

Biologics and Personalized Medicine in Severe Asthma: One Step at a Time



Richard Beasley, DSc^a, and Lee Hatter, MBBS^a Wellington, New Zealand

Biologic therapies represent a major advance in the treatment of difficult-to-treat severe asthma, providing a therapeutic option that is highly effective in reducing severe exacerbation risk in selected patients with specific phenotypes. They also provide an opportunity to reduce patient dependence on high-dose oral corticosteroid (OCS) and inhaled corticosteroid (ICS) therapy and the associated risks of systemic adverse effects. The research programs that led to their development have likewise contributed to the important concept of personalized medicine in asthma, in which specific therapies are chosen based on specific clinical characteristics.¹ More broadly, they have contributed to the concept of treatable traits in asthma, in which it is recognized that poor quality of life, inadequately controlled symptoms, and exacerbation risk may not only be due to asthma, but also numerous overlapping disorders that can present with symptoms indistinguishable from asthma, comorbidities that may require treatment in their own right, and if appropriately addressed alongside lifestyle or environmental factors, may lead to better respiratory health than by simply increasing asthma-specific treatment.¹

Currently, biologics are recommended as the final step of asthma treatment for patients who have poorly controlled asthma and frequent exacerbations despite receiving otherwise optimal treatment, which may include maintenance OCS, and have the specified eosinophilic or allergic biomarkers. However, their introduction has led to their widespread use well beyond their evidence base for efficacy, safety, and cost effectiveness.²⁻⁴

It is in this contemporary real-world scenario that Louis et al⁵ publish in the *Journal* a clinical trial of standard-of-care background medication reduction with the extended use of benralizumab, an interleukin-5 receptor alpha (IL-5Ra)-directed cytolytic monoclonal antibody therapy. This was a 56-week single-arm open-label extension substudy of the 24-week randomized, double-blind, placebo-controlled study in which benralizumab was shown to halve the rate of asthma exacerbations in adults with severe eosinophilic asthma.⁶ In the extension study, the authors report substantive reductions in corticosteroid burden with ongoing benralizumab treatment, when patients

were regularly reviewed with the intent to reduce background asthma medications while maintaining asthma control, according to a standardized protocol. At the completion of the study, 42% of non-OCS-dependent patients achieved at least 1 adapted Global Initiative for Asthma (GINA) step reduction, and in OCS-dependent patients, one-half eliminated OCS and three-quarters achieved a prednisolone equivalent dose of 5 mg or less at the end of treatment. These findings provide robust evidence that it is possible to markedly reduce OCS and ICS exposure with long-term benralizumab treatment, when closely monitored and treatment intensity is reduced according to their published algorithm, which can now be recommended for clinical practice.

It is informative to consider these findings in the broader context of corticosteroid reduction in severe asthma. An earlier placebo-controlled ICS dose-reduction study of the monoclonal anti-immunoglobulin E antibody therapy omalizumab in severe atopic asthma patients taking fluticasone propionate at a dose of 1,000 µg/d or greater, after a 16-week add-on randomized treatment period, ICS doses were reduced by a median of 50% with placebo (vs 60% with omalizumab) over the following 16-week ICS dose-reduction period, while randomized treatment was continued.⁷ These findings not only illustrate the importance of a placebo arm when studying corticosteroid-reduction strategies but also are consistent with the known ICS therapeutic dose-response relationship in asthma, in which 80% to 90% of the maximum obtainable efficacy of ICS for key clinical outcomes including severe exacerbation and mortality risk is achieved with ICS daily doses around 100 to 250 µg fluticasone propionate or equivalent.⁸ In a placebo-controlled trial of the monoclonal anti-IL-5 antibody therapy mepolizumab in OCS-dependent asthma, OCS doses were reduced by a median of one-third with placebo (and three-quarters with mepolizumab).⁹ These findings suggest that it is common clinical practice to titrate up, but not down, OCS and ICS therapy in the management of severe asthma and that OCS and ICS dose reduction will often be achievable in patients receiving continuous OCS or high-dose ICS therapy, while maintaining asthma symptom control.

These findings question whether there are other therapeutic approaches that might reduce exacerbation risk and corticosteroid burden in severe asthma. The importance of addressing inhaler technique and medication adherence is well recognized.² Another complementary approach is the switch to ICS/formoterol maintenance and reliever therapy (MART), which can achieve a reduction in severe exacerbation risk by about one-quarter (and associated reduced OCS exposure of a similar magnitude), despite half the maintenance ICS dose when compared with maintenance high-dose ICS/long-acting beta₂-agonist and as-needed short-acting beta₂-agonist therapy.¹⁰

^aMedical Research Institute of New Zealand, Wellington, New Zealand
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Corresponding author: Richard Beasley, DSc, Medical Research Institute of New Zealand, Private Bag 7902, Wellington 6242, New Zealand. E-mail: Richard.Beasley@mrinz.ac.nz.

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In addition to severe exacerbation risk, MART also treats the traits of airways inflammation, symptoms, airflow obstruction, systemic corticosteroid adverse effects, polypharmacy, and poor ICS adherence. A case can now be made that patients should be switched to ICS/formoterol MART prior to initiating monoclonal antibody therapy, as a simple, effective, and relatively inexpensive means of optimizing their treatment.

More generally, the systematic investigation and treatment of other traits should be undertaken before embarking down the pathway of monoclonal antibody therapy in severe asthma. The systematic investigation of overlapping disorders, comorbidities, lifestyle, and environmental factors can be considered important in the work-up of a patient for biologic therapy in severe asthma.¹ In clinical practice, this may lead to many patients receiving an alternative therapy instead of, or in addition to, biologic therapies, resulting in a markedly better overall outcome. A greater reduction in corticosteroid exposure might have been achieved in the extension of the benralizumab clinical trial if a systematic investigation and treatment of other traits had been undertaken.

Finally, rather than the current trend to expand the use of biologics well beyond their evidence base, a case can be made to limit their use to those for whom individualized prediction models indicate an enhanced response and thereby improve the cost effectiveness of these expensive therapies. This approach has been investigated in a *post hoc* analysis of 2 multinational randomized controlled trials of mepolizumab, in which it was possible to identify patients who will obtain minimal benefit from treatment and others who have an enhanced response, based on multiple patient characteristics.¹¹

To conclude, the research and development of biologic therapies in severe asthma has been instrumental in establishing the concept of personalized medicine in airways disease. Not only has it highlighted the importance of specific clinical characteristics in identifying patients who might preferentially respond to specific biologic treatments, but it has also led to the broader realization of the importance of the investigation and treatment of pulmonary, extrapulmonary, and environmental/lifestyle factors that may contribute to poor respiratory health in asthma (and chronic obstructive pulmonary disease). However, owing to

their marked efficacy, we now run the risk of the widespread non—evidence-based use of biologic therapy in patients for whom efficacy and safety has not been demonstrated, their inhaled asthma treatment has not been optimized, and without consideration of other treatable traits that may be more important in contributing to good respiratory health. We propose a personalized approach to the management of severe asthma in which a systematic assessment and management of treatable traits is routinely undertaken, including a trial of the ICS/formoterol MART regimen, before biologic treatments are initiated.

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