

REVIEW

Severe asthma: future treatments

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Summary

Background Patients with severe refractory asthma have not achieved asthma control, even with high doses of ICS, usually in combination with LABAs and other maintenance treatments.

Objective The most promising approaches currently under investigation are those which reduce airway eosinophils in patients with severe refractory asthma and a persisting airway eosinophilia.

Results Monoclonal antibodies against IL-5 have been shown to improve lung function, improve asthma control, reduce exacerbation risk and allow reduction or elimination of maintenance oral corticosteroids in this subset of patients. Bronchial thermoplasty may provide benefit in improving control and reducing exacerbations in selected patients. The addition of the muscarinic antagonist, tiotropium also improves airflow obstruction, but its benefit on exacerbation risk is not yet established. Other developments being evaluated in severe refractory asthma are CXCR2 antagonists in patients with a persisting neutrophilic airway inflammation, and CRTh2 antagonists, both of which are small molecule antagonists, and hMabs against IL4 and IL-13. Finally, other approaches to reduce receptor numbers, using inhaled anti-sense, has shown to reduce allergen-induced airway eosinophilia, and combining different anti-sense against different targets may become a feasible treatment option.

Conclusions A variety of new treatment options are being investigated to help improve overall asthma control in patients with severe refractory asthma. These include medications to optimize lung function; bronchial thermoplasty to reduce airway smooth muscle in central airways; and those which target specific inflammatory cells or receptors of inflammatory mediators.

Clinical Relevance Patients with severe refractory asthma have the greatest unmet treatment needs to improve asthma control and reduce exacerbation risk. New treatment approaches have been identified which will benefit subsets of these patients. Phenotyping patients is necessary to select those likely to benefit.

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Introduction

There have been a variety of definitions for 'severe or difficult asthma' [1–3]. The most recent of these [4] has made the important distinction that the term 'difficult asthma' should be used for asthma that is poorly controlled, despite the prescription of optimal asthma treatment. This lack of control may be due to a variety of factors, including poor adherence to treatment; psychosocial factors, vocal cord dysfunction; persistent exposure to allergens or toxic substances; or undertreated co-morbidities such as chronic rhinosinusitis, gastroesophageal reflux or obstructive sleep apnea. The most

common reason for poor asthma control, is poor adherence and improved methods, or biomarkers for monitoring adherence in clinical practice would be a very valuable addition to improve patient management.

The term 'severe refractory asthma' should be "reserved for patients with asthma in whom alternative diagnoses have been excluded, co-morbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked, but still have poor asthma control or frequent (≥ 2) severe exacerbations per year despite the prescription of high-intensity treatment or can only maintain adequate control when taking systemic corticosteroids

and are thereby at risk of serious adverse effects of treatment" [4].

Patients with severe refractory asthma represent a small subset of the asthmatic population, between 5% and 10% of all patients, but are the greatest burden to the health care system [5], and they are the patient population most in need of new treatment approaches [6]. Efforts have been made to phenotype patients with severe refractory asthma, and these have included unbiased cluster analyses [7, 8] and phenotyping based on the type of inflammatory cells that is usually present in the airway [9]. The latter approach has proven, to date, to be the most useful approach in identifying new treatments for severe refractory asthma. It has, however, become clear that there is no one specific phenotype to explain all severe refractory asthma, and no one treatment approach which will improve asthma control in all severe refractory patients.

A variety of approaches have been attempted to improve outcomes in patients with severe refractory asthma. These have included:

- Optimizing bronchodilation
- Reducing airway smooth muscle
- Reducing airway inflammatory cell number and/or activity
- Targeting specific airway effector mediators.

Although none of these approaches has yet revolutionized the treatment of severe refractory asthma, there are several which show real promise, at least, for some patients. This review will consider new treatments options for severe refractory asthma, which have already been evaluated in clinical trials in asthmatic patients.

Optimizing bronchodilation

Airflow obstruction is a hallmark of severe refractory asthma. Treatment recommendations suggest that efforts be made to optimize bronchodilation with regular use of long-acting inhaled β_2 -agonists (LABA), together with inhaled corticosteroids (ICS) [10, 11], as well as using a rapid-onset inhaled β_2 -agonists as rescue therapy [10, 11]. Some of the benefits achieved with the use of inhaled β_2 -agonists are lost with regular use. This is particularly true for the benefits achieved by functional antagonism (protecting against the onset of bronchoconstriction) [12]. This partial loss of effect is termed tachyphylaxis or tolerance, but the loss of benefit from regular use is much less obvious for the effects of inhaled β_2 -agonists in reversing established bronchoconstriction. Thus, even with regular use of a β_2 -agonist over 1 year the magnitude of bronchodilation can be maintained [13]. This is likely because the

intracellular mechanisms which result in bronchodilation, require activation of only a relatively small fraction of the available β_2 -receptors on an airway smooth muscle to evoke a maximal response.

