Difficult-to-treat asthma : mechanisms and risk factors

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Chapter 1

General Introduction

Introduction

Difficult-to-treat asthma is a heterogeneous disorder characterized by persistent symptoms, frequent exacerbations and fixed airflow limitation, despite treatment with high doses of inhaled (or oral) corticosteroids and long-acting bronchodilators (1-3). It is this group of patients seen regularly by pulmonologists in their practice, which sometimes pose a major clinical challenge. Apart from oral corticosteroids and anti-IgE, which has recently become accessible for patients with severe atopic asthma (4), there are no alternative add-on drugs currently available. Therefore, patients with difficult-to-treat asthma are often suffering from persistent symptoms of dyspnoea, night time awakenings, reduced exercise tolerance, side effects from (oral) corticosteroids, frequent emergency visits and hospital admissions.

From a clinical perspective, patients with difficult asthma represent a heterogeneous group: they can for example be atopic or not (5), have childhood onset or develop asthma later in life (6), have frequent or infrequent exacerbations (7) have normal lung function between asthma attacks or persistent airflow limitation (8-10). For the clinician it is important to recognize these various asthma phenotypes as well as their underlying mechanisms in order to optimize asthma treatment for the individual patient (2;5).

Treatment of patients with asthma should not only consist of drug therapy but includes a thorough evaluation of asthma history and symptoms, drug adherence and side effects and the presence of potential asthma aggravating factors such as persistent allergen exposure, severe sinonasal disease, gastro-oesophageal reflux, psychopathology and overweight (7). The ideal asthma drug would be a “one size fits all” therapy, and corticosteroids come close, but then without accompanying severe side effects (11;12). However, since we are dealing with a heterogeneous disorder with only a limited number of available therapies it is more rational to select those patients that benefit from certain drugs, and aim at individualized or phenotype-specific therapy. In order to reach this goal a meticulous description of asthma phenotypes describing clinical, physiological and inflammatory features is important.

Numerous studies in the field of difficult-to-treat asthma have focused on this subject in the recent past, but more work needs to be done (2;5). Apart from defining asthma phenotypes other issues remain: why do certain patients with asthma become difficult-to-treat, how can we identify patients that will develop certain phenotypes at an early stage and do phenotypes last over time? The studies in this thesis have tried to make a modest contribution in addressing these questions.

Mechanisms that may explain the development of persistent airflow limitation

The first two studies are cross-sectional studies looking at mechanisms that can explain persistent airflow limitation in asthma. Persistent airflow limitation is common in difficult-to-treat asthma (up to 49% of patients) (13) but the pathophysiological mechanisms are still poorly understood. Structural alterations in the airways possibly induced by chronic airway inflammation are thought to cause persistent airway hyperresponsiveness and fixed airway obstruction (14). It remains unclear**,** however**,** which components of the airway wall (centrally or peripherally) can be held responsible for this mechanism (15).

Genetic (16), environmental (17) and inflammatory factors (6;8;10;18) have been associated with accelerated decline in lung function. A genetic deficiency in alpha-1-antitrypsin production is known to predispose to the development of chronic airflow limitation and emphysema (19). Furthermore, heterozygous AAT phenotypes have been associated with airway hyperresponsiveness (20). In chapter 3 we investigated whether alpha-1-antitrypsin deficiency could contribute to persistent airflow limitation in difficult-to-treat asthma.

In chapter 4 we discuss the role of peripheral airway disease in asthma. Inflammation of the distal lung in asthma has been demonstrated in post mortem tissue in patients who died from an asthmatic attack (21;22), in resected lung tissue (23) and in transbronchial biopsies from patients with asthma (24;25) and has been suggested to contribute to instability of the disease (26), therapy resistance (27) and excessive airway narrowing (28). In this study we hypothesize that the degree of peripheral airway dysfunction and inflammation are interrelated and associated with asthma severity.

The obese phenotype

One of the clinical features that has been related to asthma severity is obesity (body mass index (BMI) ≥ 30). It has been demonstrated that obesity leads to a state of low-grade inflammation, in which adiponectin and leptin produced by the obese tissue are involved. This systemic inflammation might influence inflammatory processes in the airway wall thereby exacerbating asthma. Other mechanisms that may play a role in the association between the two disorders are the mechanical effect of adipose tissue on lung function and the presence of co-morbid factors (29). In chapter 4 we investigated whether obese patients with difficult-to-treat asthma differ in clinical, physiological and inflammatory features from the non-obese patients.

