paediatric and adult Severe Asthma) Working Group in 2023[55]. They performed a multi-step consensus approach to identify meaningful standardised outcomes in patients who are treated with biologics. Their process involved four stakeholder groups (patients, caregivers, healthcare regulators and pharmaceutical representatives). This resulted in selection of the following core outcome measures; expiratory volume in 1 s (FEV_1) (z-score), the annual frequency of severe exacerbations, maintenance use of oral corticosteroids (mOCS) and asthma control questionnaire (ACQ(6)). The newer PROM; severe asthma questionnaire (SAQ)[56], was also included (Figure 7.3). Although this document is a big step forward in addressing the need for harmonised core outcome measures (COM)-sets for severe asthma clinical trials, it still lacks some other patient-centred outcome measures that are also mentioned in results of the narrative studies discussed above[46, 53]. These include for example: hospital admissions, adverse effects of OCS, and work and school impairment (Figure 7.3). This was reflected on in **chapter 6.** In this editorial[42], we suggested additional outcome measures to the minimal set of COMs and other outcome measures to consider in the future. We also discussed the potential positive effect on asthma outcomes by improvement of comorbidities which are targeted by the same biologics. This possible association of improvement in asthma outcomes with improvement in comorbidity outcomes is also addressed by a recent cohort study using international severe asthma registry data of 21 countries[57]. They focused on T2-related comorbidities and found that the presence of chronic rhinosinusitis with or without nasal polyps (CRS+/- NP) may be considered as a predictor for biologic effectiveness in patients with severe asthma. As in our editorial, we highlighted the need for systematic comorbidity assessment and integrative disease-specific COM sets.

Thus, patients with severe asthma experience a high burden of disease and treatment. Fortunately the introduction of disease modifying biologics can be life-changing for a subgroup of patients with severe asthma. To better understand and define non-response and response to biologic therapy and to set realistic expectations for patients starting with therapy, there is a need to include more patient-centred outcome measures, in addition to traditional outcome measures such as exacerbation rate and OCS maintenance dose.

Perceptions and experiences of patients with severe asthma on home treatment with intravenous biologics

The current shift by healthcare organisations to focus more on the patient's home environment and less on traditional hospital-based care is part of a wider trend, also known as decentralised healthcare and home-based care[58-60]. In the Netherlands, this trend is being driven by a number of factors; including advances in technology, a reduction in

the overall number of hospitals, and a desire to reduce healthcare costs while maintaining access to healthcare for all Dutch citizens ('integraal zorgakkoord' (IZA)[61]). In addition, there is a growing recognition of the benefits of providing care in more comfortable and familiar settings and reduce the burden of disease experienced by patients due to frequent hospital visits[46, 53]. The increased use of healthcare resources and demand on hospital beds during the COVID-19 pandemic was an extra argument to transfer care from the hospital to home. Therefore, in **Chapter 5**, we assessed the feasibility and safety of home administration of the intravenous administered anti-IL5 biological; reslizumab in two different hospitals in The Netherlands[62]. In addition we evaluated PROMs, such as patient satisfaction and perception of safety of home treatment, ACQ and AQLQ during home treatment. The results of this study revealed that home administration of intravenous reslizumab for severe asthma was safe, relatively easy to implement and improved the perceived burden of treatment and satisfaction in the majority of patients. Interestingly, this study also shows that patient preference for home administration varies. 49% of patients who completed ≥4 months of hospital treatment chose not to participate in home administration, and 17% of patients deliberately discontinued home administration during this study. Following our study, a large international study (including the Netherlands) was conducted to gain more insight into the perceptions and experiences of patients and clinicians regarding the home administration of biologics for severe asthma[63]. Similar to previous studies[64, 65], the majority of patients included in this study (68 of 75) used subcutaneous biologics. A practical finding of this study was that patients mentioned the saving of time by not having to travel to the hospital as an advantage of home treatment. This also enabled them to have more time for work or family. On the other hand, an often mentioned disadvantage of home treatment in this international study[63] was the lack of personal contact with healthcare providers, including the absence of the safe environment of the hospital. The latter two were also referred to in our study.

Although the organisation of intravenous biologics requires more organisation than the self-administration of subcutaneous biologics (which is the standard of care today), the results from **chapter 5** , including the findings from Flokstra-de Bok et al[63], add to our knowledge of the different perceptions that patients and clinicians may have about home treatment and emphasise the need for personalised care and treatment decisions. Meanwhile, intravenous home administration of reslizumab appears to be safe and feasible. This will allow us to extend this initiative to more hospitals and other diseases that require repeated intravenous treatment.

METHODOLOGICAL CHALLENGES

Several studies with different designs, measurements and results have been used for this thesis. This section discusses the potential limitations of these studies. The limitations of this thesis are mainly related to observational (including retrospective-) and real-world studies in general[66, 67]. For observational studies, these limitations include for instance; selection bias, lack of a control group and the risk of known and unknown confounders. Other potential limitations, particularly for real-world studies, include differences in routine asthma care and use of diagnostic tests between different hospitals,

and differences in evaluation of response to treatment between individual healthcare providers, missing data and lack of follow-up. As data for real-world studies, such as the SABEBIO study in **chapter 3**, are extracted from electronic patient files, research nurses are dependent on the documentation and retrievability of these data for accurate data entry. This can also be considered a limitation. It is likely that in the future, greater use of automated data extraction software (see 'Future perspectives') will help to address this type of limitation.

For **chapter 2**, we used data from a severe asthma cohort from a single severe asthma centre in the Netherlands. This allowed us to obtain detailed information on clinical, functional, microbial and radiological measurements. This detailed information made it possible to ensure that the patients included had truly severe asthma according to the international ERS/ATS guidelines[68]. We were also able to review the CT- scans to check that a correct diagnosis of bronchiectasis had been made and to assess the type and extent of bronchiectasis. Despite these strengths, we had to exclude patients with severe asthma who did not have a CT scan, which may have introduced a selection bias.

Unlike the small but detailed study population for our study in **chapter 2**, for our study in chapter 3, we were able to use multicentre data from the Dutch registry for severe asthma (RAPSODI). This allowed us to identify a relatively large group of patients with severe asthma and CT-confirmed comorbid bronchiectasis treated with anti-IL-5/5Ra biologics. In contrast to the single-centre asthma cohort described in **chapter 1**, this registry study lacked detailed data on, for example, the type, extent and severity of bronchiectasis. This can be seen as a limitation. Given the reported positive treatment effects in the placebo arms of previous RCTs of biologics in severe asthma [36, 69, 70], we recognise the inherent risk of overestimating treatment effects in our study without a control group. With the actual number of patients in the registry, it should have been possible to include a control group of patients with severe eosinophilic asthma without bronchiectasis. However, this would have had important implications for the design and statistical analysis of this study as complete data sets for such a control group were not available in the RAPSODI registry at that time and would have required new data collection in individual hospitals and pharmacies.

Because different European severe asthma registries use different data sets, it is difficult to compare our results in **chapter 3** with the results of the Italian and Spanish real-world studies[16, 41] that followed ours. For example, the annualised exacerbation rate is categorised in the Dutch RAPSODI registry as 0-1, 2-5, >5 exacerbations/year. This makes it impossible to compare this outcome with the percentage of exacerbation-free patients reported by Campisi et al. In addition, the categorisation in the RAPSODI registry makes it difficult to use the definition of disease remission, which is currently being used more widely. This highlights the need for more harmonised data sets and outcome measures between international asthma registries. Fortunately, efforts are being made to achieve this[71, 72].

