Severe asthma
Current and future treatments

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SUMMARY. Most forms of asthma can be controlled by inhaled corticosteroids (ICS), but a substantial number of patients still experience symptoms and limitations in their personal and social life despite being on appropriate maintenance therapy. These patients with severe asthma account for almost half of the cost of the disease and most of its morbidity and mortality. To date, the use of ICS and long acting bronchodilators (LABAs) is the basis of severe asthma treatment, but the optimal use and dosage of these drugs should be determined based on the available evidence. Anti-immunoglobulin E (anti-IgE) has been recently established for the treatment of patients with severe allergic asthma whose symptoms are inadequately controlled with ICS/LABA. The use of long-acting anticholinergics (LAMA) as add-on therapy is currently under investigation in clinical trials. Alternative forms of treatment, such as macrolide therapy, have produced conflicting results, while an approach based on anti-tumour necrosis factor-α (anti-TNFα) has proven ineffective. The targeted inhibition of interleukin (IL) 2, IL 4, IL 5, IL-9 and IL 13 is currently being investigated. A non-drug treatment, bronchial thermoplasty (BT), has been reported to provide some benefits to patients with severe asthma, but the long-term benefit/risk ratio for BT is unknown at present. In view of the heterogeneity of severe asthma, the present challenge is to determine the appropriate phenotype for current and innovative forms of treatment. *Pneumon 2011, 24(4):405-413.*

INTRODUCTION

Over the past years, extensive research into the mechanisms and treatment of asthma has led to a better understanding of the disease and to a more comprehensive approach to its therapy. Clinical studies show that most patients with asthma can achieve control and lead normal lives with the use of the currently available medications[1-3]. On the other hand, surveys show that, in real life, a substantial number of patients still experience symptoms and limitations in their personal and social activities[4,5]. This is a

matter of concern for both the medical community and health authorities, as control of asthma can and should be achieved in the majority of patients[6]. It is also apparent that some patients with asthma have a more severe form of the disease than others, comprising a small but clinically important group with a substantial financial, societal and personal burden of disease. Patients withsevere asthma may experience frequent or debilitating symptoms and limitation of their activities; they have frequent exacerbations and hospitalizations and they account for over half of the cost of the disease and most of its mortality[7,8].

Many definitions and terms regarding severe asthma have been used in the literature; "refractory asthma", "difficult-to-treat asthma", "therapy resistant asthma", "steroid-dependent asthma", "brittle asthma", etc., are some of the terms used to label this condition. In 1999, the European Respiratory Society (ERS) Taskforce on severe asthma agreed on the term "difficult to treat asthma" to include all such cases of asthma[9]. Difficult/therapy resistant asthma was defined by this taskforce as "asthma, which is poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airway obstruction and a continued requirement for short-acting β-2-agonists despite delivery of a reasonable dose of inhaled corticosteroids". One year later, the American Thoracic Society (ATS) Workshop reached a consensus on the term "refractory asthma"[10], to describe this subgroup of asthmatic patients with troublesome disease. In the current global initiative for asthma (GINA) guidelines[11], the diagnosis of "severe asthma" in patients who are receiving regular asthma medication is based on both the clinical features present and the step of the daily medication regimen that the patient is currently on. According to this definition, both those patients who need oral corticosteroids to remain under control and those with ongoing asthma symptoms despite appropriate maintenance therapy for moderate asthma [i.e., high dose inhaled corticosteroids (ICS) combined with long-acting β-2-agonists] should be regarded as having severe asthma. The ERS, ATS and GINA definitions fit in with the updated World Health Organisation (WHO) workshop report on uniform definition of asthma severity, control, and exacerbations[12]. In this report, severe asthma is defined by the level of current clinical control and risks as "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity".

