EDITORIAL

New treatment approaches for asthma

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Introduction Guidelines for asthma management have identified that achieving asthma control is the primary goal of treatment. Asthma control consists of two domains. These include optimizing current (day-to-day) control, defined as the minimization of both daytime and night-time symptoms, no limitation of activity, minimal rescue bronchodilator use, and no airway narrowing; and minimizing future risk, defined by long-term decline in lung function, severe asthma exacerbations, and unwanted effects from medications (FIGURE 1). The two domains that define asthma control are not independent. The more poorly controlled day-to-day asthma is, the greater the risk of a severe asthma exacerbation.[1]

In the past, physicians were often confused by the terms "asthma control" and "asthma severity". It was perceived that well-controlled asthma was synonymous with mild asthma, and poorly controlled asthma was synonymous with severe asthma. This perception is incorrect.[2] Severity is the intensity of the underlying disease process before treatment, and control is the adequacy of the response to treatment. Patients with severe asthma, if treated appropriately can be well-controlled and patients with mild asthma, if they fail to follow treatment guidelines, will have inadequately controlled asthma, which may be perceived as severe. The goals of asthma management are the same for all degrees of asthma severity. Although patients with severe asthma will often be more difficult to control with an intervention, effective treatment can potentially fully control patients with severe asthma.

Despite the availability of effective and safe medications to treat asthma, the most important of which are inhaled corticosteroids (ICS), either alone or in combination with long-acting inhaled β_2-agonists (LABA), some patients remain poorly controlled.[3] The most important reason for this is poor adherence to treatment regimens.[4] When patients are taking their asthma medications, many can achieve well-controlled asthma[5]; in some instances, however, asthma may be only partly controlled and a decision needs to be made by the patients and their managing health care professional whether to increase the treatment or to accept partly controlled asthma. However, all guidelines indicate that if asthma is uncontrolled, treatment options should be carefully evaluated and additional treatment added.[6]

New treatment approaches There is a subset of asthmatic patients who, despite treatment with optimal doses of asthma medications, have uncontrolled asthma and are at risk for severe asthma exacerbations. These are considered severe refractory asthmatics, and constitute from 5% to 10% of the asthma population.[7] This is the group of patients where phenotyping (determining patient characteristics), with relation to their atopic status and the type of airway inflammation present, may provide additional useful information with regards to treatment options. Indeed, a number of new treatment approaches have been identified for patients with severe refractory asthma, which have targeted therapy against specific inflammatory cell types thought to be important in the persistence of asthma, or in severe asthma exacerbations.

Targeting airway eosinophilia One of these new approaches was developed as a result of the identification of patients with severe refractory asthma, who have persistent airway eosinophilia.[8] Studies have demonstrated that inhibition of airway eosinophilia with a humanized monoclonal antibody against interleukin (IL)-5 (mepolizumab) reduces the risk of severe asthma exacerbations[9,10] and can improve lung function and asthma control.[11] A subsequent larger double-blind, placebo-controlled trial was reported of the effects of treatment with mepolizumab in a population of patients with a history of recurrent severe asthma exacerbations, and evidence of eosinophilic inflammation (FIGURE 2).[12] Patients were treated with 1 of 3 doses of intravenous mepolizumab or placebo over 1 year. The rate of severe asthma exacerbations was significantly reduced by 50% with mepolizumab treatment, with no evidence of increasing benefit with increasing doses of treatment. Taken together, these studies indicate