A completely different type of study to the previous chapters is discussed in **chapter 4.** This narrative study has other potential limitations[73]. Firstly, the patients interviewed

for this study were selected randomly, partly based on their motivation to participate. This may have introduced a selection bias. Secondly the age form the respondents included ranged from 49 to 70 years, therefore a large group of patients of a certain age, particularly between 18 and 49 is underrepresented in this study. This may decrease generalizability to the overall population of adult patients with severe asthma. On the other hand, for this type of study in depth interviews are needed, which are time consuming and therefore limits the number of patients. But it is precisely these interviews that will provide detailed information on patients' experiences which are strongly needed to get researchers and clinicians more in line with patients' needs and expectations. In addition, when results of these type of studies are combined, such as in the narrative review of from Coleman [46], it may shine a broader light on the topic and increase generalizability to broader populations of patients with severe asthma.

This thesis includes both prospective and retrospective studies. All included studies are national studies, while the editorial in **chapter 6** was written together with an international colleague, which may have contributed to a broader perspective on the topic discussed.

We did not conduct an intervention study, except for the HOMES study (**chapter 5)** which is more of an implementation and/or feasibility study. This study was set up as an innovative project to transfer care from the hospital to patients home. An important strength of this study is that it was conducted in two hospitals in different cities in the Netherlands, which may increase external validity. The primary outcomes for this study were largely based on PROMs and other questionnaires. This resulted in a large number of questions to be answered by the included patients. Over the course of the study there were increasing numbers of patients who did not finish the questionnaires or did so incompletely. This could be seen as a limitation, as it may have introduced non-response bias. Furthermore, it would have been valuable to add a business case for the intervention of home treatment, which could help convince policy makers and health insurers to continue the project after the initial study. Unfortunately, this was not done. Partly due to lack of time during the COVID-19 pandemic, but also due to lack of knowledge and no pre-defined agreements for this specific intervention among our financial advisors.

FUTURE PERSPECTIVES

Although important progress has been made for patients with severe asthma, complemented by the studies presented in this thesis, several questions remain unanswered and new research questions have arisen as a result of the findings of our studies.

Future perspectives regarding `Treatable Traits`

One of the most promising trends of the past decades is the recognition of precision medicine, also known as personalized medicine. Severe asthma and bronchiectasis are both heterogeneous diseases in which separate phenotypes have been recognized [74, 75]. Personalized treatment is therefore essential. Treatable traits play a key role in this. Treat-

able traits are therapeutic targets identified by for example; imaging, lung function, microbiology, inflammatory biomarkers or patient related outcome measurements (PROMs).

In line with the publications in this thesis, several concepts for treatable trait identification for asthma as well as for bronchiectasis have been published[21, 62, 63]. Although the treatable trait concept is still more broadly accepted for asthma then for bronchiectasis. Patients with severe asthma and co-existent bronchiectasis may need a broad spectrum of treatments, including other non-asthma specific treatments, such as treatment of impaired mucociliary clearance and inhaled or systemic maintenance antibiotic therapy. The 'treatable trait concept' (Figure 7.2) is a 'label free approach' and can help to cover all these potential targets in patients with overlapping chronic airway diseases such as severe asthma and bronchiectasis[21, 61].

Comorbid diseases can be considered as a component of the treatable traits, but are mostly subdivided in more detailed individual traits. For bronchiectasis some of the most clinically relevant treatable traits are; chronic airway infection, microbiology (specific pathogens such as pseudomonas or non-tuberculous mycobacteria (NTM)), airflow obstruction, sputum production, mucus plugging and ABPA. Most of these traits are part of the characteristics identified in our study in **chapter 2**.
Imaging can help to identify treatable traits, such as mucus plugging and small airway disease, and is becoming increasingly important in the management of chronic airway diseases such as bronchiectasis and severe asthma[76]. Performing a chest CT can also reveal co-existent pulmonary diseases or treatable traits, such as emphysema or allergic bronchopulmonary aspergillosis (ABPA), in the systematic workup of severe asthma[12, 77]. Additional studies are needed to investigate if standard performance of CT scan in patients with severe asthma is cost- effective or performing these tests should be considered on a case by case basis.

Not only imaging, but also specific inflammatory and microbiologic features of patients with severe asthma and bronchiectasis can help the clinician to identify potential treatable traits. These features were outlined in the section 'main findings' and in **chapter 2.** In this study we characterized patients in a relatively simple manner, by using, i.a., blood eosinophils, atopy and the results of sputum cultures. New studies are already using more than 30 inflammatory markers obtained from sputum and serum to identify inflammatory molecular endotypes in bronchiectasis[78]. Analysis of the microbiome, by sequencing technologies that will allow for a more comprehensive profiling of the bacterial communities in the airways, is another way to more accurately endotype patients with bronchiectasis and asthma[79]. In addition to new biomarkers in asthma, existing biomarkers, such as blood and airway eosinophils, are being further defined and differentiated by type[80]. These new and better customised biomarkers will hopefully help us to better target treatment and predict response to expensive biologics in the near future. The search for additional and better biomarkers in asthma and bronchiectasis will continue to be important in the coming years[1, 17, 74].

As treatment options for severe asthma and bronchiectasis increasingly overlap, as described in this thesis, the treatable trait approach may help to select the best suited

therapy for the individual patients with severe asthma and bronchiectasis and hopefully lead to better outcomes. It can also help reduce the fragmentation of care caused by the increasing super-specialization of healthcare physicians in Western European countries, including The Netherlands[81, 82]. Therefore it seems interesting and clinically relevant to initiate future studies to evaluate implementation of the treatable trait concept (for example during MDT meetings) in overlapping chronic respiratory diseases such as severe asthma and bronchiectasis.

Future perspectives regarding biologic treatment in patients with severe asthma and bronchiectasis

As new biologics continue to emerge, and treatment indications expand, new research questions arise. First, we need longitudinal studies with repeated CT-scans, to evaluate the effect of asthma biologics on the progression and emergence of bronchiectasis in patients with severe asthma. As discussed in the section 'main findings and implications' early recognition of bronchiectasis in patients with severe asthma may reduce (further) harm, by timely initiation of targeted therapy. In keeping with the 'vicious cycle' hypothesis by Cole[32], treatment with T2 targeted biologics could, theoretically, also prevent further progression of bronchiectasis (Figure 7.1). Complete or partial reversible bronchiectasis have previously been described in children and post infectious bronchiectasis[83, 84]. More recently a case-report of a 65 year old women with severe asthma and bronchiectasis, revealed substantial radiologic improvement of bronchiectasis and complete remission of mucus plugging, on treatment with dupilumab[85]. No large studies on the reversibility of bronchiectasis in asthma have been performed to date.
Second, it seems relevant to evaluate the effectiveness of currently available asthma biologics in patients with 'pure bronchiectasis'. Up to date no specific biologics are approved for the treatment of 'pure' bronchiectasis. Except for a case series of 21 patients[86], no large trials on the effectiveness of anti-IL-5/5R therapy in patients with eosinophilic bronchiectasis without asthma have been performed. There are, however, studies underway to investigate this (Efficacy and Safety of Benralizumab in Patients with NCF Bronchiectasis (ClinicalTrials.gov, NCT05006573(87)).
Third, the anti-IL-4/IL-13 biologic, dupilumab, needs further consideration. In 'mucus driven' asthma, IL-13 seems to play an important role [40, 88] by upregulating 'mucin 5AC' production, which results in the formation of mucus plugs. Therefore it seems reasonable that dupilumab also has the potential to target this treatable trait in eosinophilic bronchiectasis.

Lastly, the new upstream biologics or 'epithelial alarmines', such as tezepelumab, may also be effective in the largest group of bronchiectasis patients with non-eosinophilic or neutrophilic inflammation as they show efficacy in less pronounced eosinophilic inflammation as well[89]. Because tezepelumab targets epithelial derived cytokines, it may affect epithelial barrier dysfunction and for instance result in improving mucociliary clearance and reducing infectious exacerbations in patients with bronchiectasis[90]. Therefore, tezepelumab has the potential to target other specific treatable traits, such as mucus plugging and hypersecretion (Figure 7.2), relevant to patients with bronchiectasis.