Recently, studies have evaluated the benefits of a different approach to optimizing bronchodilation, which is to add the long-acting muscarinic antagonist, tiotropium, to conventional therapy. One study which compared adding tiotropium to adding the LABA, salmeterol, and to doubling the dose of ICS in patients with severe refractory asthma [14] demonstrated that both tiotropium and salmeterol were superior to doubling ICS dose for improving lung function, measured by improvements in peak expired flows (PEF) and the forced expired volume in 1 s (FEV₁), as well as improving asthma control. However, tiotropium was superior to salmeterol in improving evening measurements of PEF and in the pre-bronchodilator FEV₁. These authors concluded that tiotropium is equivalent to the LABA in improving outcomes in severe refractory asthma. Another study has evaluated the benefits of adding tiotropium to ICS/LABA treatment in severe refractory asthma [15]. This is a more clinically relevant situation, as this is the currently recommended treatment approach. The authors concluded that the addition of tiotropium to high-dose ICS plus LABA significantly improved lung function, as measured by FEV₁ over 24 h, in patients with severe refractory asthma. These studies provide evidence which suggests that tiotropium is an effective additional bronchodilator in severe refractory asthma. One issue that the studies did not address, however, is whether tiotropium plus ICS has a beneficial effect in reducing the risks of severe asthma exacerbations that the combination of LABA plus ICS have [13, 16]. This has been previously demonstrated in patients with COPD [17].

Reducing airway smooth muscle

Bronchial thermoplasty is a bronchoscopic therapeutic procedure, where the airways are heated using radiofrequency energy to 65°C [18]. The procedure is done using a catheter passed through the bronchoscope, and can only treat the larger airways. A complete period of treatment requires three bronchoscopies, spaced several weeks apart. There is convincing evidence that the procedure reduced the volume of airway smooth muscle in the treated airways [19].

The benefits achieved using bronchial thermoplasty were initially demonstrated in patients with relatively well-controlled asthma [18]. These were a reduction in mild and severe asthma exacerbations and an improvement in asthma control. Subsequently, bronchial thermoplasty was studied in patients with severe refractory asthma [20]. This study confirmed that thermoplasty

resulted in an improvement in FEV₁ and a clinically important improvement in asthma control. A larger study, which was the first blinded, sham treatment controlled study, also demonstrated a reduction in severe asthma exacerbations, and a significant improvement in days lost from school or work because of asthma [21].

Bronchial thermoplasty is, however, associated with unwanted effects. Some patients have experienced atelectasis and occasionally have required hospitalization following the procedure [20, 21]. These events have all fully been resolved.

Reducing airway inflammatory cell number and/or activity

Approximately 50% of severe asthma exacerbations are eosinophilic in nature, whereas many of the remaining are neutrophilic [22]. Several studies have demonstrated that making asthma treatment decisions based on minimizing airway eosinophils (measured in induced sputum) can reduce the risks of severe exacerbations [23, 24]. In addition, treatment of patients with severe refractory asthma, who were dependent on oral corticosteroids to minimize airway eosinophilia, with an anti-interleukin (IL)-5 monoclonal antibody (hMab) (mepolizumab) reduced the number of blood and airway eosinophils into the normal range [25]. In addition, treatment with mepolizumab allowed the reduction of oral corticosteroids, and in most patients, their withdrawal. Despite the reduction in oral corticosteroids, mepolizumab treatment reduced the number of severe asthma exacerbations (Fig. 1) and improved the FEV₁ and measures of asthma control. This benefit of me-

polizumab has also been shown for asthmatics with refractory asthma, but not requiring oral corticosteroids to manage their airway eosinophilia [26]. More recently, treatment with a different anti-IL-5 hMab (reslizumab) has demonstrated benefits in improving FEV₁ and asthma control, again in patients with severe refractory asthma and a persisting airway eosinophilia [27]. When these antibodies were evaluated in patients with moderate to severe refractory asthma, but who were not selected on the basis of a persisting airway eosinophilia, no clinical benefit could be demonstrated [28, 29]. These studies emphasize the benefit of careful patient selection (personalized medicine) in deciding on a new treatment in severe refractory asthmatics.

