

Anti-IL-5 for Severe Asthma

Aiming High to Achieve Success



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Asthma affects > 300 million people worldwide and is severe in 10% of these individuals.¹ Advances in approaches to phenotype the heterogeneity of severe asthma have established the importance of eosinophilic inflammation, and several new therapies beyond corticosteroids and anti-immunoglobulin E are designed to target type 2-mediated immunity to inhibit this inflammation, with the aim of reducing exacerbation frequency. Current therapies against type 2 immunity include anti-IL-4R α , IL-5, IL-5R, IL-13, and the type 2 prostaglandin D2 receptor.²

The most advanced therapeutic target is IL-5, which is an attractive target because it is an obligate cytokine for eosinophil maturation and survival. Its inhibition is thus predicted to reduce bone marrow production of eosinophils and promote apoptosis. Persistent eosinophilic inflammation is present in approximately half of individuals with severe asthma. In those without eosinophilic inflammation, about half have emergent eosinophilic inflammation following corticosteroid reduction, suggesting that this phenotype is very

common. Eosinophilic inflammation is present with or without atopy, as a type 2-mediated response can occur following allergic sensitization, with consequent release of IL-5 from Th2 cells, or in response to airway damage and infection through activation of the type 2 innate lymphoid cells.

The IL-5 neutralizing antibodies mepolizumab and reslizumab were licensed in the United States and Europe in 2015 following successful phase III studies demonstrating reductions in severe exacerbations. Benralizumab, an anti-IL-5R biologic, was also successful in its pivotal phase III studies. Although all these anti-IL5R approaches consistently reduce exacerbations, beneficial effects on lung function, asthma control, and health status are more variable. Small effects on lung function were observed in the phase III study for mepolizumab,³ which were not seen in a phase II study,⁴ whereas effects on these outcomes were more robustly observed following treatment with reslizumab⁵ and benralizumab.⁶ Whether these larger effects on lung function and symptoms in response to reslizumab and benralizumab are real or chance observations is unclear. However, the limited bronchoscopic biopsy data suggest that benralizumab reduces bronchial mucosal eosinophilia to a greater extent⁷ than does mepolizumab.⁴ This raises the intriguing possibility that improvements in lung function might be related to the magnitude of the reduction in the airway eosinophilia. To date, no biopsy studies have been reported for reslizumab.

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In all the late-phase anti-IL5R, studies, the blood eosinophil count has been a valuable biomarker. In this issue of *CHEST*, Bjermer et al⁸ and Corren et al⁹ undertook two similarly designed randomized placebo-controlled trials of reslizumab administered IV every 4 weeks for 16 weeks in patients with poorly controlled asthma. Corren et al included individuals with asthma with and without an elevated blood eosinophil count (≥ 400 cells/ μ L), whereas Bjermer et al included two doses of reslizumab and only patients with asthma with an elevated blood eosinophil count. In the former study, the subgroup of patients with, but not those without, an elevated baseline blood eosinophil count showed

improvements in lung function and asthma control following treatment with reslizumab when compared with placebo, even though no significant relationship was detected between baseline blood eosinophil levels and a change in lung function. Likewise, Bjermer et al showed that reslizumab significantly improved lung function and asthma control vs placebo, with greater effects seen with the higher dose. These findings support the view that an elevated blood eosinophil count is associated with a good clinical response but did not find a clear correlation between the intensity of the baseline eosinophil count and response. In contrast, improvements in exacerbation frequency observed following treatment with mepolizumab were related to the baseline blood eosinophil count with clinical benefit in asthmatics with a blood eosinophil count ≥ 150 cells/ μ L.¹⁰ Thus, the best cutoff for the blood eosinophil count to apply clinically remains uncertain. From a patient perspective, there is an argument to select a low or no cutoff, as there is some benefit even with low baseline eosinophil counts, whereas from a payer's perspective, the health economic benefit is better with a higher cutoff. Post-licensing studies will need to continue to address the effectiveness of these therapies in real-world studies.

In the next few years, it is likely that we shall have several new therapies for severe asthma. For the clinician to understand how to select the right therapy for the right patient, we shall need to better understand the phenotype-specific mechanistic role of different elements of the immune response and to have biomarkers of these mechanisms, as it is likely that some changes in airway inflammation and remodeling will contribute more to exacerbation risk, whereas others might be more related to symptoms or lung function. For example, in contrast to the success of anti-IL5R in phase III studies, the anti-IL-13 biologic lebrikizumab was only successful in achieving its primary outcome of reducing asthma exacerbations in one of two pivotal phase III studies. However, lebrikizumab has consistently improved lung function, perhaps in part due to its effects on airway smooth muscle rather than eosinophilic inflammation, and improvements were greatest in those patients with an activated IL-13 pathway, as evidenced by increased blood levels of periostin.² The outcome of phase III studies of another anti-IL-13 therapy, tralokinumab, are awaited, but earlier studies again demonstrated a

more consistent effect on lung function, with the greatest reductions in exacerbations observed in those with bronchodilator reversibility and elevated blood periostin or dipeptidyl-peptidase-4 levels.¹¹ Dupilumab shows promise and targets both IL-4 and IL-13 signaling through anti-IL4R α , which might have a more profound effect on airway inflammation.² Importantly, it is unknown whether these approaches reduce eosinophilic airway inflammation. Fevipiprant, a small-molecule type 2 prostaglandin D2 receptor inhibitor, has demonstrated beneficial effects on lung function and eosinophilic inflammation in sputum and bronchial biopsy samples.¹² Whether this translates into a benefit in exacerbation frequency is unknown, and findings from phase III studies are awaited.

We are moving into a new era of type 2 immunity-mediated therapies that will bring new opportunities for clinicians and our patients, but with this opportunity comes new challenges. Biomarkers will increase in importance to help drive precision medicine, but we need to understand how to use them, and in particular what cut points to apply. For anti-IL-5 approaches we probably need to look toward elevated blood eosinophil counts, as aiming for a high cutoff is most likely the best way we shall achieve success.

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