Future perspectives regarding severe asthma registries and data extraction

It is a great step forward for healthcare and society that today we have real world registries for chronic diseases such as severe asthma and bronchiectasis. To make research with this type of real-world registries more feasible and sustainable in the future, several aspects could be improved or modernised. The first is support for reliable and less time-consuming data entry. Data extraction software is already able to automatically transfer data from electronic patient records to data management systems. Of course, to protect patient privacy, such software must have guaranteed security measures.

Secondly, there is a strong need to integrate and connect different data files. This includes integrating international registries and local data management.

Meanwhile, great progress has been made in combining and harmonizing national severe asthma registries into one European registry, named SHARP (The Severe Heterogeneous Asthma Registry, Patient-centred)[91]. Although challenging to realize, a combination of different disease registries with detailed data on bronchiectasis (such as EMBARC[64]) and severe asthma (such as SHARP[65]), could increase opportunities and improve overall quality of 'real-world' studies in a more heterogeneous population, as is the case in **chapter 2 and 3**. This may contribute to better understanding of the underlying pathophysiological mechanisms and the most optimal treatment strategies for this complex patient group with overlapping diseases.

In addition, there is a need for integration of national data files. Various relevant data files for patients with severe asthma in the Netherlands are, for example: the electronic patient file, the LSP[92] (as applied for the outcome of cumulative OCS use in **chapter 3**), but also asthma E-health applications that contain data on adherence to inhalation medication or PROMs, such as ACQ. Unfortunately, up to now, most of this data is not yet automatically linked. This may even be a burden for patients, who might be requested to answer the same questionnaires at the same time-point in different systems. In conclusion, healthcare providers, patients, researchers and policy makers could all be helped by improving our current data management systems. This will require collaboration between ICT specialists, hospital security officers and clinicians, including input from patients themselves.

Future perspectives regarding core outcome measurements

The figure of current and potential COMs from our editorial in **chapter 6** gives us an insight into several other future research questions and is therefore reproduced in this section (Figure 7.2). The first outcome measure that is certain to become prominent in the future is disease remission. Current asthma biologics have the potential to provide long-term asthma control. This has led to a major shift in thinking about treatment response[93] and means that preventing disease progression or achieving remission may be realistic treatment goals for patients with severe asthma. Asthma remission will therefore, most likely, be one of the core outcome measurements in future asthma biologic trials. The most commonly used definition for asthma remission includes; symptom

control (based on ACQ-score), the absence of exacerbations, and normalisation or optimisation of lung function (based on FEV_1)[94]. There are however still considerable (international) differences in the definition of remission which needs further considerations.

In addition, there is a need for other more patient-centred outcome measures. The newly introduced severe asthma questionnaire is a good example of this.

Fortunately, in recent years there is also more focus on timely involvement of patients in research projects or healthcare management in general. Ideally patients or patients representatives should already be involved during the initial development phase of a study. Meanwhile, national and international multiple initiatives have been started to realize this (https://participatiekompas.nl/, https://eupati.eu). In the RAPSODI registry, patients are also part of the scientific committee who review new research applications.

Future perspectives regarding health care organization

With the current pressure on hospital capacity and rising healthcare costs, there is an urgent need for home treatment with intravenous medicines for chronic patients, such as those with severe asthma. Our reslizumab home treatment study may motivate health authorities to implement this type of home treatment more widely, for different types of treatments and diseases. By including other patient groups in home treatment within a hospital's organisation, efficiency and cost-effectiveness will increase. This has already been successfully implemented in one of the hospitals included in the study. For future studies, it would also be interesting to combine the home treatment intervention with an intervention to promote the use of e-health and home monitoring by patients, thereby increasing self-management. An important consideration when designing such future studies is the fact that not all patients prefer to transfer treatment from hospital to home, as our study showed. This may also be the case for e-health interventions. Ideally we therefore need to maintain a wide range of treatment and monitor options and select the most appropriate option in an informed and shared decision making process with the patient. However, it is not inconceivable that some of the options now being offered, may be abandoned in the future for economic or logistical reasons.

Last but not least, this thesis may also have demonstrated the complexity of severe asthma. The burden of disease and treatment experienced by patients is made clear in **chapter 4**, and in **chapter 3** we have shown the impressive effects of current asthma biologics on exacerbation frequency and OCS use. Hopefully future health policy makers will be aware of the impact of severe asthma on patients' lives. This should not be confused with the largest group of patients with mild, well-controlled asthma, for whom primary care in the Netherlands is well suited.
We encourage Dutch health policy makers and hospital directions to look not only at the direct healthcare costs of severe asthma treatment, but also pay attention at the savings in indirect costs when patients have been properly treated[95]. Specialized care is needed to achieve the best outcomes for the minority of patients with severe or difficult to treat asthma. With specialized severe asthma centres and the sharing of up to date insights

through asthma care networks, this type of care can remain sustainable and cost-effective for years to come.

CONCLUSION

How does it all fit together? Our findings fit together to emphasise the multifaceted nature of severe asthma management and the need for individualised and personalised care. We have highlighted the importance of recognising bronchiectasis as an important and common comorbidity in severe asthma, shedding light on its specific characteristics. In addition, our studies argue against excluding certain groups of patients, especially those with severe asthma and comorbid bronchiectasis, from biologic therapy.

Incorporating patients' perspectives on biologic treatment adds depth, as demonstrated by our in-depth interviews with patients. Our exploration illustrating the differences in experience between home and hospital-based biologic treatment further underscore the importance of personalized care. Finally, the emphasis on seeking improved, more patient-centred outcome measures aligns with the broader goal of improving patient care and tailoring treatments to individual needs. This thesis, combining the different elements, underlines the need for more comprehensive and patient-centred approaches to the management of severe asthma.

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CHAPTER 8

- English summary
- Nederlandse samenvatting

ENGLISH SUMMARY

Asthma is a chronic inflammatory airway disease, caused by both genetic and environmental factors, and characterized by reversible airflow limitation and airway hyper responsiveness.
Around 300 million people of all ages worldwide suffer from asthma, with a prevalence in the Netherlands of about 370.000 adult patients.
Fortunately the majority of patients with asthma are well controlled and have minimal symptoms when treated with inhaled corticosteroids (ICS) and bronchodilator therapy.
A minority of all patients, approximately 5-10%, have severe refractory asthma, where asthma remains uncontrolled and patients experience recurrent exacerbations, despite adherence to inhaled steroids.
These are the patients who are treated in secondary or tertiary care and form the main population of the studies included in this thesis.

The understanding that asthma is not a single disease, but should be considered as a syndrome consisting of different phenotypes with different underlying pathophysiological mechanisms, is now widely accepted.
This has led to an increasing number of new therapeutic options for patients with severe asthma. For a large group of these patients who previously had to rely on oral corticosteroids now alternative targeted treatment options, in the form of biologics (monoclonal antibodies), are available. Most of the current biologics are administered subcutaneously by patients themselves at home, with the exception of reslizumab which is administered intravenously every four weeks.

Not only is asthma a heterogeneous disease in itself but many patients also suffer from comorbid diseases. Comorbidity is more common in severe asthma and contributes to uncontrolled disease. Bronchiectasis is a common pulmonary comorbidity in patients with severe asthma and is associated with increased disease severity. In bronchiectasis, the airways are widened, thickened and/or scarred. Patients with bronchiectasis commonly experience symptoms of cough, sputum production and recurrent respiratory infections.

Because of the complexity and heterogeneity of severe asthma, especially when combined with comorbidities such as bronchiectasis, there is a strong need for more personalised and patient-centred care.
To promote patient-centred care, patient-reported outcome measures (PROMs) have been developed. These PROMs measure outcomes of healthcare from the patients' perspective and their perceptions of their health and disease. Fortunately, PROMs are now increasingly being included as core outcome measurements in asthma clinical trials.
Another way to gain a better understanding of patients' values and needs are narrative studies. These insights can help clinicians to customize treatment plans to meet the unique needs of each individual patient.