Predictors of an accelerated decline in lung function

In 1998, a study among more than 17000 individuals, of whom 6% had self-reported asthma, showed that patients with asthma had an average decline in FEV_1 of 38 ml/yr as compared

to 22 ml/yr in the healthy individuals (17). This result together with the finding that up to 49% of patients with difficult-to-treat asthma has persistent airflow limitation (13) raised the question which patients are at risk of having an accelerated decline in lung function.
Previous cross-sectional studies have shown that persistent airflow limitation is associated with eosinophilic airway inflammation (6;8;10) and that infection with pathogens including *Chlamydia Pneumoniae* is associated with increased lung function decline especially in non-atopic adults (9), which was confirmed in a longitudinal study (30). Furthermore, lung function decline has been related to CD8+ cells in bronchial biopsies (18) and exacerbations (31;32) in other longitudinal studies.

In 1998 a cohort of 136 patients with difficult-to-treat asthma from 10 academic and non-teaching hospitals in the Netherlands was recruited at the Leiden University Medical Centre to define phenotypes of difficult-to-treat asthma (7;9). All patients fulfilled the criteria proposed by the ERS Task Force on difficult/therapy-resistant asthma (3). In order to identify risk factors of accelerated lung function decline we re-assessed this cohort 5-6 years later. The results of this study are discussed in chapter 6.

Persistence of the eosinophilic phenotype
Difficult-to-treat asthma is a heterogeneous disorder not only from a clinical perspective but also with respect to the type and extent of inflammatory changes in the airways. Several inflammatory phenotypes have been described in the past years, in particular the non-eosinophilic and eosinophilic subtype (33-36). In cross-sectional studies it has been demonstrated that patients with persistent eosinophilia in sputum or bronchial biopsies have poorer lung function, more ICU visits and more sinus disease (6;8;36). When studying phenotype specific treatments in clinical trials it is crucial that these specific features are not a once-only observation but that they represent longstanding characteristics of these patients. In chapter 7 we therefore discuss whether the (non-) eosinophilic phenotype is a permanent characteristic of patients over a 5 years interval.

Aims of the studies

Chapter 2: In this chapter we give an overview of the current literature about the difficult-to-treat asthmatic patient. The review is written from a clinical perspective to offer all those who work with these patients, whether they are nurses, doctors in training, pulmonologists or researchers, a practical outline.

Chapter 3: In this study we hypothesized that a heterozygous (non-PiM) alpha-1-antitrypsin (AAT) deficient phenotype is a risk factor of persistent airflow limitation in patients with asthma. To test this hypothesis we assessed the prevalence of a non-PiM phenotype in patients with difficult-to-treat asthma with or without persistent airflow limitation, compared lung function parameters between PiM and non-PiM phenotypes, and analysed whether a non-PiM phenotype was associated with a more impaired lung function as compared to a PiM AAT phenotype.

Chapter 4: The hypothesis of this study was that parameters of peripheral airway dysfunction and peripheral airway inflammation are interrelated and associated with asthma severity. To that end we investigated a new parameter of peripheral airway inflammation, alveolar nitric oxide, and compared this with established parameters of peripheral airway dysfunction in patients with mild-to-moderate and severe asthma.

Chapter 5: Obesity has been related to the prevalence of asthma and to asthma severity through different possible mechanisms. In this study we investigated whether obese patients with difficult-to-treat asthma have different clinical and inflammatory profiles as compared to non-obese patients.

Chapter 6: It has been demonstrated that lung function decline in patients with asthma is increased and that up to 49% of patients with difficult-to-treat asthma have persistent airflow limitation. The aim of this study was to assess the rate of lung function decline in patients with difficult-to-treat asthma and to identify risk factors of accelerated decline in lung function.

Chapter 7: In this final study we investigated whether the so called “eosinophilic phenotype”, which has been determined in cross-sectional studies, is a permanent finding over 5 years and assessed whether permanent sputum eosinophilia is associated with certain clinical or inflammatory characteristics.

Chapter 8: in this chapter data from the different studies are summarized and the implications are discussed from clinical or research perspectives.

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