Another treatment under investigation to treat persisting airway eosinophilia is to use anti-sense approaches to reduce the levels of messenger RNA and prevent translation of the RNA into proteins that are needed for the production of cytokine receptors, which mediate the effects of cytokines needed for eosinophil maturation, survival and migration. This approach has been developed to prevent the expression of the common β -chain on inflammatory cells, which is a part of the receptor mediating the effects of IL-5, as well as IL-3 and GM-CSF. A second anti-sense against the chemokine receptor (CCR)-3, which mediates the effect of the eosinophil chemoattractant, eotaxin, was included in a combination. This combination of anti-sense has been shown to significantly reduce allergen-induced airway eosinophilia in mild asthmatic subjects [30], and to do so in a dose-dependent way [31] (Fig. 2). It has not yet been evaluated in patients with severe refractory asthma with a persisting airway eosinophilia.

In patients with severe refractory asthma, but without an airway eosinophilia, an increased number of airway neutrophils can sometimes be demonstrated [9]. IL-8 is a chemokine which may be important in the chemotaxis of neutrophils into the airways and this effect is mediated by the chemokine receptor CXCR2. An antagonist of CXCR2 has been developed, which has been demonstrated to prevent ozone-induced airway neutrophilia in normal subjects [32], and which has shown promise in early studies in patients with severe refractory asthma, who have an airway neutrophilia [33].

Allergic asthma requires the presence of T-helper-2 (Th-2) lymphocytes in the airways, which produce a variety of cytokines needed for the initiation and persistence of allergic inflammation, and also possibly airway remodelling, which characterizes asthma [34]. These cytokines include IL-3, IL-4, IL-5, IL-9 and IL-13. Nagata *et al.* [35] initially described that Th-2 cells possess a receptor on the cell surface, which is activated by prostaglandin D₂ (PGD₂). This receptor has been called chemoattractant receptor-homologous molecule expressed on Th-2 cells (CRTh2). This is a G-protein cou-

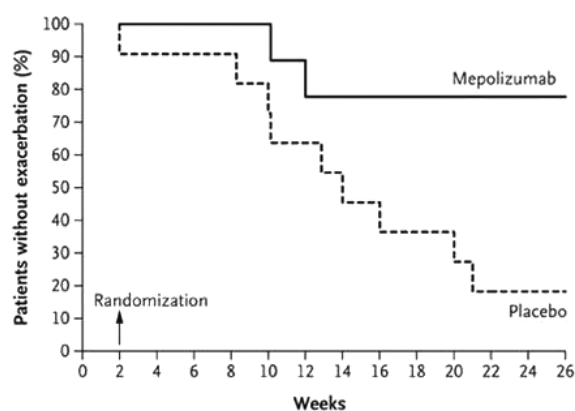


Fig. 1. Kaplan-Meier analysis of the proportion of patients with severe refractory asthma and an airway eosinophilia, without an asthma exacerbation during treatment with mepolizumab or placebo and during oral corticosteroid reduction (reproduced with permission from reference [25]).

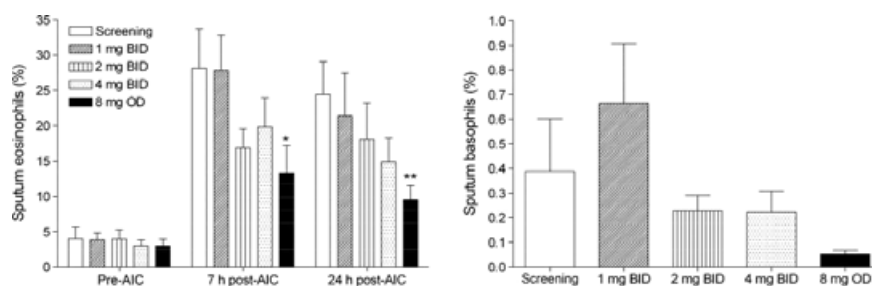


Fig. 2. Pre- and post-allergen challenge sputum % eosinophils and % basophils, in response to increasing doses of pre-treatment with the anti-sense,TPI ASM8 before allergen inhalation challenge. Data are shown as mean $\pm$ SEM with statistical difference between levels at screening (placebo) and indicated doses denoted by * $P < 0.05$, ** $P < 0.01$ (reproduced with permission from reference [29]).

pled receptor, and as such is amenable to antagonism by a small molecular weight antagonist. Subsequently, these same investigators identified CRTh2 on other cells important in asthma, particularly eosinophils and basophils [36]. Activation of this receptor induces eosinophilic airway inflammation [37] in mouse models.

Several different CRTh2 antagonists are now available and are being studied in asthmatic subjects. These studies have demonstrated, to date, that treatment with a CRTh2 antagonist in patients with persisting asthma, but who were not using regular treatment, improved FEV₁, asthma related quality of life, night-time symptom scores and sputum eosinophil counts (although this effect was not statistically significant) [38]. There are no results available, as yet, in patients with severe refractory asthma.