In this thesis we described issues from daily clinical practice related to the characterisation and treatment of patients with severe asthma. In particular, there was a focus on a

sub-group of patients who have comorbid bronchiectasis in addition to severe asthma. This thesis also looked at treatment with biologics and how this is perceived by patients, both in hospital and via intravenous administration at home. Finally, it reflected on 'core outcome measures' and patient-reported outcome measures in severe asthma trials with biologicals.

In **Chapter 2** we used data from the severe asthma cohort of the HagaHospital to study clinical, functional, radiological, inflammatory, and microbial characteristics associated with bronchiectasis in patients with severe asthma.
The study showed that the presence of bronchiectasis in patients with severe asthma is more common in patients with a longer duration of asthma, older age at presentation, and sensitization to Aspergillus fumigatus. Compared with patients with severe asthma without bronchiectasis, patients with co-existing bronchiectasis had a lower lung function, a higher blood eosinophil count, more positive sputum cultures and more infectious exacerbations. Based on a combination of inflammatory biomarkers and clinical characteristics (atopy, age of asthma onset) in our study population, we also suggested that bronchiectasis might be more prevalent in a subgroup of patients with severe asthma, namely the 'late-onset eosinophilic' asthma phenotype.
These results can possibly contribute to early recognition and targeted treatment of this patient group.

Chapter 3 describes the real-world effectiveness of anti-interleukin (IL)-5 biologic therapy in 97 adult patients with severe eosinophilic asthma and bronchiectasis (confirmed by computed tomography scan of the lungs).
For this study we used real-world data from the Dutch severe asthma registry (RAPSODI). We found an important reduction in exacerbation frequency and daily maintenance and cumulative oral corticosteroid (OCS) dose after 12 months of treatment with anti-IL-5/5Ra therapy. The number of patients with ≥2 exacerbations per year, decreased from 75% to 22% and in the OCS-dependent patients the maintenance OCS dose decreased from median of 10.0 mg/day to 2.5 mg/day. In addition, an important and clinically relevant improvement in asthma symptoms, measured by the asthma control questionnaire (ACQ)-6 score, was seen.
These findings suggest that anti-IL-5/5Ra biologics should be considered as add-on therapy for patients with severe eosinophilic asthma regardless of comorbid bronchiectasis.
Since patients with bronchiectasis often suffer from recurrent lung infections and the use of OCS can suppress immunity, the demonstrated OCS-sparing effect may be particularly relevant in this patient group. Therefore we believe that the results of this study may help to achieve better clinical care for patients with severe asthma and co- existing bronchiectasis.

Chapter 4, which is a narrative study, describes every day experiences of patients living with severe asthma and treated with biologics, including the burden of treatment and the impact of non-response to biologics. Narrative studies have the potential to shine a different light on patients experiences and can be defined as: collecting, analysing and interpreting the stories people tell from their own personal experiences.

The results of this study show how patients with severe asthma experience a high disease burden (breathlessness, fatigue, exacerbations, loss of contact with family and friends due to reduced social participation and loss of work) and treatment burden (OCS- side-effects and medication dependency). Patients who showed a good response to treatment with biological therapy, experienced relieve of both the burden of disease and treatment. This was in contrast to those for whom biologicals proved ineffective.
Lessons learned from this study are the importance of timely and accurate diagnosis of (severe) asthma, the availability of supportive communication with health care providers who are aware of the 'hidden burden' of severe asthma and the relevance of patients' perspectives on the impact of asthma on daily life. Finally this study suggests that more attention needs to be paid to the needs of patients with severe asthma not eligible for treatment with biologics.
A better understanding of the patient's perspective and individual needs and preferences can help to select the right treatment for the right patient, thereby improving care for patients with severe asthma.

In **Chapter 5** we evaluated the feasibility and safety of home administration of the intravenous administered anti-IL5 biological reslizumab in two different hospitals in The Netherlands. The results of this study revealed that home administration of intravenous reslizumab for severe asthma was safe and improved the perceived burden of treatment and satisfaction in the majority of patients. Interestingly, this study also shows that patient preference for home administration varies. Around 50% of patients who started treatment in hospital chose not to participate in home administration and one sixth of patients discontinued home administration during the study. The results of this study imply that severe asthma patients have different needs when it comes to choosing treatment at home or in the hospital. However, intravenous reslizumab could be administered safely and successfully in an outpatient setting and was relatively easy to implement.
This will hopefully encourage wider implementation of home administration of reslizumab, as well as other intravenous therapies.

Chapter 6 provides a reflection on meaningful standardised outcome measurements in patients with severe asthma who are treated with biologics. In this editorial, we suggested additional outcome measures to the minimal set of core outcome measurements, defined by the Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)- working group from the European Respiratory Society. Some of the additional outcome measures we included were: hospital admissions, cumulative OCS dose and adverse effects of OCS, and work and school impairment. All of these outcomes appear to play an important role in the perceived burden of disease and treatment in patients with severe asthma. We also speculated about possible other outcome measures to consider in the future. In terms of potential future outcome measures, we suggested, among others, biomarkers of residual airway inflammation, functional imaging and measures of small airway dysfunction.

In conclusion, with this thesis we illustrated the multifaceted nature of severe asthma management and the need for individualised and personalised care.
We have highlighted the importance of recognising bronchiectasis as a relevant and common comorbidity in severe asthma, and illustrated its specific characteristics. We also argue against excluding certain groups of patients, particularly those with severe asthma and comorbid bronchiectasis, from biologic therapy.
Including patients' perspectives on biologic treatment adds depth, as demonstrated by our narrative study with in-depth interviews with patients. Our exploration highlighting the differences in experience between home and hospital-based intravenous biologic treatment further underscores the importance of personalized care.
Finally, the emphasis on seeking improved, more patient-centred, outcome measures is consistent with the broader goal of improving patient care and tailoring treatments to individual needs.

NEDERLANDSE SAMENVATTING

Astma is een chronische inflammatoire luchtwegaandoening, veroorzaakt door zowel genetische als omgevingsfactoren, en gekenmerkt door variabele luchtwegobstructie en hyperreactiviteit van de luchtwegen.
Wereldwijd lijden ruim 300 miljoen mensen aan astma, met een prevalentie in Nederland van ongeveer 370.000 volwassen patiënten. De meerderheid van de patiënten met astma is gelukkig goed onder controle waarbij er onder behandeling met inhalatiecorticosteroïden (ontstekingsremmers) en luchtwegverwijders sprake is van minimale symptomen. Een minderheid (5-10%) van alle patiënten, heeft ernstig refractair astma, waarbij het astma, ondanks adequate behandeling met inhalatiecorticosteroïden, ongecontroleerd blijft en/of patiënten kampen met recidiverende exacerbaties (longaanvallen). Dit zijn de patiënten die in de 2e of 3e lijn onder behandeling van een longarts zijn; zij vormen de doelpopulatie van de onderzoeken die in dit proefschrift zijn opgenomen.
Het onderzoek in dit proefschrift richt zich op problemen uit de dagelijkse klinische praktijk met betrekking tot de karakterisering en behandeling van patiënten met ernstig astma. Hierbij is specifiek gekeken naar een subgroep van patiënten die naast ernstig astma ook bronchiëctasieën hebben. Daarnaast lag de focus op behandeling met biologicals en hoe deze behandeling door patiënten wordt ervaren zowel in het ziekenhuis als via intraveneuze thuistoediening. Tenslotte is er gereflecteerd op 'essentiële uitkomstmaten' (core outcome measurements) en patiënt gerelateerde uitkomstmaten bij ernstig astma trials met biologicals.
Het inzicht dat astma niet één ziekte is wordt inmiddels algemeen geaccepteerd. Astma moet worden beschouwd als een syndroom dat bestaat uit verschillende fenotypes met verschillende onderliggende pathofysiologische mechanismen. Deze ontwikkeling heeft de afgelopen decennia geleid tot een toenemend aantal nieuwe therapeutische opties voor patiënten met ernstig astma. Voor een grote groep van deze patiënten, die voorheen afhankelijk waren van orale corticosteroïden (prednison), zijn nu alternatieve gerichte behandelopties beschikbaar, in de vorm van biologische geneesmiddelen (monoklonale antilichamen, ofwel biologicals).