Although these definitions include the response to treatment, it must be taken into account that response to treatment may be slow or that a patient may appear to respond but then relapse quickly and present with new exacerbations. The term, "severe asthma" should therefore apply to patients whose asthma remains difficult to control despite extensive re-evaluation of the diagnosis and avoidance or treatment of exacerbating factors, and following a period of at least 6 months of close monitoring and tailored and rigorous management by an asthma specialist[13]. Because severe asthma is a chronic, debilitating disease and may prove fatal, it is essential to understand the associated factors and mechanisms and to treat it effectively[14]. This update presents information from recent relevant publications regarding current management options and forms of treatment under investigation for this phenotype of asthma.

THE MANAGEMENT OF SEVERE ASTHMA

The pharmacological approach to the treatment of severe asthma is similar to that used for the treatment of patients with milder phenotypes of the disease. The vast majority of patients with difficult asthma meet the criteria of the GINA[11] or National Asthma Education and Prevention Program guidelines[15] for step 5 or 6 treatment approach and require high dose ICS and inhaled long-acting β2-agonists (LABAs), along with additional medication, such as oral steroids, leukotriene-antagonists and theophylline or anti-immunoglobulin E (anti-IgE) for patients with allergic asthma. To date, ICS and LABAs constitute the basis of severe asthma treatment, but research into the use of newer compounds has already produced some promising results. Before taking the decision to increase asthma medication and/or to introduce newly available but expensive add-on treatment, the treating physicians should first confirm the diagnosis of asthma, review the patient's compliance with medications and inhaler technique, investigate possible exposure to triggers at home or work and diagnose and treat co-morbid conditions[13].

Many patients characterized as having severe/refractory asthma have in reality other conditions which may have symptoms similar to those of asthma. Chronic obstructive pulmonary disease (COPD) is often misdiagnosed as asthma, especially in older smokers[16]. Other possible diagnoses include vocal cord dysfunction, bronchiolitis obliterans (BO), bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA), Churg-Strauss syndrome and benign or malignant tumours of the airways[17]. In a recent Canadian study about one-third of individuals with physician-

diagnosed asthma were found not to have asthma when objectively assessed[18]. Another issue is compliance with the treatment, especially inhaled and oral corticosteroids. In a UK study examining the prevalence of non-adherence to corticosteroid medication in difficult asthma, 88% of severe asthmatics admitted poor adherence to inhaled therapy, while 45% of those prescribed oral steroids were not taking the medication[19]. Similar results have been reported all over the world[20-22], emphasizing the need for objective and direct measures of adherence as part of the assessment and management of severe asthma. Finally, severe asthma is frequently complicated by significant co-morbidities, such as depression, osteoporosis, diabetes mellitus (DM), hormonal dysfunction and obesity, which further debilitate patients and which should be addressed in parallel to the asthma treatment. When evaluating a patient with severe asthma, therefore, it is important to look for possible aggravating factors or co-morbidities and to try to eliminate or manage these conditions, in order to improve asthma control[23].

CURRENT TREATMENTS IN SEVERE ASTHMA (Table 1)

Inhaled corticosteroids (ICS)

ICS are extremely potent anti-inflammatory medications and are the most efficacious therapy currently available for optimal asthma management. They address most of the causes of airflow obstruction in asthma, including mucosal oedema, airway inflammation, increased mucus secretion, and airway remodelling[24]. High-dose ICS (≥1,200 μg/day of beclomethasone, or equivalent) constitute the basis of treatment of severe/refractory asthma, but additional controller medications are almost always needed and their use is recommended in the guidelines[11,15]. These regimes, however, are not always successful in patients with severe asthma and there are still many "grey" areas regarding steroid-responsiveness and safety issues.

TABLE 1. Documentation of current forms of treatment for severe asthma

TREATMENT	REFERENCES
Inhaled corticosteroids (ICS)	24, 25, 26, 27, 28, 30, 35, 36
Long-acting β2-agonists (LABA)	37, 39, 40, 41, 42, 43, 44, 45
Combination therapy (ICS+LABA)	1, 2, 46, 47, 48, 49, 50
Anti-Leukotrienes (LTRAs)	51, 52, 53, 54, 55, 56
Theophylline	53, 57, 58
Anti-IgE monoclonal antibody (Omalizumab)	61, 62, 63, 64, 65, 66, 67, 68, 69, 70
Macrolides	74, 75, 76, 77, 78, 79
Long-acting anticholinergics	80, 82, 83, 84, 88, 89
Immunosuppressives	90, 91, 92, 93

