

Dupilumab: a potential new treatment for severe asthma



In *The Lancet*, a phase 2b dose-ranging study of dupilumab, a human anti-interleukin-4 receptor α antibody that inhibits the downstream effects of the type 2 mucosal immunity cytokines, interleukin 4 and interleukin 13, is reported.¹ Over 24 weeks, dupilumab was efficacious as an add-on therapy to medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist in patients with uncontrolled persistent asthma, with improvement in baseline forced expiratory volume in 1 s (FEV₁), which was the primary endpoint, as well as a reduction in annualised exacerbation rates and improvements in quality of life and asthma control all being more evident when injections were given every 2 weeks compared with every 4 weeks. The changes observed in the whole group were clinically relevant, with a least-squares mean difference in FEV₁ of 17.75% (SE 1.84) and a risk reduction of severe exacerbations of 70.5% (95% CI 45.4–84.1) in those receiving 300 mg dupilumab every 2 weeks, the highest dose used, compared with placebo (6.06% [SE 1.89]). Adverse events were similar in the placebo and treated groups, with a higher rate of injection-site reactions with dupilumab.

The stratification used was based on the first clinical report of dupilumab in patients with persistent, moderate-to-severe asthma with blood eosinophil counts of at least 300 eosinophils per μ L,² in line with previous clinical trials of an anti-interleukin 5 antibody.^{3,4} Notably, the improvement in lung function and reduction in exacerbation rates, and also in 5-item Asthma Control Questionnaire score, Asthma Quality of Life Questionnaire score, symptoms, and nitric oxide levels in exhaled breath (FeNO) occurred in those with at least 300 eosinophils per μ L (mean 590 eosinophils per μ L) and in those with fewer than 300 eosinophils per μ L (mean 172 eosinophils per μ L). However, what eosinophil count cutoff would provide a predictable therapeutic response? This study was not powered to answer this question because there were too few participants with very low blood eosinophil counts. Another question raised here is whether blood eosinophil count is the best predictor to use because dupilumab does not block the effects of interleukin 5, a primary mediator of eosinophil production and activation. FeNO might be an alternative

biomarker because the enzyme activity of nitric oxide synthase is directly controlled by both interleukin 4 and interleukin 13, and there was a sustained reduction in FeNO of 40% caused by dupilumab. Alternatively, other circulating biomarkers regulated by dupilumab, such as eotaxin-3(CCL26) or TARC(CCL17), could be considered,² or serum periostin concentrations that segregate from non-responders to the anti-interleukin 13 monoclonal antibody lebrikizumab could be used.⁵

Also related to the blood eosinophil count is the report of a transient rise of blood eosinophil counts seen in those patients with asthma with initial counts of at least 300 eosinophils per μ L (but not in those with fewer than 300 eosinophils per μ L), observed between week 4 and week 16 of treatment. One participant developed counts that are seen in hypereosinophilic syndrome. Analysis of biomarkers in blood collected during the study could shed some light on the mechanisms that might have caused this. One possibility is that this relates to a transient rebound increase in eosinophil-active mediators such as interleukin 5 that might result from blocking interleukin 4 and interleukin 13. Clearly, caution needs to be exercised in patients with high blood eosinophil counts, and the phase 3 clinical trial of dupilumab (NCT02414854) is excluding patients with an eosinophil count of more than 1500 eosinophils per μ L.

This clinical study establishes dupilumab as a first-in-class potential new treatment for asthma, particularly for severe asthma where there is an urgent unmet

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need for new efficacious treatments, particularly in those with a type 2 high asthma phenotype.⁶ Up to 51% of the participants in this study were receiving high-dose inhaled corticosteroids and none were receiving additional controllers other than long-acting β_2 agonists. The efficacy of dupilumab in patients receiving maintenance oral corticosteroid therapy, who constitute up to 46% of patients with severe asthma and represent the most severe forms of asthma,⁷ should be established, particularly with regard to reducing maintenance corticosteroid therapy. Dupilumab has already been shown to be effective in reducing and even stopping maintenance dose of inhaled corticosteroids while maintaining improvement of asthma.² Also, in relation to severe asthma, dupilumab has been reported to be effective in the coexisting conditions that occur frequently in patients with severe asthma such as atopic dermatitis and nasal polyps.⁸⁻¹⁰

Two anti-interleukin-5 monoclonal antibodies, mepolizumab and reslizumab, have now been approved by the US Food and Drug Administration for the treatment of patients with severe asthma with an eosinophilic phenotype. Were dupilumab to be approved, clinicians would need guidance as to which patients with severe asthma would benefit most from these newly introduced specific immune therapies, which include the already available anti-IgE antibody, omalizumab. The phase 3 studies of dupilumab should provide some indication for this first-in-class anti-interleukin-4 receptor α therapy.

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I have served on the advisory boards of pharmaceutical companies GlaxoSmithKline, AstraZeneca, Novartis, and Johnson & Johnson. In the last 3 years, I have received research grants for asthma and COPD research from Pfizer, GlaxoSmithKline, Medical Research Council, European Union Innovative Medicines Initiative, and National Institutes of Health. I have received honoraria for speaking engagements from AstraZeneca and Merck Sharp & Dohme. AstraZeneca is developing an anti-interleukin 13 antibody for use in asthma.

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