Biologicals zijn geneesmiddelen die met behulp van biotechnologie worden geproduceerd uit levende cellen. Deze gemodificeerde eiwitten hebben als doel om immunologische processen te beïnvloeden, bijvoorbeeld door het remmen van de werking van ontstekingseiwitten of afweercellen. Biologicals behoren tot de dure geneesmiddelen en worden daarom pas ingezet als andere behandelopties onvoldoende effectief zijn gebleken.
De meeste van de huidige biologicals worden door patiënten zelf, thuis subcutaan toegediend, met uitzondering van reslizumab, dat intraveneus (via een infuus) wordt gegeven.

Astma is niet alleen een heterogene ziekte op zichzelf, maar veel patiënten lijden ook aan andere gelijktijdig bestaande aandoeningen ofwel comorbiditeit. Dit zorgt voor nog meer variatie in hoe de ziekte zich gedraagt. Comorbiditeit komt vaker voor bij ernstig astma en draagt bij aan een minder goede symptoomcontrole en hogere ziektelast.
Bronchiëctasieën zijn een veel voorkomende pulmonale comorbiditeit bij patiënten met ernstige astma en worden geassocieerd met een verhoogde ernst van de ziekte.

Bij bronchiëctasieën zijn de luchtwegen (bronchiën) (plaatselijk) verwijd, en zijn de bronchuswanden ontstoken en verdikt. Deze patiënten hebben vaak klachten zoals hoesten, sputumproductie en terugkerende luchtweginfecties.

Vanwege de complexiteit en heterogeniteit van ernstig astma, vooral in combinatie met comorbiditeit zoals bronchiëctasieën, is er behoefte aan meer gepersonaliseerde en patiëntgerichte zorg. Om patiëntgerichte zorg te bevorderen, zijn er patiëntgerelateerde uitkomstmaten (PROMs) ontwikkeld. Deze PROMs meten uitkomsten van zorg vanuit het perspectief van de patiënt. Gelukkig worden PROMs steeds vaker opgenomen als essentiële uitkomstmaten in klinische onderzoeken naar astma. Een andere manier om een beter inzicht te krijgen in de waarden en behoeften van patiënten zijn narratieve ofwel verhalende studies. Dit soort inzichten kunnen clinici helpen om behandelplannen te maken die passen bij de unieke behoeften van de individuele patiënt.

In **Hoofdstuk 2** maakten we gebruik van de gegevens uit een cohort van patiënten met ernstig astma uit het HagaZiekenhuis teneinde klinische, functionele, radiologische, inflammatoire en microbiële kenmerken tussen patiënten met en zonder bronchiëctasieën te vergelijken.
Deze studie liet zien dat bronchiëctasieën bij ernstig astma vaker voorkomen bij patiënten met een langere astma-duur, een hogere leeftijd bij presentatie, en sensibilisatie voor Aspergillus fumigatus. Vergeleken met patiënten met ernstig astma zonder bronchiëctasieën, hadden patiënten met gelijktijdig aanwezige bronchiëctasieën een lagere longfunctie, een hoger aantal eosinofielen in het bloed, meer positieve sputumkweken en meer infectieuze exacerbaties.
Gebaseerd op een combinatie van ontstekings-biomarkers (meetbare indicatoren, zoals bloed-eosinofielen) en klinische kenmerken (atopie, leeftijd waarop astma begon) in onze studiepopulatie, lijkt het erop dat bronchiëctasieën vaker voor komen in een subgroep van patiënten met ernstig astma, namelijk het 'late-onset eosinofiele' astma fenotype. Deze bevindingen kunnen mogelijk bijdragen aan vroegtijdige herkenning van bronchiëctasieën bij ernstig astma en gerichte behandeling van deze complexe patiëntengroep.

In **Hoofdstuk 3** evalueerden we de 'real-world' effectiviteit van behandeling met anti-IL-5/5Ra biologicals bij 97 volwassen patiënten met ernstig eosinofiel astma en bronchiëctasieën (bevestigd door een CT-scan van de longen), uit het Nederlandse ernstig astma register, RAPSODI (Register of Adult Patients with Severe Asthma for Optimal DIsease management). De respons op behandeling met anti-IL-5/5Ra biologicals (mepolizumab, reslizumab en benralizumab) bij patiënten met ernstig astma en gelijktijdig bestaande bronchiëctasieën was onbekend.
Na 12 maanden behandeling met anti-IL-5/5Ra biologicals vonden we een belangrijke afname in het aantal longaanvallen (het aantal patiënten met ≥ 2 longaanvallen per jaar, daalde van 75% naar 22%), de dagelijkse dosis van onderhouds- behandeling met prednison (een daling van mediaan 10 mg per dag naar 2,5 mg per dag) en de cumulatieve (opgetelde) dosis van alle (zowel onderhoud- als stootkuren) orale corticosteroïden (OCS). Daarnaast werd een belangrijke en klinisch relevante verbetering gezien in de astma controle vragenlijst (ACQ).

Deze bevindingen suggereren dat anti-IL-5/5Ra biologicals zouden moeten worden overwogen als aanvullende behandeling voor patiënten met ernstig eosinofiel astma, ongeacht gelijktijdig bestaande bronchiëctasieën.
Aangezien patiënten met bronchiëctasieën vaak last hebben van terugkerende longinfecties en het gebruik van OCS de immuniteit kan onderdrukken, kan het aangetoonde OCS-sparende effect extra relevant zijn in deze patiëntengroep.

Hoofdstuk 4 beschrijft in een narratieve studie ervaringen van patiënten die leven met ernstig astma en behandeld worden met biologicals, evenals de impact van non-respons op biologicals. Narratieve studies hebben de potentie om een ander licht te laten schijnen op de ervaringen van patiënten en kunnen worden gedefinieerd als: het verzamelen, analyseren en interpreteren van verhalen die patiënten vertellen vanuit hun eigen persoonlijke ervaringen.
De resultaten van deze studie laten zien hoe patiënten met ernstig astma een hoge ziektelast (ademnood, vermoeidheid, exacerbaties, verlies van contact met familie en vrienden door verminderde sociale participatie en verlies van werk) en behandellast (OCS-bijwerkingen en medicatieafhankelijkheid) ervaren. Patiënten die een goede respons vertoonden op behandeling met biologicals, hebben verlichting ervaren van zowel de 'burden of disease' (ziektelast) als de 'burden of treatment' (behandelingslast). Dit in tegenstelling tot degenen bij wie behandeling met biologicals niet effectief bleek.
Lessen die uit deze studie kunnen worden geleerd zijn; 1) het belang van een tijdige en accurate diagnose van (ernstig) astma, 2) de behoefte aan adequate en empathische communicatie met zorgverleners die zich bewust zijn van de 'verborgen last' van ernstig astma en 3) de relevantie van het perspectief van patiënten met betrekking tot de impact van (ernstig) astma op het dagelijks leven. Tot slot suggereert deze studie dat er meer aandacht moet worden besteed aan de ervaringen van patiënten met ernstig astma die niet in aanmerking komen voor behandeling met huidige beschikbare biologicals.
Een beter begrip van het perspectief van de patiënt, evenals hun individuele behoeften en voorkeuren, kan artsen ondersteunen bij het selecteren van de juiste behandeling voor de juiste patiënt. Dit bevordert het optimale gebruik van kostbare biologicals.