The optimal starting and maintenance doses of ICS for severe asthma are not clearly documented. Studies and reviews in this field demonstrate a relatively flat efficacy curve for ICS and increasing side effects with higher doses[25,26]. High doses are frequently prescribed, however, and significant side effects of high dose ICS use are reported. These issues demonstrate the need to establish the optimal/highest dose of ICS for severe asthma, and the need for titration. In a study published by Reddel et al[27], a starting dose of 3,200 μg/day of budesonide in uncontrolled asthma lead to improvement in airway hyperreactivity (AHR) than a starting dose of 1,600 μg, but patients remained equally well controlled when tapered to the lower dose (~1,600 μg). The small benefits of commencing with a high ICS dose do not warrant its routine use when compared to moderate or low dose ICS. In a study by the Leicester group, two distinct phenotypic groups were indentified in severe/refractory asthma, characterized by marked discordance between symptom expression and eosinophilic airway inflammation, namely the early-onset, symptom predominant and the late-onset, inflammation predominant variants[28]. Managing these discordant subgroups guided by inflammatory markers in addition to clinical measurements leads to a reduction in exacerbation frequency in the inflammation-predominant cluster and a significant dose reduction of ICS in the symptom-predominant cluster, without compromising asthma control. These results suggest the importance of sub-phenotypes in severe asthma and also indicate the need for current and new biomarkers to predict response to corticosteroid therapy in these patients[29,31].

Another issue with ICS therapy in severe asthma is its effect on the small airways. More severe asthma is associated with greater peripheral inflammation, as identified in peripheral lung tissue specimens taken transbronchially[32,33] and increased airway closure in washout studies[34]. These findings point to the important role of small airways disease in severe asthma and provide indications for anti-inflammatory treatment of the peripheral airway compartment. Small-particle aerosols, such as hydrofluoroalkane-134a (HFA) beclomethasone and ciclesonide, which have particle size of around 1 μm,

have recently become available. These formulations have been shown to have a greater and more peripheral lung deposition[35]. Ciclesonide, a newer ICS compound, has also shown promise in severe asthma; ciclesonide significantly reduced the need for oral corticosteroids in patients with corticosteroid dependent asthma, while maintaining asthma control[36]. Further studies focusing on severe asthma are needed to confirm these findings, to determine which patients can benefit most from this therapeutic option and to prove long-term efficacy.

Long-acting β2-agonists (LABA)

When adequate levels of asthma control cannot be achieved with medium doses of ICS, all the available guidelines recommend the addition of a LABA in patients with moderate to severe asthma[11,15]. Studies performed since the early 1990s have shown that although ICS are the best anti-inflammatory medications, combination treatment with ICS and a LABA resulted in better symptom control and fewer exacerbations compared to doubling the ICS dosage. The major benefit of LABAs in the treatment of asthma derives from their bronchodilator activity, with an additive contribution from their anti-inflammatory action[37].

In the past few years the issue of the safety of the long term use of LABAs in asthma has emerged[38]. This mainly arose from the findings of the Salmeterol Multicenter Asthma Research Trial (SMART) study, in which life-threatening exacerbations and death occurred in some patients using LABA monotherapy[39]. Recent meta-analyses, however, have clearly shown no such increased risk when LABAs are combined with ICS[40,41]. These two classes of medication can be used in a single inhaler to minimize the risk of LABA monotherapy[42].

A new class of LABAs with long half-lives, also called ultra long-acting β2-agonists (ultra-LABAs), are currently under development with the purpose of achieving once-daily dosage. One of these, indacaterol, has already been adopted in current clinical practice in the management of COPD, but to date only few clinical studies have been published of its use in asthma, for up to 28 days' duration[43-45]. Although these studies have confirmed the suitability of indacaterol for once daily dosage, along with a favourable overall safety and tolerability profile, indacaterol has not yet been approved for asthma management, and clinical studies of its use in severe asthma are still pending.

