



Perspective

Biologic medications in asthma

What have we learned from long-term studies?

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The biologics era of asthma began when the Federal Drug Administration approved omalizumab in 2003. Since then, 5 additional biologic therapeutics have been approved: Mepolizumab (2015), Reslizumab (2016), Benralizumab (2017), Dupilumab (2018), and more recently, Tezepelumab (2021). As a class, these monoclonal antibodies are all safe and effective, as demonstrated in the registry trials that varied in length from months to approximately 1 year. However, because of their immunomodulatory effects, propensity for generating antidrug antibodies, and adverse effects noted in the pivotal trials, concern remains about the long-term efficacy and risk, highlighting a need for long-term safety and efficacy data. For example, because all the approved agents modulate Type-2 inflammation, they could be associated with an increased risk of parasitic infection. Fortunately, long-term data continue to accumulate that indicate these medications are not associated with this risk or other long-term adverse events, nor with the development of neutralizing antidrug antibodies. In addition, both long-term follow-up and real-world longitudinal studies demonstrate that as a class, these agents continue to be effective for years in most patients. In this study, we reviewed these long-term data and highlight the questions and controversies associated with each class (Table 1).

With almost 20 years of experience since its approval, omalizumab certainly has the longest track record in the clinic. This humanized antibody binds to immunoglobulin (Ig)E at the FcεR1 receptor binding site, preventing IgE activation of mast cells and

basophils. It is now approved for asthma, chronic idiopathic urticaria, and chronic sinusitis with nasal polyposis and is approved for home injection by means of prefilled syringe with the need for an epi-pen. There was no open label study associated with the phase 3 trials; however, given that omalizumab has been in the clinic for years, there have been many observational studies evaluating its safety and efficacy. This is nicely summarized by MacDonald et al¹ in a systematic review of 42 studies in more than 9000 adult and pediatric patients that concluded that omalizumab is effective and safe well beyond 4 years of treatment, with durable improvements in asthma control and exacerbations and without an increase in the development of malignancy, adverse cardiovascular outcomes, (a concern based on a signal in the phase 3 trials), or adverse pregnancy outcomes.²

Approved in 2015, mepolizumab is an IgG1 humanized monoclonal antibody that is directed against interleukin (IL)-5, the canonical growth and activation factor for eosinophils. Patients enrolled in the phase 2 DREAM trial, and Phase 3 Mensa and Sirius trials rolled into several open label extension trials, including COLUMBA, COSMOS, and COSMEX, leading to more than 3 years of follow-up.^{3,4} Several important observations can be made from these studies. First, the effect of mepolizumab in reducing exacerbations is durable: 53% of patients followed from DREAM had ≤ 1 exacerbation in 4.5 years of follow-up in COSMOS. Second, patients in DREAM stopped mepolizumab before entering COSMOS. While the patients were off mepolizumab, there was an increase in exacerbations that returned to controlled levels after restarting mepolizumab. This demonstrated that stopping and starting mepolizumab (or any of the biologics) is not likely to impact effectiveness. In addition, there was no evidence in COSMOS that the risk of zoster infections was increased, and no new adverse effects were noted in the long-term studies; the most common adverse effects continued to include nasopharyngitis, upper respiratory infections, and injection site reactions. Mepolizumab has since been approved for chronic sinusitis with nasal polyps, and also for both eosinophilic granulomatosis with polyangiitis and the idiopathic hypereosinophilic syndrome.

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Table 1
Asthma Biologics With Long-Term Follow-up Data

Therapy approval	Mechanism of action	Endotype/ pivotal trial criteria	Key efficacy/safety outcomes	Notable adverse effects	Long-term studies outcomes/ follow-up
Omalizumab 2003	Humanized mAb inhibits activity of IgE	Moderate-severe allergic asthma/IgE $\geq$ 30 IU/mL, + SPT or specific IgE to perennial allergen	Improvement of asthma control Minimal improvement in lung function	Injection site reactions Hypersensitivity reactions Delayed anaphylaxis	42 observational studies, no open label extension/ Over 4 years
Mepolizumab 2015	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/ blood eosinophils $\geq$ 150 or 300 cells/ul	Decrease exacerbations by 39%-52% Weak improvement in FEV1	Injection site reactions Hypersensitivity reactions Herpes Zoster Myalgias	Open label extension studies, COLUMBA, COSMOS, COSMEX/ Over 3 y
Benralizumab 2017	Humanized mAb inhibits actions of IL-5 receptor	Severe eosinophilic asthma/ blood eosinophils 300 cells/ul	Decreased exacerbations by 45%-51% Improvement in pre-bronchodilator FEV1	Injection site reactions Hypersensitivity reactions myalgias	Open Label Extension BORA MELTEMI/ Over 5 y
Dupilumab 2017	Humanized mAb inhibits actions of IL-4 and IL-13	Blood eosinophils $\geq$ 150/ μ L FeNO > 25 ppb Blood eos < 1500 cells/ul	Decreased exacerbations by 46%-48% Improvement in pre-bronchodilator FEV1	Injection site reactions Conjunctivitis Transient increase in blood eosinophils	Open label extension TRAVERSE/ Over 3 y