In **Hoofdstuk 5** evalueerden we in twee verschillende ziekenhuizen in Nederland de haalbaarheid en veiligheid van thuistoediening van de IV toegediende anti-IL5 biological reslizumab.
De resultaten van dit onderzoek toonden aan dat thuistoediening van intraveneuze reslizumab voor ernstig astma veilig was, de ervaren last van de behandeling verminderde en de tevredenheid bij de meerderheid van de patiënten verbeterde. Interessant genoeg laat dit onderzoek ook zien dat de voorkeur van patiënten voor thuistoediening varieert. Ongeveer 50% van de patiënten die de behandeling in het ziekenhuis startte, koos ervoor om niet deel te nemen aan thuistoediening, en een zesde van de patiënten stopte met thuistoediening tijdens het onderzoek.
De resultaten van deze studie impliceren dat patiënten met ernstig astma verschillende behoeften hebben als het gaat om de keuze voor behandeling thuis of in het ziekenhuis. Echter, wel werd duidelijk dat reslizumab IV veilig en succesvol kon worden toegediend in een poliklinische setting en dat dit relatief eenvoudig was te implementeren.

Dit zal hopelijk leiden tot een bredere implementatie van thuistoediening van reslizumab en andere intraveneuze therapieën.

Hoofdstuk 6 geeft een beschouwing over gestandaardiseerde uitkomstmaten bij patiënten met ernstig astma die worden behandeld met biologicals.
In deze editorial reflecteerden we op aanvullende uitkomstmaten naast de minimale set van essentiële uitkomstmaten, gedefinieerd door de 'Core Outcome Measures sets for paediatric and adult Severe Asthma' (COMSA)-werkgroep van de European Respiratory Society. We speculeerden ook over mogelijke andere uitkomstmaten om in de toekomst te overwegen. Enkele van de aanvullende uitkomstmaten die we opnamen waren: ziekenhuisopnames, school- en werkverzuim, cumulatieve blootstelling aan OCS en daaraan gerelateerde systemische bijwerkingen. Al deze uitkomsten lijken een belangrijke rol te spelen in de ervaren ziekte- en behandellast bij patiënten met ernstig astma. Wat betreft mogelijke toekomstige uitkomstmaten, hebben we onder andere biomarkers van resterende luchtwegontsteking, functionele beeldvorming (m.b.v. radiologische technieken) en metingen van kleine luchtweg disfunctie voorgesteld.

Concluderend hebben we met dit proefschrift de veelzijdige aard van ernstig astma en de daaraan gerelateerde behoefte aan geïndividualiseerde en gepersonaliseerde zorg geïllustreerd. We hebben het belang benadrukt van bronchiëctasieën als een relevante en veel voorkomende comorbiditeit bij ernstig astma. En de specifieke kenmerken van patiënten met het gelijktijdig voorkomen van beide aandoeningen uiteengezet. Daarnaast adviseren we om bepaalde groepen patiënten, vooral die met ernstig astma en bronchiëctasieën als comorbiditeit, niet uit te sluiten van behandeling met biologicals. Het meenemen van het patiënten perspectief met betrekking tot de behandeling met biologicals geeft verdieping, zoals blijkt uit onze narratieve studie bestaande uit diepte-interviews met patiënten. Ons onderzoek naar de verschillen in ervaring van patiënten tussen intraveneuze thuisbehandeling met biologicals en behandeling in het ziekenhuis onderstreept het belang van gepersonaliseerde zorg.
Tot slot sluit de zoektocht naar betere en meer patiëntgerichte uitkomstmaten goed aan bij het bredere doel van het verbeteren van de patiëntenzorg en het afstemmen van behandelingen op individuele behoeften van mensen met ernstig astma.

Appendices

LIST OF PUBLICATIONS

Chapters of this thesis

S.A. van Nederveen-Bendien, S. van Loon-Kooij, G.B.G. Kramer, W.H.F. Huijgen, A. Ten Brinke, A.H. Maitland-van der Zee.
Bronchiectasis in severe asthma, does it make a difference? *Respiration 2020; Dec 15:1-9*

S.A. Bendien, M.M. van Leeuwen, H.S. Lau, A. Ten Brinke, L.E. Visser, E.M. de Koning, G.J Braunstahl. Home-based intravenous treatment with reslizumab for severe asthma in the Netherlands – an evaluation. *Respiratory Medicine 2021; Apr;194:106776*

de Graaff, Bert; **van Nederveen- Bendien, Sarah Alice**; van de Bovenkamp, Hester M. "Like a fish on dry land': an explorative qualitative study into severe asthma and the impact of biologicals on patients' everyday life. *Journal of Asthma. 2022;59(5):980-8.*

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Defining the questions to be asked in severe asthma trials: Data from the COMSA working group. *European Respiratory Journal 2023; 61 (4)*

Bendien SA, Kroes JA, van Hal LHG, Braunstahl GJ, Broeders M, Oud KTM, Patberg KW, Smeenk WJM, van Veen HPAA, Weersink E, Fieten KB, Hashimoto S, van Veen A, Sont JK, van Huisstede A, van de Ven MJT, Langeveld B, Maitland-van der Zee AH, ten Brinke A.
Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis.
The Journal of Allergy and Clinical Immunology: In Practice. 2023;11(9):2724-31 e2

Other publications

van Ingen J, Boeree MJ, de Lange WC, Hoefsloot W, **Bendien SA**, Magis-Escurra C, Dekhuijzen R, van Soolingen D. Mycobacterium xenopi clinical relevance and determinants, the Netherlands. *Emerg Infect Dis. 2008 Mar;14(3):385-9.*

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CURRICULUM VITEA

Sarah Alice van Nederveen-Bendien werd geboren in Groningen en voltooide haar HAVO en VWO aan de Koninklijke Scholengemeenschap Apeldoorn. In 1994 keerde ze terug naar Groningen om daar geneeskunde te gaan studeren aan de Rijksuniversiteit Groningen. Ze behaalde haar artsexamen cum laude in 2001 en werkte vervolgens een periode als ANIOS interne geneeskunde in het Zuiderziekenhuis in Rotterdam.

In 2003 begon ze haar opleiding tot longarts in het Radboud Universitair Medisch Centrum in Nijmegen, waar een belangrijk deel van de opleiding plaatsvond in het toenmalige Universitair Longcentrum Dekkerswald.
Na het afronden van haar opleiding in 2008, trad ze toe tot de vakgroep longziekten van het HagaZiekenhuis in Den Haag. Daar heeft ze de ernstig astma zorg verder vorm gegeven, wat onder andere heeft bijgedragen aan de totstandkoming van het kenniscentrum ernstig astma. Daarnaast heeft ze zich toegelegd op de COPD zorg en het verrichten van endobronchiale echografie (EBUS). In 2019 was ze medeauteur van de Nederlands Huisartsen Genootschap (NHG) standaard 'astma bij volwassenen'. Tussen 2020 en 2023 was ze voorzitter van de Federatie Medisch Specialisten (FMS) werkgroep 'multidisciplinaire richtlijn astma en zwangerschap'. Daarnaast is ze bestuurslid en onderwijs coördinator van de werkgroep cursorisch onderwijs van de NVALT. Vanaf 2023 levert ze als bestuurslid, een bijdrage aan de patiëntenvereniging; astma Vereniging Nederland en Davos (VND).

Sinds 2017 combineert ze haar klinische werk als longarts, met wetenschappelijk onderzoek, aanvankelijk onder begeleiding van dr. Harry Heijerman, tegenwoordig hoogleraar longziekten aan het UMC Utrecht. Vanaf 2019 heeft ze haar wetenschappelijk werk, in de vorm van een promotietraject, onder leiding van Professor dr. Anke-Hilse Maitland van der Zee en dr. Anneke ten Brinke voortgezet.
Saar is getrouwd met Bastiaan van Nederveen en samen met hun dochter Marie wonen ze in het Regentessekwartier in Den Haag.