Combination therapy (ICS+LABA)

It is now well recognized from both *in vitro* and *in vivo* studies that administration of ICS in combination with LABA produces additive or even synergistic anti-inflammatory effects, providing a strong rationale for the use of LABA/ICS combination therapy in asthma, and especially in the severe phenotype of the disease[46]. ICS/LABA therapy improves lung function, asthma control days and asthma-related quality of life, and reduces the risk of hospitalization and emergency room visits[1,2]. Combinations of ICS and LABA (containing budesonide and formoterol) have been used lately, not only as maintenance therapy but also as rescue/relief treatment (single inhaler strategy)[47]. Numerous clinical trials performed in both adults and children have shown clinical benefits with this strategy, mainly in the reduction of exacerbations[48]. The long-term consequences of single inhaler therapy in severe asthma have not yet been studied, however, and its prolonged use has been associated with significant increases in sputum and biopsy eosinophilia[49]. This approach may be less suitable for patients with severe asthma who are poor perceivers of symptoms or who require very high daily doses of ICS.

On the other hand, it appears that not all patients with severe asthma necessarily need high dose ICS/LABA therapy. A recent study aiming to assess the response of high-dose salmeterol/fluticasone combination in a large cohort of patients with severe or difficult-to-treat asthma concluded that some achieve a better outcome while receiving a low-dose ICS/LABA combination[50]. This study showed a limited value of high-dose ICS/LABA combination compared with the alternatives in this particular group of patients with severe asthma. The problem is that the vast majority of patients with severe asthma remain symptomatic despite the use of combined LABA and ICS therapy. In these patients the addition of at least a leukotriene antagonist, slow-release theophylline or even oral corticosteroids and anti-IgE is advocated[11,15].

Anti-Leukotrienes (LTRAs)

LTRAs are currently included in the guidelines as add-on therapy for the treatment of severe asthma[11,15]. As the biosynthesis of leukotrienes is corticosteroid independent and increased urinary leukotriene levels are observed in severe asthma, it is thought that anti-leukotrienes would be beneficial in these patients[51]. Although guideline recommended, currently used leukotriene modifiers have been proven efficacious in improving pulmonary function, reducing symptoms, decreasing night-time wakenings and rescue medication needs, mainly in the mild-moderate phenotype of the disease[52], there is no definite evidence of benefit in patients with severe asthma: studies have

shown either improvement in only a small subgroup of such patients or no improvement at all[53-55]. The addition of a leukotriene modifier to corticosteroid therapy for aspirin intolerant asthma may lead to clinical benefit and is recommended for this population[56]. Prospective controlled studies using anti-leukotrienes as add-on therapy in severe asthma need to be performed.

Theophylline

Theophylline is recommended as add-on treatment to ICS, although studies show that LABAs are more effective in reducing symptoms and improving lung function[57]. Its benefit in severe asthma is unclear, but a recent study has demonstrated that it provides further bronchodilatory action when added to a medium dose of ICS/LABA combination in symptomatic patients[58]. There is also documentation to suggest that inhaled salmeterol and oral slow-release theophylline exert additive bronchodilating effects in patients with moderate to severe airflow limitation[59]. On the other hand, a clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma failed to improve asthma control, despite improved lung function[53]. Studies on the use of xanthines in combination with high doses of ICS and LABA are clearly lacking, and the theory that theophylline may "unlock" the resistance to corticosteroids in severe asthma[60] remains to be confirmed in targeted clinical trials.

Anti-IgE monoclonal antibody (Omalizumab)

IgE plays a central role in the pathogenesis of allergic asthma. Antigen specific IgE is produced by B cells that have undergone isotype switching from IgM to IgE production under the influence of interleukin (IL) 4 and IL 13. The circulating IgE binds to high affinity receptors expressed by mast cells and circulating basophils, initiating asthmatic inflammatory reactions. Omalizumab is a murine anti-human IgG monoclonal antibody directed against an epitope on the fragment of IgE (Cε3) which binds to the alpha chain of the high affinityIgE receptor, thus preventing the binding of IgE with this receptor[61].