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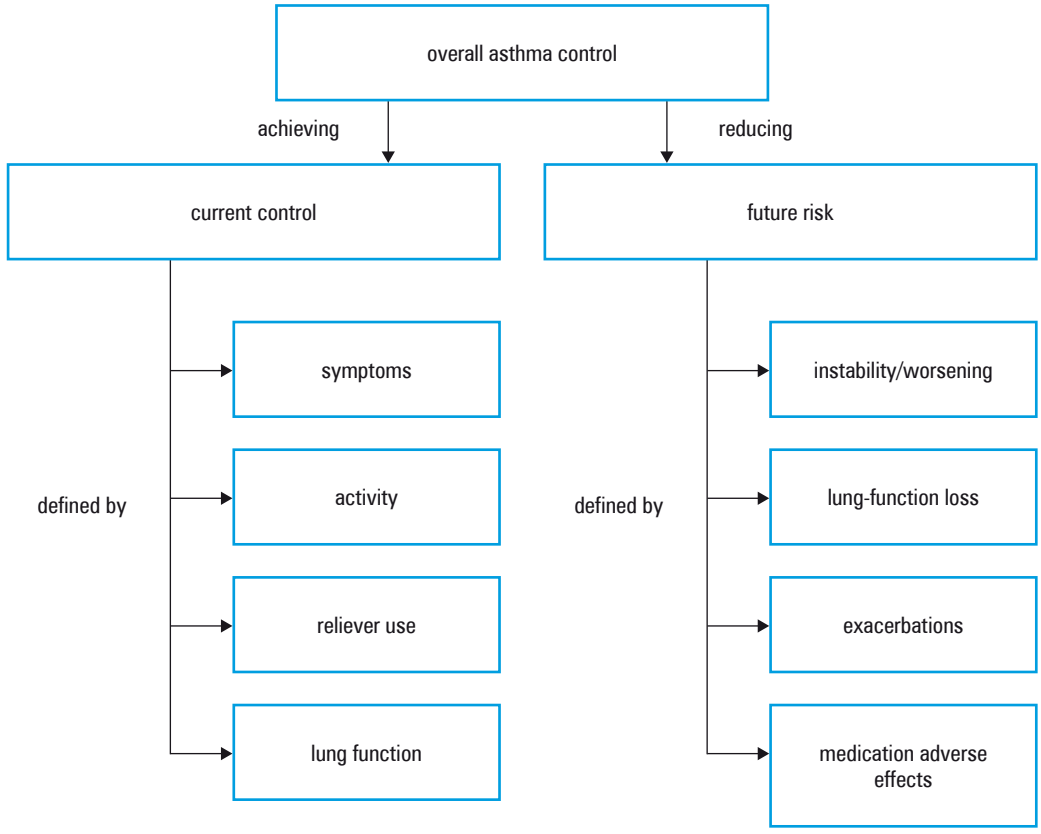
FIGURE 1 Definition of overall asthma control



that targeting IL-5 will provide substantial clinical benefit in patients with severe refractory asthma and persistent airway eosinophilia.

Targeting airway neutrophilia About half of the patients with asthma have a noneosinophilic airway inflammation, which is often neutrophilic.[13] It is unclear, however, whether neutrophils contribute to the lack of asthma control or to exacerbations. Neutrophil migration is, in part, mediated by activation of a chemokine receptor CXCR2, which is a G-protein-coupled receptor, amenable to antagonism by small-molecular-weight antagonists and with a number of agonists, including IL-8 and growth-regulated oncogene α and β. One such antagonist (SCH527123) was studied in a small randomized, 4-week, double-blind study in 32 patients with severe refractory asthma and airway neutrophilia.[14] Treatment with SCH527123 caused a significant reduction in both blood and sputum neutrophils, with significantly fewer mild exacerbations and a trend towards improvement in the asthma control questionnaire score. This study suggests that airway neutrophils may play a role in the persistence of severe refractory asthma in some patients, but larger studies of longer duration are needed to evaluate the effect on other outcomes of asthma, including severe exacerbations.

Targeting T-helper type 2 cells CRTH2 is another G-protein-coupled receptor that has been implicated in asthma, via the activation of T-helper 2 lymphocytes, eosinophils, and basophils by prostaglandin D_2.[15] A double-blind, placebo-controlled study has evaluated the potential benefit of a selective CRTh2 antagonist in asthma.[16] In contrast to the above studies, patients enrolled into this trial were not using regular ICS to manage their asthma. Treatment with the antagonist significantly improved the forced expiratory volume in 1 second (FEV_1) – by 9.2% compared with 1.8% with placebo (but only in the per-protocol population). There were also significant improvements in the quality of life scores and night-time symptoms. The magnitude of clinical benefit is, however, less than the one that would be observed with low doses of ICS in this patient population. Another recently published short-term study of 12 weeks evaluated the benefit of a CRTh2 antagonist in asthmatic patients not controlled while on ICS treatment, and described no benefit on asthma control.[17] It appears unlikely that this treatment approach will benefit patients with severe refractory asthma.