Targeting specific airway effector mediators

It has been argued that it is impractical to target a single mediator that might be involved in the development or persistence of asthmatic inflammation and expect to find a significant clinical benefit. However, cysteinyl leukotriene receptor antagonists have provided a clinical benefit in some asthmatic patients [39] and are widely used. Patients with severe refractory asthma do not present as a single, easily identifiable phenotype, but rather as a number of different phenotypes, or endotypes (phenotypes with a distinct pathobiological origin of their refractory asthma) [40]. This makes it likely that different mechanisms are important in the development and persistence of airway inflammation and/or airway remodelling in these endotypes, and that targeting specific effector mediators, which may be important in one endotype, may not be effective in another.

This has been demonstrated in studies of asthmatic patients, which have evaluated the efficacy of antibodies which prevent the binding of IL-13 to the IL-4/IL-13 receptor complex. These two receptors share a common α -chain (IL-4R α), which can bind either IL-4 or IL-13. These mediators have been demonstrated to be necessary for IgE production, mucous gland hyperplasia,

eosinophilic airway inflammation and airway hyperresponsiveness. Much of this work has been done in mouse models of allergic asthma [41]. Several approaches have been used to block the activation of these receptors. One approach has been to develop an IL-4 variant, a 'mutene' molecule, which inhibits binding of IL-4 and IL-13 to IL-4R α . This molecule has been shown to attenuate allergen-induced late asthmatic responses in mild asthmatic subjects [42]. In addition, hMabs have been developed which also prevent binding of IL-4 or IL-13 to their receptors. One study, in allergic asthmatic subjects, has shown that a hMab which prevents binding of IL-13 to IL-4R α , but not a hMab which prevents binding of IL-13 to IL-13R α 1 (the remaining component of the IL-13 receptor) or IL-13R α 2 (which may be a natural antagonist of IL-13), also attenuates allergen-induced early and late asthmatic responses, but not allergen-induced eosinophilic airway inflammation nor airway hyperresponsiveness [43].

Studies in patients with persisting asthma have yielded interesting results. In one study, treatment with a hMab, which prevents binding of IL-4 and IL-13 to IL-4R α , did not demonstrate significant benefit in improving lung function or asthma control, but did show a trend in reducing asthma exacerbations [44]. Interestingly, some benefit was seen in patients with the most poorly controlled asthma. Another study, in patients with severe refractory asthma, has reported that an antibody which binds to IL-13 and prevents its attachment to the IL-4/IL-13 receptor complex did not significantly improve FEV₁ values in the patient population as a whole, but did provide a significant and clinically useful improvement in patients with high blood periostin levels [45]. Periostin is a protein which was described as a component of subepithelial fibrosis and whose release from epithelial cells is stimulated by IL-13 [46] and which has been identified as being epithelial cell gene up-regulated in asthma [47]. This is the first evidence of an IL-13 dependent endotype in severe refractory asthma.

Other treatment approaches which have targeted specific effector mediators with success, include anti-IL-5

treatment in selected patients with persisting airway eosinophilia (described above), and antibodies which block binding of IgE to its receptor (FcεR1)(omalizumab), which have been shown to reduce severe asthma exacerbations in severe refractory asthmatics, with an elevated serum IgE [48].

Conclusions

Patients with severe refractory asthma have, by definition, not achieved asthma control, even with high doses of ICS, usually in combination with LABAs and another maintenance treatment, such as a leukotriene receptor antagonist, or omalizumab, and who often require oral corticosteroids as a maintenance treatment or to treat exacerbations. Although these patients represent somewhere between 5% and 10% of all asthmatics, they have the greatest unmet treatment needs, and are the group who most require novel treatment approaches to improve asthma control and reduce exacerbation risk. The most promising approaches currently under investigation are those which reduce airway eosinophils in patients with severe refractory asthma and a persisting airway eosinophilia. Monoclonal antibodies against IL-5 have been shown to improve lung function, improve asthma control, reduce exacerbation risk and allow reduction or elimination of maintenance oral corticosteroids in this subset of patients.

Bronchial thermoplasty may provide benefit in improving control and reducing exacerbations in selected patients, most likely those with very variable airflow obstruction. The addition of the muscarinic antagonist, tiotropium also improves airflow obstruction, but its benefit on exacerbation risk is not yet established. Other developments which are likely to be evaluated in severe refractory asthma are CXCR2 antagonists in patients with a persisting neutrophilic airway inflammation, and CRTh2 antagonists, both of which are small molecule antagonists, and hMabs against IL4 and IL-13. Finally, other approaches to reduce receptor numbers, using inhaled anti-sense has shown to reduce allergen-induced airway eosinophilia, and combining different anti-sense against different targets is a feasible option.

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