Omalizumab, has been recently approved for the treatment of patients with moderate to severe asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS/LABA therapy[11,15]. In general, the administration of omalizumab has been shown to be safe and its potential effectiveness in patients with severe asthma has been documented[62,63]. A recent review of data from more than 7,500 patients reported an incidence of anaphylaxis of 0.14% in omalizumab-treated patients, but no evidence of increased risk of malignant neoplasia or thrombocytopenia[64]. Multiple studies in severe asthma have reported that the addition of omalizumab is associated with the reduction of exacerbations and hospitalizations, improvement of asthma-related quality of life (QoL), amelioration of asthma symptoms and lung function and reduction in steroid usage[65-68]. Omalizumab thus appears to be an effective therapy for some patients with severe asthma, but probably more than half of them are nonatopic and hence the use of omalizumab for this group may be a limited option. Another issue is the optimal duration of treatment with omalizumab, which is still unspecified. Studies showed that discontinuation of omalizumab may lead to recurrence of symptoms in severe asthma[69], while some patients were able to stop treatment after 5 or 6 years and maintain disease stability[70].

Macrolides

The potential contribution of chronic infections to the severity of asthma is currently under examination. Infection with *Chlamydia pneumoniae* has been associated with a lower forced expiratory volume in one second (FEV_1) for a given duration of asthma[71] and in addition, the composition of bronchial airway microbiota is associated with the degree of AHR among patients with suboptimally controlled asthma[72]. Although antibiotics have no role in the routine management of asthma, certain macrolide antibiotics have been shown to have anti-inflammatory activity[73,74]. In patients with serological evidence of Mycoplasma infection, treatment with macrolides resulted in clinical benefit, with improvement in FEV_1 and reduction in inflammatory cytokine levels and AHR[75,76]. In severe refractory asthma, an 8 week course of clarithromycin significantly reduced airway IL-8 levels and numbers of neutrophils and improved the QoL[77]. In a case report of prolonged treatment with clarithromycin in three elderly patients with prednisone-dependent asthma, two of the three patients were able to discontinue corticosteroid therapy after one year of clarithromycin treatment[74]. On the other hand, in a recent study by the Asthma Clinical Research Network (ACRN), clarithromycin treatment in adults with mild-to-moderate asthma did not improve asthma control, even though there was improvement in AHR[79]. Although initial data on the use of clarithromycin in severe asthma provide promising results, additional well-conducted studies are needed to evaluate their true value and to determine which patients can benefit most from this therapy.

Long-acting anticholinergics

Inhaled anticholinergics, which antagonize muscarinic receptors in the airways, are very effective in patients with COPD. In asthma, anticholinergics are considerably less effective than ß2-agonists but they are sometimes used as add-on treatment in asthma exacerbations[80]. A Cochrane review concluded that there is no evidence to support the use of anticholinergics as part of the add-on treatment for patients whose asthma is not well controlled by standard medication regimes[81]. However, this review was based on data from the use of ipratropium in chronic asthma and the newer long acting anticholinergic, tiotropium, was not evaluated.

More recently, a preliminary Japanese study on a small number of patients with severe asthma indicated a rationale for using tiotropium bromide to treat severe asthma with a non-eosinophilic sputum profile[82]. In a study from Korea, Park et al. found that 30% of patients with severe asthma who had reduced lung function responded to adjuvant tiotropium, and that the presence of Arg16Gly polymorphism in the b2-adrenoreceptor was associated with this good response[83]. Lastly, 6 months ago a double-blind trial involving 210 patients with uncontrolled asthma, comparing tiotropium with salmeterol and a double dose of ICS, was published[84]. In this study, tiotropium treatment was associated with improved symptoms and lung function in patients with inadequately controlled asthma and the improvement was equivalent to the addition of salmeterol. These findings generated considerable discussion and criticism, with comments not only in the *New England Journal of Medicine*[85,86] but also in other journals[87]. Looking at upcoming trials, there are 2 randomized, double-blind, placebo-controlled studies in the database of ClinicalTrials.gov (http://clinicaltrials.gov), evaluating the long term efficacy and safety of tiotropium as add-on treatment in patients with severe persistent asthma (*Study I - NCT00772538 and Study 2 - NCT00776984*)[88,89]. Patient recruitment has been completed (approximately 900 patients) and the final data collection date for the primary outcome measures is estimated for July 2011. These studies are expected to provide valuable information regarding the value of tiotropium as an add-on therapy in severe asthma.