Antimuscarinics Another new treatment approach for patients uncontrolled while on treatment with the combination of ICS/LABA has been the evaluation of inhaled long-acting muscarinic antagonists (LAMAs), which are the mainstay of treatment for chronic obstructive pulmonary disease, but have not yet been demonstrated useful in asthma. Two replicate, randomized, placebo-controlled trials evaluated the benefit of the LAMA tiotropium or placebo for 48 weeks, when added to treatment, on lung function and asthma exacerbations.[18,19] Treatment with tiotropium significantly improved the trough (pre-dose) FEV_1 from baseline in both studies, when compared

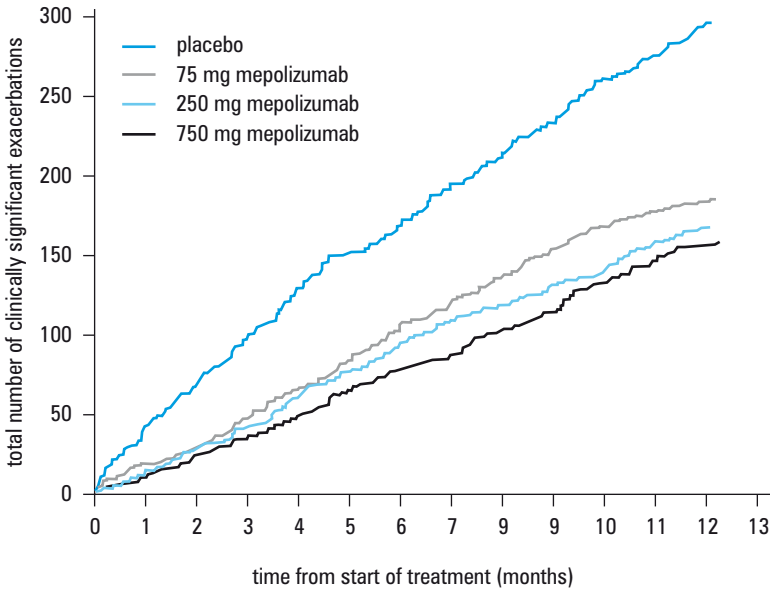


FIGURE 2 Effects of treatment with 3 doses of an anti-interleukin-5 monoclonal antibody, mepolizumab, compared with placebo, on clinically significant asthma exacerbations over 1 year; all 3 doses significantly reduced asthma exacerbations and there was no significant dose-dependency (reproduced with permission from Pavord et al.[12])

to placebo, and significantly reduced the risk of severe asthma exacerbations. Thus, it is likely that tiotropium will be a useful third-line drug to add to the ICS/LABA combination in these patient populations.

Reducing airway smooth muscle Bronchial thermoplasty is a bronchoscopic therapeutic procedure where the airways are heated using radiofrequency energy to 65°C.[20] The procedure is done using a catheter passed through the bronchoscope and can only treat the larger airways. A complete period of treatment requires 3 bronchoscopies, spaced several weeks apart. There is convincing evidence that the procedure reduced the volume of airway smooth muscle in the treated airways.[21]

The benefits achieved using bronchial thermoplasty were initially demonstrated in patients with relatively well-controlled asthma.[20] 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.[22] This study confirmed that thermoplasty resulted in an improvement in FEV_1 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.[23] Bronchial thermoplasty is, however, associated with unwanted effects. Some patients have experienced atelectasis and occasionally have required hospitalization following the procedure.[20,22]

Conclusions These studies provide future promise for the management of severe refractory asthma. The studies using anti-IL-5 monoclonal antibodies and the CXCR2 antagonist suggest that phenotyping patients, based on the airway inflammatory cell type, will be useful in deciding whether to begin treatment with these compounds. Antagonists of CRTh2 are unlikely to be of great benefit in the management of severe refractory asthma. Tiotropium will likely be used as an add-on to ICS/LABA, as most patients with severe refractory asthma have airflow obstruction. Bronchial thermoplasty will provide benefit in a subgroup of patients who remain symptomatic despite the absence of ongoing airway inflammation.

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