Perspective

Current and emerging treatments for severe asthma

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Abstract: Severe asthma, which is poorly controlled despite the elimination of modifiable factors and the correct use of standard therapy, accounts only for 5% of people with asthma but it contributes to approximately 50% of the economic costs of asthma. Because of this unmet need, novel therapies have been developed for optimal treatment of these patients. The use of tiotropium, omalizumab, mepolizumab and thermoplasty in well-selected patients provides better control and most importantly a reduction in asthma exacerbations.

Keywords: Severe asthma; tiotropium; omalizumab; mepolizumab; thermoplasty

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Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of symptoms including wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (1). According to WHO estimates, globally 235 million people suffer from asthma. Worldwide, asthma prevalence rates have been rising on average by 50% every decade (2). Severe persistent asthma is considered to be asthma, which is poorly controlled despite the elimination of modifiable factors and the correct use of standard therapy. Patients with severe poorly controlled asthma are at increased risk of asthma exacerbations that may be serious and require unplanned medical intervention and sometimes hospitalization, and have reduced quality of life (QoL). Although this group accounts for only around 5% of people with asthma, it contributes to approximately 50% of the economic costs of asthma. Because of the unmet need for this patient population group novel therapies have been developed for these patients (3).

Economic burden of severe asthma

The economic costs associated with asthma are estimated to rank as one of the highest among chronic diseases due to the significant healthcare utilization associated with this condition. The cost of asthma includes both direct and indirect costs. Direct costs include inpatient care, emergency visits, physician visits, nursing services, ambulance use, drugs and devices, blood and diagnostic tests, research, and education. Indirect costs or morbidity costs include school days lost, traveling, waiting time, and lost productivity for the caretaker of asthmatic children. Direct costs have been shown to exceed indirect costs, and the major components of the direct medical costs include pharmacological expenditures and hospital admissions (4). Not surprisingly disease of greater severity was associated with higher total costs. The per-patient cost ratio of asthma increased from 1 to 1.5 to 2.6 across the severity levels of asthma (mild-moderate and severe) (5). Poor asthma control was found to be associated with a greater likelihood for hospitalization and unscheduled physician visits in the previous year; and undoubtedly higher asthma related costs were also found (6).

Distinguish between uncontrolled and severe asthma

If severe asthma is suspected, differential diagnoses that may mimic asthma should first be ruled out by getting

Table 1 Diseases that may mimic asthma or contribute to apparent poorly controlled asthma

Congenital or acquired immunodeficiency
Primary ciliary dyskinesia
Cystic fibrosis (CF)
Vocal cord dysfunction (VCD)
Central airway obstruction
Recurrent aspiration
Bronchiolitis
Gastroesophageal reflux disease (GERD)
Psychogenic hyperventilation
Chronic obstructive pulmonary disease (COPD)
Heart failure
Drug side effects (e.g., ACE inhibitor-induced cough)

a detailed clinical history (*Table 1*). It is also important to rule out diseases associated with asthma including aspirin-exacerbated respiratory disease (AERD), allergic bronchopulmonary aspergillosis (ABPA), and Churg-Strauss syndrome (CSS). The most common cause for uncontrolled asthma, and therefore apparent severe asthma, is non-adherence to prescribed anti-inflammatory therapy. Moreover ongoing exposure to asthma triggers may contribute to poor control. Because of this, adherence and triggers should always be systematically investigated before additional medication is prescribed. In addition, comorbidities that affect asthma severity, such as chronic rhinosinusitis, gastroesophageal reflux, sleep related breathing disorders, vocal cord dysfunction (VCD) or heart disease, must be sought and effectively treated (7).

Most patients with asthma respond well to inhaled corticosteroids; and if control is sub-optimal then to the addition of long acting beta agonist (LABA). Despite the efficacy of these treatments, many patients remain uncontrolled and a small minority of about 5% to 10% can be classified as having severe asthma. In such patients, after appropriate review of adherence and inhaler technique, additional therapies as outlined below can be considered.