PhD PORTFOLIO

Courses	Year	Workload (ECTS)
Clinical epidemiology course, LUMC-HAGA	2019	1.0
Evidence based richtlijnontwikkeling (EBRO) training, federatie medisch specialisten (FMS)	2020	0.2
Observational Clinical Epidemiology (AMC Graduate School)	2022	1.0
Good Clinical Practice (GCP) (Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers)	2020, 2023	1.0
Training samen beslissen, Q-academie	2023	0.1
Research Presentations		
Poster presentation: Bronchiectasis in severe asthma, does it make a difference? European Respiratory Society, Research seminar, Barcelona	2019	0.2
Poster presentation: HOMES; Home Administration Of Monoclonal Il-5 Antibody Reslizumab: An Evaluation By Severe Asthma Patients, EAACI Annual Congress, Krakow	2021	0.2
Poster presentation: Real-world effectiveness of anti-IL-5/5R therapy in severe eosinophilic asthma with comorbid bronchiectasis, European Respiratory Society Annual Congress, Barcelona	2022	0.2
Seminars and Conferences		
Invited participant ERS Research Seminar, "The interaction between airway diseases and bronchiectasis"	2019	0.3
European Academy of Allergy & Clinical Immunology (EAACI), Annual Congress, Krakow	2021	2.0
European Respiratory Society, Annual Congress, Barcelona	2022	2.0
Brainfeed, Masterclass Farmacologie, Leersum	2022	0.3
International severe asthma forum (ISAF), Rome	2023	0.4
European Academy of Allergy & Clinical Immunology (EAACI), Annual Congress, Valencia	2024	2.0
Other activities		
Board member, Co-author Practice guideline 'Asthma in adults' from the Dutch College of general practitioners (NHG)	2019-2020	
Board member, Werkgroep inhalatoren astma/COPD, Dutch College of general practitioners (NHG)	2021	
Board member, working group biologicals European Academy of Allergy & Clinical Immunology (EAACI)	2022-2024	

Other activities	Year	Workload (ECTS)
Chair, working group an co-author "Dutch multidisciplinary practice guideline on asthma and pregnancy"	2020-2023	
Board member CASPIR begeleidings- commissie CAHAG (COPD en Astma Huisartsen Advies Groep)	2021-2022	
Board member and teaching coordinator Commissie Cursorisch Onderwijs (CCO) NVALT	2022	
Abstract reviewer for the EAACI Annual Congress	2023-2024	
Board member patient federation; Astma Vereniging Nederland en Davos (VND)		
Organisation and chair first Dutch masterclass on Severe Asthma	2024	
Lecturing		
Invited speaker, Workshop "management of asthma during pregnancy", EAACI annual congress, Lisbon	2019	0.2
Webinar: 'Update of new asthma guidelines' for general practitioners and respiratory physicians	2020	0.2
Plenaire lezing, 'Astma en zwangerschap; van zorgevaluatie naar richtlijn', najaarscongres NVALT	2022	0.2
Webinar RAPSODI/severe asthma registry, presentation with and for patients, 'Severe asthma and Bronchiectasis study with RAPSODI data'	2023	0.2
Flemish Interuniversity Postgraduate course, 'Taking care of pregnancy and underlying respiratory diseases'	2023	0.1
Presentatie en organisatie bespreking: 'Patiënten participatie bij wetenschappelijk onderzoek', HAGAZiekenhuis	2023	0.1
Plenary lecture, 'Asthma and Pregnancy, the new guideline', Symposium, 'Op de Hoogte van Astma', Davos	2024	0.2
'Clinical year in review, asthma' Longartsendagen, Annual Congress, NVALT, Papendal	2024	0.2
Landelijke onderwijsdag Longziekten, AIOS ziekenhuisfarmacie, astma onderwijs	2024	0.2
Tutoring and mentoring		
Supervising research projects and paper writing of master students and residents pulmonary medicine	2017-2024	6.0

DANKWOORD

Onderzoek kan nooit tot stand komen zonder de hulp van velen, en het doorlopen van een promotie traject al helemaal niet. Dit proefschrift is dan ook het eindresultaat van veel intercollegiaal brainstormen en samenwerken, zoom overleggen, reisjes op en neer naar Amsterdam en Leeuwarden, opbouwende en leerzame supervisie van mijn promotor en copromotor, goede gesprekken met vrienden en familie en de inbreng van patiënten.
Mijn motivatie om me te gaan bezighouden met onderzoek naast mijn vak als longarts was niet ontstaan zonder het dagelijkse contact met patiënten. Door hun verhalen tijdens het spreekuur, realiseerde ik me dat er binnen ons vak nog veel ruimte voor verbetering is en dat onze patiënten ons vertellen en leren, waar verder onderzoek zich op zou kunnen richten. Daarvoor, en voor de medewerking aan verschillende onderzoeksprojecten in dit proefschrift door patiënten, wil ik allereerst mijn dank uitspreken.

Mijn promotor en copromotor, Professor dr. Maitland-van der Zee en dr. Ten Brinke, wil ik bedanken voor het bieden van de mogelijkheid om dit promotie traject onder jullie begeleiding te doorlopen.
Ik waardeer het geduld en de ruimte die jullie mij hebben geboden om dit te volbrengen. Nadat Lous Rijssenbeek me bij jou, Anke-Hilse, had geïntroduceerd op de ATS in Washington, heb je me welkom ontvangen voor een eerste kennismakingsgesprek in het AMC. Jouw gedrevenheid en positieve instelling waren voor mij een belangrijke aanmoediging om daadwerkelijk de knoop door te hakken om een promotie traject te starten.
Anneke kende ik al langer als een schoolvoorbeeld van een klinisch onderzoeker, die haar dagelijkse werk met patiënten met ernstig astma, combineert met onderzoek en zo belangrijk bijdraagt aan de hoge kwaliteit van astma zorg, die wij in Nederland bieden. Over en weer brachten we elkaar een werkbezoek, jij kwam een dagje meekijken bij onze astma zwangeren poli en het MDO, en wij mochten bij jou, in het MCL leren hoe we sputuminductie ter fenotypering van ernstig astma zelf konden gaan implementeren in het HagaZiekenhuis. Ik kijk er naar uit om in de komende jaren nog veel kennis en ervaring met elkaar te delen.

De leden van de beoordelingscommissie, Professor Fokkens, Professor Heijerman, Dokter Terheggen-Lagro, Dokter van Boven, Professor Chavannes, en Dokter Weersink, wil ik bedanken voor het beoordelen van dit proefschrift.

Mijn vakgroep longziekten in het HagaZiekenhuis ben ik veel dank verschuldigd. Het is bijzonder dat jullie mij tijd hebben gegund om mijn passie te volgen en me te kunnen bezig houden met klinisch onderzoek. Ik hoop dat we elkaar blijven stimuleren om onszelf maximaal en in de volle breedte te blijven ontwikkelen. Het is soms uitdagend maar vooral heerlijk dynamisch om in een groep te werken met zulke gevarieerde en getalenteerde collega's. Ondanks de rush van de dag, is er toch altijd begrip en oprechte aandacht voor elkaar. Laten we dat vasthouden.

Jeroen van Exsel, jou positieve gemoed en eindeloze geouwehoer, liefst met koffie erbij, zijn van onschatbare waarde voor mijn werkplezier. We hebben door veel werk te verzetten, samen de ernstig astma zorg in het HagaZiekenhuis en voor de regio op een hoog niveau kunnen brengen. Daarnaast ben jij onze vakgroep in een moeilijke periode tegemoet gekomen door een aantal jaren onze vakgroep voorzitter te zijn. Dit heeft veel betekend.

Margot, Ilonka en Manon, onze research coördinatoren, wat zijn jullie een topteam. Zonder jullie ondersteuning, zijn we nergens. Jullie werkplek naast de koffieautomaat, nodigt uit om zo nu en dan binnen te lopen voor een praatje. Dat kan over alles gaan. Ik ben blij dat jullie ook daarvoor tijd maken. Het grootste compliment krijgen jullie van onze patiënten zelf, die tijdens de klinische trials, zo goed door jullie worden begeleid en opgevangen, dat ze het liefst blijven komen, ook als de trial al is afgerond.
De longverpleegkundigen van het HagaZiekenhuis, Femke, Willemijn, Zohreh en Arjan. Jullie bijdrage aan de zorg voor onze patiënten is en was van grote betekenis en onmisbaar. Dank voor jullie geweldige inzet en de fijne samenwerking.

