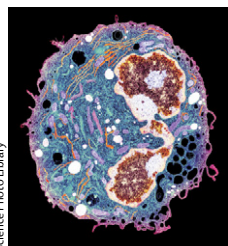


Targeting IL-5 in severe asthma: a DREAM come true?



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It is now accepted that severe asthma is not one phenotype but a heterogeneous mixture of syndromes in which various clinical, physiological, and inflammatory markers determine disease severity.¹ In the past few years, several attempts have been made to categorise severe asthma into subphenotypes by application of unsupervised cluster analyses. The most prominent phenotype that has emerged is characterised by eosinophilic airway inflammation despite the use of high-intensity anti-inflammatory treatment.^{2,3} About a third of patients with severe asthma have this refractory eosinophilic asthma phenotype,⁴ which is associated with frequent asthma exacerbations,⁵ fixed airflow limitation,⁶ air trapping,⁷ and nasal polyposis.⁸ Patients with this phenotype require frequent bursts of, or even depend on, daily oral corticosteroids, which lead to serious adverse effects and a poor quality of life.⁴

The importance of eosinophils in the pathogenesis of severe asthma was confirmed after introduction of antibodies against interleukin 5 (IL-5) as a possible treatment for patients with refractory eosinophilic asthma.⁹ IL-5 is a key factor in regulation of the growth, differentiation, recruitment, activation, and survival of eosinophils.⁹ Findings from two proof-of-concept studies with mepolizumab^{10,11}—a humanised monoclonal antibody against IL-5—suggested that this drug is effective as a steroid-sparing agent, reduces the frequency of severe exacerbations, and improves quality of life in patients with severe refractory eosinophilic asthma.

In *The Lancet*, Ian Pavord and colleagues¹² provide further convincing evidence for mepolizumab as an effective, well tolerated, and safe treatment in severe eosinophilic asthma. In the multicentre, double-blind DREAM trial, they gave 616 patients with poorly controlled asthma and evidence of eosinophilic inflammation one of three different doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or matched placebo every 4 weeks for 12 months. Compared with placebo, mepolizumab reduced the rate of clinically significant asthma exacerbations, the primary outcome measure (48% reduction with 75 mg, 95% CI 31–61%; 39% with 250 mg, 19–54%; and 52% with 750 mg, 36–64%). Visits to emergency departments and admissions also fell, although with varying statistical support (60% reduction with 75 mg,

19–81%; 42% with 250 mg, –12% to 70%; 48% with 750 mg, –2% to 73%). These effects are very promising and give hope to many patients for whom no effective drugs are available without significant adverse effects.

However, several questions remain unanswered. First, mepolizumab reduced the rate of exacerbations, as in earlier studies,^{10,11} but did not produce consistent improvements in symptoms or lung function. This striking dissociation between clinical and functional measurements on the one hand and exacerbations on the other suggests that they represent different aspects of the disease, with separate underlying pathophysiology. Lung function and asthma symptoms could be closely related to variations in airway calibre because of contraction of hyper-responsive smooth muscles, whereas severe exacerbations are elicited by recurrences of eosinophilic inflammation in large and small airways. As a result, for comprehensive treatment of patients with severe refractory eosinophilic asthma, combination treatment should target both IL-5 and smooth muscle.

Second, to whom should mepolizumab be prescribed? After Pavord and colleagues' study, the best candidates for successful treatment are patients with asthma and active eosinophilic inflammation despite adequate intake of high doses of inhaled corticosteroids, particularly those with frequent exacerbations and a good response to oral corticosteroids. Therefore, targeted treatment against IL-5 is not suitable for patients with other subphenotypes of severe asthma, such as the non-eosinophilic obese or β_2 -agonist-dependent phenotypes.²

Mepolizumab could also play a part in eosinophilic diseases other than severe asthma. Individuals with refractory eosinophilia represent a substantial proportion of non-smoking patients with severe asthma, but eosinophilia is also common in patients with asthma who are past or present smokers and in those with chronic obstructive pulmonary disease and frequent exacerbations.¹³ Therefore, investigation of the effects of treatment targeting IL-5 in these patient populations could be interesting. Another category of patients to consider is those with refractory eosinophilic nasal polyposis and only mild to moderate asthma. Nasal polyposis is a known risk factor of late-onset asthma and often precedes progression to severe forms

of the disease. Treatment targeting IL-5 significantly decreases severity scores of nasal polyps in patients whose disease is refractory to corticosteroids¹⁴ and might thereby prevent asthma from becoming severe and dependent on corticosteroids.

Finally, how can a mepolizumab responder be best identified in ordinary clinical practice? In the two previous studies,^{10,11} refractory eosinophilic asthma was defined on the basis of 3% eosinophils or more in induced sputum. With this criterion, the researchers were able to show a decrease of 43% in the number of exacerbations with 750 mg mepolizumab monthly for 1 year,¹⁰ which is similar to the results of DREAM.¹² However, in DREAM, patients could also be selected on the basis of less direct markers of eosinophilic airway inflammation, such as blood eosinophil counts of greater than 0.3×10^9 cells per L, exhaled nitric oxide levels greater than 50 ppb, or prompt deterioration of asthma control after a greater than 25% reduction in regular maintenance inhaled or oral corticosteroids. Use of these indirect criteria—particularly blood eosinophil count—makes identification of responders easier, which is important progress towards implementation in clinical practice.

The next step will be to assess the steroid-sparing effects of mepolizumab in a large population of patients who are dependent on oral corticosteroids. Ideally, treatment targeting IL-5 should not only reduce the number of exacerbations, but also facilitate tapering of oral corticosteroids, thereby preventing serious steroid-induced side-effects. If these effects are confirmed, the most severely affected patients with asthma would benefit greatly.

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Azithromycin in bronchiectasis: when should it be used?

In *The Lancet*, Conroy Wong and colleagues provide clear evidence for a beneficial effect of an inexpensive treatment for non-cystic fibrosis bronchiectasis in a large prospective study.¹ They randomly assigned 141 patients who had had a diagnosis of bronchiectasis to receive 500 mg azithromycin or placebo for 6 months. At the end of the treatment period, the rate of event-based exacerbations was lower in the azithromycin group (0.59 per patient) than in the placebo group (1.57; rate ratio 0.38, 95% CI 0.26–0.54; $p < 0.0001$). The

researchers should be commended for this achievement. Furthermore, the difficulties of undertaking this study in a specialty that has not attracted major public health investment or proactive involvement by public health groups should not be underestimated.

However, as is so often the case when a potentially worthwhile treatment benefit is first identified, the selection of patient subgroups appropriate for treatment in clinical practice is problematic. The investigators advocate careful selection of patients for

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