IMMUNOSUPPRESSIVES

To minimize the long-term systemic side effects of corticosteroids, alternative corticosteroid "sparing" drugs have been used in controlled and uncontrolled studies, including cyclosporine, methotrexate and gold salts[90-92]. In general, these medications have been offered to patients with very severe disease, but the results are unsatisfactory and side-effects are notable, so steroids remain the cornerstone of severe asthma treatment[93].

FUTURE FORMS OF TREATMENT FOR SEVERE ASTHMA (Table 2)

Anti-tumour necrosis factor-α (anti-TNFα) monoclonal antibody

Tumour necrosis factor-α (TNFα) is a major therapeutic target in a variety of chronic inflammatory disorders characterized by the Th1 immune response, in which neutrophils are involved. Although asthma is predominantly considered an eosinophilic disorder involving Th2 cytokines, as the disease becomes more severe and chronic, it develops Th1-type characteristics, with greater involvement of neutrophils[94]. TNF-α has been implicated in many aspects of the airway pathology in asthma and emerging evidence suggests that it plays an important role in severe refractory disease[95]. As increased TNF-αlevels appear to be a feature of more persistent and corticosteroid-refractory asthma, anti-TNF-α monoclonal antibody therapy has been evaluated in this phenotype group.

Preliminary studies demonstrated an improvement in the QoL, lung function and AHR and a reduction in exacerbation frequency in patients with severe asthma treated with anti-TNF-α therapy[96-98]. The results of two more recent studies, however, have dampened the ini-

TABLE 2. Documentation of future forms of treatment for severe asthma

TREATMENT	REFERENCES
Anti-TNF-α monoclonal antibody	96, 97, 98, 99, 100
Anti-CD25 (Daclizumab)	101, 102
Anti-IL-4	103
Anti-IL-5 monoclonal antibody (Mepolizumab)	106, 107, 108, 109, 110, 111
Anti-IL 9	113, 114, 115
Anti-IL 13	117, 118, 119, 120, 121
Phosphodiesterase (PDE) Inhibitors	122, 123, 124, 125, 126
Bronchial thermoplasty	127, 128, 129, 130, 131

TNF = Tumour necrosis factor, IL = Interleukin

tial enthusiasm for the efficacy of anti-TNF-α therapy. In the largest clinical trial using an anti-TNF monoclonal antibody (golimumab) in severe persistent asthma (309 patients), an unfavourable risk-benefit profile led to early discontinuation of the study at 24 weeks, with no definite clinical efficacy detected at that time point[99]. The serious adverse events reported in this study included sepsis, tuberculosis (TB) reactivation, an increased rate of malignancy and one death. The second trial published a few months ago was a 12-week, phase 2 trial in 132 subjects with moderate-to-severe persistent asthma. Although no unexpected adverse side effects were observed during this study, no clinical efficacy of anti-TNF monoclonal antibody (etarcenept) was documented in this study population[100]. Studies in specific phenotypes could provide a clearer answer as to whether there really is a role for anti-TNF therapy in patients with asthma, but anti-TNF-α agents are not currently in use for the treatment of severe asthma.

