



Perspective

Asthma biologics

Underuse, overuse, and best use?

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Uncontrolled asthma is a significant problem worldwide. It is important to acknowledge that many patients with uncontrolled asthma can be brought under control using medications that have been available now for decades. Unfortunately, nonadherence to regular use of inhaled corticosteroids (ICSs) and long-acting β -agonists (LABAs) is incredibly common, and solving the complex reasons for nonadherence is not straightforward. Recently, 5 injectable asthma biologic medications have become available. These medications are intended for patients whose asthma is not controlled with ICSs or LABAs and who have specific features, such as high IgE levels (omalizumab), high eosinophil counts (benralizumab, mepolizumab, and reslizumab), and/or high T_H2 cell counts (dupilumab). In this Perspective, we consider the opportunities to optimize biologic medication use through the lens of an asthma medication prescriber.

A careful assessment of current adherence to asthma treatment guideline recommendations is an important first step when considering an asthma biologic. In a large multicenter study of 3421 patients who had uncontrolled asthma, Bateman et al¹ found that 71% had well-controlled asthma after 1 year of dose escalation with ICSs or LABAs and guideline-recommended care. Importantly, this finding suggests that there are likely to be a substantial number of patients whose asthma is not controlled with guideline care and ICSs or LABAs. Looking more closely at 3399 patients who started omalizumab treatment, 73% had a medication possession ratio of 0.75 or less, and 49% had very low adherence (medication

possession ratio ≤ 0.5).² These findings reinforce that prescribers of asthma biologics should consider how best to assess and improve medication adherence to ICSs and LABAs before considering the use of a biologic agent. Health care teams may have access to a variety of different tools that can assist in an objective assessment of medication adherence, such as inflammatory biomarkers to estimate ICS use, pharmacy refill records, or smart inhalers that track actuations. Along with medication adherence, other important areas to consider before prescribing asthma biologics include identification and mitigation of asthma triggers; treatment of comorbidities, such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease; and confirmation of proficient inhalation device technique.

Choosing from 5 available asthma biologics is the next step. On publication of trials for the fifth asthma biologic (dupilumab) in the *New England Journal of Medicine*, Editor Jeffery Drazen³ wrote this in an accompanying editorial: "Although there are minor differences in the outcomes of some of the major clinical trials ... we regard them as essentially equivalently effective treatment" and calls for a head-to-head approach of comparing the biologics in new studies. Several recent attempts to use network meta-analysis and indirect comparison methods to help prescribers select the most effective asthma biologic have reached different conclusions, likely because the only network or indirect comparisons are through a placebo node. Certainly, a prescriber can use the selection criteria from each medication trial as a guide. However, the criteria for many of these studies substantially overlap, making patients eligible for multiple and in some cases all the biologic agents. Furthermore, many patients with severe asthma do not have a T_H2 -high phenotype and thus will not be eligible for any of the currently available asthma biologics. Prescribers could use patient treatment goals other than reduction in asthma exacerbations as another way to select asthma biologics, such as reducing systematic corticosteroids (benralizumab,

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dupilumab, mepolizumab), improving pulmonary function (benralizumab, dupilumab, reslizumab), or improving disease-specific quality of life (dupilumab, mepolizumab). Practical guidance for selecting asthma biologics was recently published, but much further work is needed.⁴

There are additional challenges that complicate the use of asthma biologics in clinical practice. Even after ensuring guideline and medication adherence, considering harms and benefits of these agents, and using available biomarkers to estimate likely treatment response, the patient still needs to have access to the biologic agent. Access should not be assumed. From 2003 to 2015, when the only asthma biologic available was omalizumab, fewer than 3 in 1000 individuals with asthma were taking omalizumab.² Patients who received omalizumab, compared with patients matched for similar levels of asthma control, were different in age, sex, geography, and specialist access.² The costs of asthma biologics are an important factor for patients' access to the medications. Cost-effectiveness analyses of asthma biologics with current prices reveal clinical benefits with a high associated cost.⁵ Specifically, the base case discounted incremental model estimated the following cost per quality of life-year gained: omalizumab, \$313,000; mepolizumab, \$344,000; reslizumab, \$412,000; benralizumab, \$412,000; and dupilumab, \$464,000.⁵ To achieve conventional cost per quality of life-year gained thresholds, the cost of each asthma biologic would need to be lowered by several hundred percent. Most people are unable to pay for asthma biologics without financial assistance from a health insurance or charitable program. A prescriber's current role includes working with payers as an advocate for their patients. In addition, it is important to assess a patient's response to the asthma biologic to avoid long periods of treatment without clear clinical benefit. Some may discontinue omalizumab treatment

because their asthma outcomes did not improve as much as expected. Still others may struggle with adherence to asthma biologics for similar reasons they struggle with adherence to ICS and LABA treatment. In data from omalizumab users from 2003 to 2015, approximately 50% of patients who start use of omalizumab are still using it 1 year later (M.A.R., unpublished data, 2017). Comparison studies of adherence to asthma biologics that use different dosing frequency and administration locations are needed to incorporate likelihood of adherence into prescribing decisions.

We are fortunate to have new solutions to offer our patients with uncontrolled asthma. We have a multitude of scientists, trial participants, study coordinators, pharmacists, pharmaceutical companies, governmental agencies, foundations, and clinical investigators to thank for this progress. However, we still have much work to do to deliver the optimal benefits of asthma biologics to our patients.

References

1. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? the Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170(8):836–844.
2. Jeffery MM, Shah ND, Karaca-Mandic P, Ross JS, Rank MA. Trends in omalizumab utilization for asthma: evidence of suboptimal patient selection. *J Allergy Clin Immunol Pract*. 2018;6(5):1568–1577.
3. Drazen JM, Harrington D. New biologics for asthma. *N Engl J Med*. 2018;378(26):2533–2534.
4. Mauka LA, Wechsler ME. Selecting the right biologic for your patients with severe asthma. *Ann Allergy Asthma Immunol*. 2018;121(4):406–413.
5. Institute for Clinical and Economic Review. *Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks: Draft Evidence Report*. Boston, MA: Institute for Clinical and Economic Review; 2018.