

Anti-interleukin-5 therapy in patients with severe asthma: from clinical trials to clinical practice



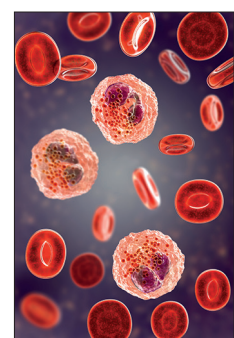
The development of monoclonal antibody therapy targeting the type 2 inflammatory pathway and the application of personalised medicine through the identification and management of treatable traits represent two major advances in the management of asthma within recent decades. These two approaches are intricately linked. Biomarkers are used to identify patients with a type-2-predominant endotype and select the likely responders to such therapeutic regimens. However, uncertainties exist that limit application in clinical practice. In *The Lancet Respiratory Medicine*, two randomised placebo-controlled trials of reslizumab, an anti-interleukin-5 (IL5) monoclonal antibody, in patients with severe asthma have advanced knowledge in this field and brought into focus the important clinical uncertainties that are relevant to the application of these therapies in clinical practice.¹

In study 1, asthma exacerbation frequency was not significantly reduced with subcutaneous administration of reslizumab 110 mg once every 4 weeks for 52 weeks, compared with placebo, in the intention-to-treat population of patients aged 12 years or older with uncontrolled severe asthma, two or more exacerbations in the previous year, and a blood eosinophil count of 300 cells per μL or more (rate ratio 0.79, 95% CI 0.56–1.12; $p=0.19$), but was reduced in the prespecified subgroup with blood eosinophil counts of 400 cells per μL or more (0.64, 95% CI 0.43–0.95). This finding highlights the importance of targeting a patient population in which biomarkers indicate dominance of the specific inflammatory process against which treatment is directed and are therefore most likely to respond. For example, studies of the related anti-IL5 therapies mepolizumab² and benralizumab³ have shown an association between increasing blood eosinophil count, increasing risk of a severe exacerbation, and increasing relative risk reduction with treatment, resulting in a proportionate increase in absolute benefit. This association is relevant not only to the design of clinical trials to investigate efficacy, but also to the criteria for funding and use of this medication class in clinical practice to ensure greatest therapeutic benefit and cost-effectiveness.

In study 2, no significant difference in daily oral corticosteroid dose reduction was observed between subcutaneous reslizumab 110 mg once every 4 weeks for 20–24 weeks and placebo in adolescents and adults with oral corticosteroid-dependent asthma (odds ratio for a lower category of oral corticosteroid use in the reslizumab group vs the placebo group, 1.23, 95% CI 0.70–2.16; $p=0.47$). Similar to the results from previous studies of monoclonal antibody therapy in patients with severe asthma, which showed a marked placebo response,⁴ the authors found that 20 (22%) of 89 patients in the placebo group were able to reduce their oral corticosteroid dose by 90–100%, and 32 (36%) by at least 50%. The mechanisms underlying this response are likely to be multifactorial and include the neurobiological and psychological response to placebo, response to the intensive follow-up delivered in a clinical trial setting, and improved adherence to baseline medication.⁴ A marked response to monoclonal antibody therapy in a patient with severe asthma, such as a 50% reduction in oral corticosteroid dose, might simply represent a placebo response, indicating the limitations of a therapeutic trial in clinical practice.

In both studies, patients used fixed-dose inhaled corticosteroids (at least medium dose in study 1 and the highest labelled dose available at research sites in study 2) plus an additional controller medication, such as a long-acting β_2 agonist (LABA). However, evidence suggests that inhaled combination corticosteroid plus formoterol maintenance and reliever therapy (MART) reduces the risk of severe exacerbations compared with inhaled corticosteroid and LABA plus short-acting β_2 agonist reliever therapy.⁵ Indeed, the relative rate reduction in severe exacerbations of 46% with MART in a high-risk population⁶ compares favourably with the 36% reduction in clinical asthma exacerbations in the highly selected population with a blood eosinophil count of 400 cells per μL or more in study 1. This finding indicates the importance of ensuring that management is optimised with simple and inexpensive treatment before considering monoclonal antibody therapy.

A related consideration is the presence of co-existing disorders such as dysfunctional breathing and vocal



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cord dysfunction, which are common in populations with severe asthma.⁷ These disorders can masquerade as symptomatic asthma, and only through a systematic assessment can these disorders be identified and treated, potentially avoiding escalation to a treatment that is not targeted to the relevant or predominant trait. Neither study included such an assessment for treatable traits. Like other studies of biological therapies for eosinophilic asthma, both studies required participants to have bronchodilator responsiveness (or bronchial hyperreactivity in study 2). Although commonly used, these inclusion criteria are not related to the biological trait that is being targeted by the treatment and might, therefore, limit the external validity of the results.⁸ As a result of these factors, the ability to extrapolate efficacy shown in a clinical trial population that was highly selected to a complex, heterogeneous, real-world population with severe uncontrolled eosinophilic asthma is limited.

Finally, anti-IL5 therapies must be directly compared, not least because head-to-head comparisons of drugs with different mechanisms of action might help to inform the choice of drug in the clinic, depending on the patient characteristics and clinical situation. For example, the effect of benralizumab to induce eosinophil cytotoxicity and achieve a profound and early onset eosinopenia⁹ raises the possibility that the drug might have a differing efficacy profile, including a potential role in the treatment of acute severe exacerbations.¹⁰ Comparative clinical trials through existing or novel research networks are a priority.

In the interim, funders, prescribers, and patients will need to consider these and other clinical issues to ensure that the right patients receive the right

monoclonal antibody therapy at the right time to achieve optimal cost-effective reductions in morbidity and mortality risk.

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