Anti-CD25 (Daclizumab)

Airways inflammation in asthma is triggered and maintained by CD4+ (Th2) cells which are activated by IL-2. Daclizumab is a humanized IgG1 monoclonal antibody against the IL-2R alpha chain (CD25) of activated lymphocytes, which decreases T-cell proliferation and cytokine production and decreases IL-2 binding to its receptor[101]. Only one clinical study has been published that evaluated the efficacy and safety of daclizumab in 115 patients withmoderate to severe asthma[102]. Daclizumab treatment improved pulmonary function and asthma control and prolonged time to exacerbation in this population, with a good safety profile, although some serious adverse events were reported (including an anaphylactoid reaction and viral meningitis) in the active drug group. This study demonstrates that daclizumab may have a role as an add-on therapy in severe asthma but further studies are needed.

Anti-Interleukin 4

IL-4 mediates important pro-inflammatory functions, and studies in mouse models of asthma have shown that IL-4 blockade greatly suppresses the allergic inflammatory response[103]. Altrakincept is a human recombinant soluble IL-4 receptor (IL-4R) acting as an IL-4 antagonist. In early studies in patients with mild-moderate asthma, nebulized administration of altrakincept prevented the decline in the FEV_1 and symptom increase that was seen in the placebo group after ICS therapy withdrawal[104], but the efficacy of this drug was not reproduced in a larger trial or in patients with severe asthma.

Anti-IL-5 monoclonal antibody (Mepolizumab)

IL-5 is a Th2 cytokine that plays a pivotal role in the recruitment, activation and survival of eosinophils in allergic asthma[105]. In theory, IL-5 blockade with anti-IL-5 monoclonal antibodies would be expected to deplete the eosinophils and improve symptoms in subjects with asthma. Indeed, in preliminary studies, anti-IL-5 significantly reduced the numbers of eosinophils in the sputum and peripheral blood, but no changes were observed in lung function or AHR[106]. In addition, in early clinical trials, mepolizumab treatment did not appear to add significant clinical benefit according to many parameters of asthma control, including changes in lung function, QoL and reduction in symptoms[106-108].

Two recent trials focusing on asthmatic patients with persistent airway eosinophilia showed that mepolizumab treatment reduces exacerbations and improves asthma control without any serious adverse events[109,110]. These results indicate that this specific asthma phenotype (i.e., refractory eosinophilic asthma) is likely to be the main beneficiary of anti-IL-5 treatment. The database of ClinicalTrials.gov (http://clinicaltrials.gov) includes one ongoing randomized, double-blind, placebo-controlled trial (*Study NCT01000506*)[111], which aims to provide further evidence in this field. Patient recruitment is complete (approximately 600 patients) and the first results are expected next year.

Anti-Interleukin 9

IL-9 is a cytokine produced by CD4+ T-helper cells that acts as a regulator of mast cells in the airways[112]. *In vitro* and *in vivo* studies have shown that IL-9 is an important inflammatory mediator in asthma and contributes to the development of airway inflammation, mucus production and AHR[113]. Blocking IL-9 reduces the numbers of eosinophils and prevents airway hyperreactivity in a mouse model of asthma[114]. In a recently published, phase II study of MEDI-528, a humanized anti-IL-9 monoclonal antibody showed an acceptable safety profile and findings suggestive of clinical activity in subjects with mild to moderate asthma[115]. Studies of its use in severe asthma are lacking.

Anti-Interleukin 13

IL-13 is produced by a variety of cell types including Th1

and $CD4^+$ Th2 activated cells. IL-13 shares many functional properties with IL-4, as both cytokines have the ability to bind to a common receptor sub-unit, IL-4R[116]. The available data suggest that through combined actions on epithelial cells and smooth muscle cells, IL-13 can induce a variety of the pathological features of asthma[116]. In a mouse model of asthma, anti-IL-13 monoclonal antibody inhibits AHR, eosinophil infiltration and airway remodeling[117]. The first study of two humanized anti-IL 13 antibodies, IMA-638 and IMA-026, on allergen-induced airway responses in mild asthma has recently been published[118]. IMA-026 appeared to reduce the late-phase asthmatic response, but the reduction did not reach statistical significance. Furthermore, pitakinra, an inhaled formulation that inhibits the effects of both IL-4 and IL-13 by binding to IL-4R, has been shown in a Phase IIa trial to decrease levels of exhaled NO and to improve lung function in patients with asthma[119]. On the other hand, other studies in which patients with uncontrolled asthma were treated with anti-IL 13 IMA-638[120] or AMG 317, another IL-4R antagonist, no clinical efficacy was demonstrated[121]. Further studies are required to determine whether anti IL-13 targeting therapy will be beneficial in chronic severe asthma.