Het werken in een opleidingsziekenhuis houdt je scherp en bij de tijd. Ik prijs met gelukkig met onze AIOS en ANIOS. Niks leuker dan het begeleiden van een aantal van jullie tijdens wetenschappelijk onderzoek en het samen bezoeken van een congres om ons onderzoek te presenteren en hierover te discussiëren met de internationale experts. Ik hoop dat ik jullie nog lang mag begeleiden en mijn passie voor ons vak op jullie kan overbrengen.

Gert Jan Braunstahl, Jasper Kappen en Hans in 't Veen uit het Franciscus Gasthuis & Vlietland wil ik bedanken voor de fijne samenwerking en de mooie initiatieven die we tussen onze ziekenhuizen tot stand hebben weten te brengen. Gert-Jan, jou in het bijzonder voor je laagdrempelige bereikbaarheid en praktische adviezen, ook met betrekking tot de organisatie van de astmazorg.

Met Hans Kroes heb ik mogen samenwerken aan het onderzoek met de RAPSODI-data. Jouw nuchtere kijk op de zaak werkt relativerend en jou inzichten zijn een grote bijdrage geweest in het aanscherpen van onze gezamenlijke studie. Simone Hashimoto, dank voor het altijd super snelle schakelen en je positieve aanmoediging bij vragen over RAPSODI.

Harry Heijerman en Bert Roldaan wil ik bedanken voor het feit dat ik als eerste vrouwelijke longarts binnen jullie mannenclub mocht toe treden tot de vakgroep. Voor het vertrouwen in mij om de astma zorg, die jullie hadden neergezet, op te pakken en verder uit te mogen bouwen. Harry, voor de vrijheid die je me in het begin van mijn loopbaan hebt gegeven om mijn eigen keuzes te maken waardoor ik vanuit intrinsieke motivatie vol voor de ernstig astma zorg wilde gaan.

Thomas Eiwegger, Thank you so much for trusting me to get involved in some of your studies and in the biological working group. I learned a lot from this and hope to continue working with you in the future.

De klinische en poliklinische apothekers van het HagaZiekenhuis voor de samenwerking, vooral met betrekking tot de astma biologicals. In het bijzonder wil ik bedanken, Maarten Ploeger voor je blijvende aanzet tot innovatie en je originele en nuttige ideeen en voor het betrekken van de astma zorg hierbij.
Luc Doeve heeft me bijgestaan met zijn goede gevoel voor de Engelse taal. Ook je spontane appjes met adviezen over nieuwe software waren heel welkom, en niet op zijn minst je gevoel voor humor waarmee het je wonderbaarlijk goed lukt om mij soms even uit mijn hoofd en denkmodus te halen.
Maurik van den Heuvel, zelfs op de terugweg naar huis, midden in de nacht na een gestrande vlucht bij Düsseldorf kon jij mij nog enthousiast je visie op mijn statistische analyses geven. Het is altijd fijn om in het gezelschap van jou en Iske te zijn en met een zelfde bevlogenheid over onderzoek te kunnen praten als over lekker eten en goed koken.
Pieter, één van mijn oudste maatjes uit het ziekenhuis. We ontmoetten elkaar tijdens onze opleidingstijd in het Zuiderziekenhuis, en vervolgden onze weg toevallig samen naar het Radboud UMC. In Nijmegen deelden we plezier in culturele uitstapjes. Nog altijd heb ik bewondering voor het talent en de passie die jij en Margot voor muziek hebben.
Annelies Beukert. Hoe leuk is het om samen met jou naar een congres te gaan, bij te praten in hippe koffiebarretjes en vooral ook veel lol te hebben over onze favoriete sprekers op de EAACI. Hoop dat we samen blijven sparren over onze visie op de astmazorg in Nederland.

Mijn vriendinnen Heleen Feitsma (Feits) en Caroline Gerding (Gert) die mij, onder andere, vanuit hun coach opleiding konden voorzien van persoonlijk advies en mooie levenslessen. Onze wandelingen gaven hier veel ruimte voor. Ik hoop dat we deze traditie blijven voortzetten.
Fleurisca Korteweg wil ik bedanken voor haar openhartigheid tijdens een minder makkelijke periode. Het delen van persoonlijke ervaringen op zulke momenten is ondersteunend. Verder volg ik jou carrière verloop natuurlijk op de voet en heb ik bewondering voor de keuzes die je maakt.

Mijn paranimfen. Renske, natuurlijk moest jij hierbij zijn. Je bent voor mij zowel een trouwe vriendin als fijne collega. Met jou kan ik eindeloos reflecteren op het traject van een promotie maar ook op het leven zelf. Het is veel waard dat we elkaar wisten te blijven motiveren om naast onze drukke baan en onze PhD trajecten nog tijd vrij te maken om recepten en tuintips uit te wisselen, lekker te koken en iets anders dan vakinhoudelijk te lezen.
Lieve Eva, wat fijn dat jij als paranimf en zus aan mijn zijde wil staan. Jou positieve instelling en relativerend vermogen geven vertrouwen. We hebben als zussen veel gedeeld de afgelopen jaren en het samen lopen van de GR5 was een mooi moment om hier bij stil te staan. Ik hoop dat we dat nog vele jaren blijven doen.

Lieve pappa en mamma. Mijn ongecompliceerde en warme jeugdjaren bij jullie thuis in Grijpskerk en Apeldoorn vormen een solide basis voor mijn latere leven en carrière. Dat is heel veel waard. Pappa, je brede interesse, je drive om je te willen blijven verdiepen en je eindeloos kunnen verliezen in een goed boek, die eigenschappen heb

ik waarschijnlijk van jou. Jij nam mij, vanuit je vak als kindercardioloog en radioloog, als kind al mee naar de echo's in het ziekenhuis waar ik geïntrigeerd raakte door de persoonlijke contacten met patiënten en het menselijk lichaam. Als ik eens klaag over hoe druk het is op mijn werk, blijf je me zeggen dat ik het mooiste vak van de wereld heb, en dat is ook zo.
Lieve Mamma, van jou heb ik veel geleerd: je talent voor organiseren, je creativiteit en niet in de laatste plaats, het leven bij de dag ('het echte feest is altijd nu'). Tijdens mijn promotie traject was de vroege ochtend mijn favoriete tijd om in stilte te schrijven of te lezen. Door jou ingegeven, start ik de dag nu met een rondje door de tuin en heb ik dit serene moment van de dag nog meer leren waarderen.
Oostum, gelegen in het uitgestrekte Groningse platteland, was de ideale plek om ongestoord aan mijn onderzoek te werken en tegelijkertijd op te laden in de natuur. Ik hoop dat we daar nog vele mooie momenten samen met jullie en onze gezinnen mogen beleven.

Lieve Bas, zonder jou was dit hele proces niet mogelijk geweest. Je hebt me veel tijd gegeven en gegund om dit tot een mooi einde te brengen. Ik vrees dat ik soms onuitstaanbaar of onbereikbaar was omdat ik weer met mijn hoofd in de boeken zat, maar de successen hebben we altijd samen gevierd. Ik hoop dat we nog jaren lang, zoals wij dat kunnen, samen kunnen genieten van de simpele en eenvoudige bijzondere momenten die het leven biedt. Dank voor al je geduld en je liefde voor ons gezin.

Lieve Marie, je weet me altijd weer te ontroeren met je stevige knuffels en originele opmerkingen. Je bent super sportief en vooral jezelf. Dat zijn hele mooie eigenschappen. Ik geniet elke dag van jou en prijs me gelukkig met de allerliefste dochter van de wereld.