Abbreviations: FEV, forced expiratory volume; Ig, immunoglobulin; IL, interleukin; IU, international units; SPT, skin prick test.

Benralizumab is a humanized IgG4 monoclonal antibody that targets the IL-5 receptor and prevents IL-5 receptor hetero-dimerization and signal transduction. In addition to the inhibitory effect of binding to the IL-5 receptor, Benralizumab causes antibody-directed cellular cytotoxicity and apoptosis of the antibody bound cell. The phase 3 pivotal trial program consisted of 2 companion trials, SIROCCO and CALIMA, that evaluated the effect of benralizumab on exacerbation rates and prebronchodilator FEV1. Patients from these studies were invited to enroll in the open label extension studies BORA and MELTEMI. This has led to an additional 5 years of safety and efficacy data.⁵ Adverse and serious adverse event rates remained low and did not increase with exposure; only 8 patients discontinued benralizumab because of adverse events. Notably, among patients with blood eosinophils greater than or equal to 300 cells/ μ L, at least 75% of subjects had 0 exacerbations per year during the follow-up period.

Dupilumab, approved for the treatment of atopic dermatitis in 2017 and eosinophilic asthma in 2018, is an IgG4 kappa directed against IL-4Ra, a co-receptor for both IL-4 and IL-13 pathway signaling. Patients from the Liberty pivotal trial program, QUEST and VENTURE, rolled into the open label extension trial TRAVERSE.⁶ Asthma exacerbation rates remained low, and prebronchodilator FEV1 improvements were durable for 3 years of follow-up. Importantly, rapid, sustained improvements were observed in dupilumab-treated patients who previously received placebo in parent studies, whereas further improvements in asthma control and health-related quality of life were observed in patients who continued receiving dupilumab. Blood eosinophils (which initially rose during the Liberty studies) and serum total IgE decreased progressively below pretreatment levels, suggesting that T2 inflammation may continue to decrease with years of treatment. Dupilumab has now also been approved for chronic sinusitis with nasal polyps.

The long-term studies of approved biologics have been invaluable, providing reassurance regarding the long-term safety and efficacy of these novel therapies, just as long-term studies of inhaled corticosteroids and bronchial thermoplasty have given us reassurance regarding their long-term use. To the best of our knowledge, no new treatment-related adverse events have been observed for any of these biologics, and the sustained efficacy after years of use is particularly exciting and highlights the value of open label extension studies asthma therapies that emerge in the future. Indeed, the anti-Thymic Stromal Lymphopoietin therapy tezepelumab that was most

recently approved is also being studied long-term in the DESTINATION study. An interesting feature of DESTINATION is the continued use of a placebo arm to evaluate the long-term benefits compared with the placebo.

Just as important as these long-term efficacy trials have been are real-world clinical effectiveness studies. All the biologics that have been evaluated in this manner have shown efficacy similar to that observed in clinical trials, albeit without a placebo treatment arm for comparison.

In conclusion, it is clear that long-term studies and real-world evaluations have provided valuable information, but gaps remain in our knowledge of biologics, which affects patient care. What is really needed is long-term head-to-head studies comparing biologics so that clinicians can weigh the risks and benefits for every patient phenotype over the long term. Although studies that evaluate the withdrawal of biologics after long-term use will also provide insight into the potential to reduce airway remodeling and modify disease severity, it would also be extremely useful to evaluate if biologics can affect underlying biology and modify the disease permanently; genomics, biopsy, and imaging studies of patients on biologics could provide substantive data regarding the true biological impact of these targeted therapies in our populations with difficult-to-treat asthma.

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