Tiotropium bromide

Tiotropium is a long acting anti-muscarinic agent that has been mostly used in COPD. However, the role of tiotropium as a treatment for asthma has only recently been a subject of clinical investigation. Most of the studies used the Respimat device to administer 2.5-mcg tiotropium twice daily. In patients with poorly controlled asthma despite treatment with twice daily ICS and LABA, the addition of tiotropium increased pulmonary function close to or reaching the minimal clinically important difference (MCID). Furthermore, adding tiotropium reduced asthma exacerbations by 21% (number needed to treat "NNT", 17). It also improved Asthma Control Questionnaire 7 (ACQ-7) and Asthma Quality of Life Questionnaire (AQLQ) scores and other secondary outcomes, although these improvements did not reach their respective MCIDs (8). This difficulty of achieving MCIDs with add on therapy has recently been documented by Bateman *et al.* (9).

Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds IgE at the same epitope on the Fc region that binds to the IgE receptor. The coexistence of severe asthma refractory to the conventional pharmacological approach, with an elevated IgE in the appropriate therapeutic range and sensitization to at least one perennial allergen represent the current indications for omalizumab prescription. It is usually administered as a subcutaneous injection every 2 to 4 weeks. The dose and frequency of dosing are guided by a nomogram that is derived from the total serum IgE level and the body mass index (3,10). In a systematic review of long-term trials involving patients with persistent uncontrolled allergic asthma, omalizumab significantly reduced the incidence of asthma exacerbations and ICS use and improved scores on the global evaluation of treatment effectiveness (GETE) and AQLQ, compared with control subjects. Additionally, omalizumab was well tolerated and demonstrated an acceptable safety profile. This is an expensive intervention, but the drug may be cost-effective if used in patients with severe allergic asthma (3).

Mepolizumab

Mepolizumab, a humanised monoclonal antibody against interleukin 5, selectively and effectively inhibits eosinophilic airway inflammation. In the DREAM trial, patients were randomized to placebo, 75, 250 and 750 mg mepolizumab intravenously every 4 weeks; mepolizumab significantly reduced the number of asthma exacerbations in patients with severe eosinophilic asthma and lowered blood and

sputum eosinophil counts compared with placebo but there were no consistent improvements in symptoms or lung function. It was well tolerated for 12 months (11,12). In the MENSA trial, patients with severe asthma and persistent blood eosinophilia (>150 per microlitre), treatment with mepolizumab (100 mg SC and 75 mg IV) reduced exacerbations by approximately one half, improved QoL, and resulted in better asthma control. Both intravenous and subcutaneous doses were effective and had acceptable side-effect profiles (13). This novel treatment will likely be soon available for management of this group of patient population.

Thermoplasty

Thermoplasty is a novel intervention, which aims to reduce smooth muscle in the airways of patients with uncontrolled asthma (14). Its efficacy, in reducing asthma exacerbations, has been shown in randomized controlled trials but is relatively invasive and requires three bronchoscopies to complete a satisfactory treatment. Additional considerations include the need for up to 8% of patients requiring hospitalization in the immediate post bronchoscopy period (15). Despite this long term efficacy up to five years after the procedure has been shown (16).

Summary

Although severe asthma accounts for only around 5% of people with asthma, it contributes to approximately 50% of the economic costs of asthma; therefore novel therapies have been developed for optimal treatment of these patients. If severe asthma is suspected, differential diagnoses that may mimic asthma should first be ruled out followed by ruling out diseases associated with asthma and poor treatment adherence and/or persistent triggers. The use of tiotropium, omalizumab, mepolizumab and thermoplasty in well-selected patients provides better control and most importantly a reduction in asthma exacerbations. In the next few years multiple other targeted treatments for severe asthma will become available. The challenge will be to ensure these therapies are provided to the appropriate patient and also that given there inherent high costs that they are rigorously evaluated for there cost effectiveness.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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