Phosphodiesterase (PDE) Inhibitors

Increased PDE4 function, due to an increase in either protein expression or activity, provides a plausible mechanism to account for the pathogenesis of asthma. Preclinical studies of allergic inflammation in animal models have documented the ability of PDE4 inhibitors to inhibit two of the characteristic features of asthma, the recruitment of eosinophils to the airways and AHR[122]. Roflumilast, an oral, PDE 4 inhibitor administered once daily, has been shown to improve pulmonary function and asthma symptoms and reduce rescue medication use in patients with mild-to-moderate asthma[123,124]. Dose limiting side effects of nausea, diarrhoea and headache have, however, tempered the enthusiasm for this drug class in the treatment of asthma and other respiratory diseases. A strategy to overcome the side effects of oral PDE4 inhibitors has been to deliver the drugs by inhalation, and preclinical and clinical investigation of inhaled PDE4 inhibitors is ongoing[125,126]. The potential role of this class of medication in more severe asthma awaits further investigation.

Bronchial thermoplasty

Bronchial thermoplasty (BT), a bronchoscopic procedure to reduce the mass of airway smooth muscle and attenuate bronchoconstriction, has been tested in humans for the treatment of asthma. Four clinical trials using BT have been published in the past 5 years[127-130]. The largest and most recent trial (AIR2) enrolled 288 adult subjects with severe asthma who had remained symptomatic despite treatment with high-dose ICS and LABA, and randomized them to BT or a sham procedure in a 2: 1 ratio[128]. BT significantly improved asthma-specific QoL, with a reduction in severe exacerbations and healthcare use in the post-treatment period. A higher rate of side effects was observed in the immediate post treatment period (6 weeks after the last treatment) including cough, asthma exacerbations and mucous plugging of the airways, but these effects were generally well tolerated. Data on the long-term safety of bronchial thermoplasty were published few months ago[131]; patients enrolled in the AIR trial participated in long-term follow-up, which showed absence of clinical complications and maintenance of stable lung function (assessed by FVC and FEV_1) over a 5-year period post-BT. BT has recently been approved by the US Food and Drug Administration (FDA) for patients aged over 18 years with severe persistent asthma uncontrolled by ICS and LABA.

BT is, however quite a complex procedure and its duration for a single lobe is often considerably longer than that of a routine bronchoscopy. For this reason BT should be considered a complex interventional bronchoscopy and must be performed by experienced bronchoscopists and in an asthma centre to ensure that it is performed safely. BT is expected to be used in addition to currently available medications in order to provide longer lasting improvements in overall asthma control in patients with severe asthma.

CONCLUSIONS

Despite intensive multi-drug treatment with high dose inhaled or oral corticosteroids, LABAs and other controller medications, in patients severe asthma remains uncontrolled and there is urgent need for new, more effective forms of medication. Prospective, randomized, double-blind, placebo-controlled add-on trials focusing on severe asthma should be performed to examine the benefit of individual medications and their combinations. In addition, prospective testing is needed to determine whether those markers that are shown to predict responses in mild-moderate asthma, such as AHR and sputum and tissue

eosinophilia, are relevant in the case of severe asthma. These studies need to be performed in well-characterized patients, with phenotypic and probably, genotypic markers, in order to carefully assess response. Studies should include patient-centred goals (e.g., symptom-control, QoL assessment and prevention of exacerbations) in addition to traditional measures (lung function, AHR and inflammatory markers). For the evaluation of most treatment outcomes, and especially asthma control and exacerbations, the duration of the study should be at least 6 months and preferably longer. The appropriate pharmaceutical treatment is available for the majority of patients with asthma, but something more is urgently needed for the severe phenotype of the disease.

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