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Perspective

Keeping risk in context while rethinking the setting of asthma biologics in patient-centered care

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Asthma is a common disease, affecting 8% to 9% of the US population.[1] Among these individuals, 5% to 10% have severe asthma and a more considerable burden of disease, leading to increased costs and impaired quality of life.[2] Despite trigger identification, allergen avoidance, and inhaled corticosteroids, even highly adherent patients fail to achieve adequate asthma control.[2] The use of asthma biologics to treat severe asthma represents an effective strategy to mitigate the risk of more severe asthma-related consequences.[2]

In 2003, omalizumab became the first US Food and Drug Administration (FDA)—approved asthma biologic.[2] Because omalizumab was associated with a low rate of anaphylaxis, medical observation after injection was recommended in the original prescribing information, and a boxed warning was added in 2007. The Omalizumab Joint Task Force also established a series of recommendations regarding length of medical observation after administration.[3] Omalizumab remained the only FDA-approved biologic available for patients with severe asthma until 2015, when mepolizumab was approved for patients with severe eosinophilic asthma. Despite no association with anaphylaxis, the mepolizumab prescribing information also recommended the drug be administered by a health care professional, with postinjection monitoring. In 2019, with approval of a prefilled syringe, home administration of mepolizumab became an option, joining dupilumab, which was approved for home use in 2017. In the past year, benralizumab was also approved for home use in the United States, and in Europe, an omalizumab prefilled syringe is approved for home use from the fourth dose onward.[3] In 2020, the FDA issued a letter to health care professionals that informed them of approval of temporary self-administration of omalizumab during the coronavirus disease 2019 pandemic for select patients with moderate to severe asthma. These collective actions imply safety of home biologic use. For the allergist, this policy would represent a fundamental evolution in the use of asthma biologics, albeit one that may alter in-office revenue streams. For the patient, this policy could offer opportunities to improve access to treatments previously limited by logistics, particularly in the setting of a global pandemic.

Balancing access to home asthma biologic therapy while managing unexpected potential drug-induced anaphylaxis from these agents is difficult.[3] The standard practice has been office-based omalizumab administration and observation, which prioritize additional safety over potential logistical inconvenience and access for many patients who need an asthma biologic. The bigger question is whether the risk of anaphylaxis remains truly great enough to justify such a policy. The care paradigm that has evolved has seemed reasonable and is well accepted, but the danger is that this pathway was created without explicitly

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considering patient values and preferences, while also erecting barriers to care. Such barriers may have inadvertently worsened the financial burdens and risks of severe asthma through how we have mandated biologics be administered. The establishment of this initial care model for omalizumab was unchallenged until dupilumab was approved for home use in 2017.[3]

In 2020, patients have multiple asthma biologic therapy options available in prefilled syringes for home administration, with proper training. Although omalizumab has not yet received permanent FDA approval for home administration in the United States, it is certainly reasonable to anticipate this could occur. One way to consider the overall risk-benefit assessment of such a decision is to evaluate what trade-offs the in-office approach forces us to make, considering practicality of such a decision in light of those trade-offs. Indeed, our group recently published an analysis of home vs in-office omalizumab and mepolizumab administration, taking the unique approach of incorporating travel distance to primary care and allergy offices vs at-home administration. The analysis found a high cost and low relative benefit of supervised administration and that home administration was far more cost-effective.[3] What leveraged this conclusion? Consider which is the riskier activity: driving to the office to receive the injection and be observed or the risk of anaphylaxis (and fatality) from the injection itself? This question may seem like a cheap shot, but it strikes at the very nature of the trade-offs we are asking our patients to make and perhaps our own understanding of risk prioritization and anaphylaxis management. Because anaphylaxis from a biologic is infrequent and the incidence of fatal anaphylaxis being prevented from in-clinic observation is even more rare, an in-clinic observation policy simply forces the patient to accept a potentially greater risk of a fatal automobile accident driving to the clinic (1.18 per 100,000,000 vehicle miles) to have observed administration of a biologic with a very low risk of fatal anaphylaxis. This risk became highly apparent at total driving distances greater than 24 miles. When considering a tertiary care allergy clinic in Northern New England, the mean 1-way travel distance greatly exceeded that of local primary care (49 vs 12 miles). Clinic-observed omalizumab administration was still not cost-effective even if the agent was given at a primary care office 12 miles from home, with costs exceeding $500 million per death prevented. Clinic-observed omalizumab administration would only be cost-effective with anaphylaxis rates of 6.2% and fatality rates of 11.3%.[3] We admit this is an unorthodox approach, but it *drives* home the point eloquently when considering what we are asking of our patients and why.

We all want a safe environment for biologic administration, but adopting a conservative practice has unintended consequences beyond increased motor vehicle accidents. Opportunity costs of repeated clinic travel are high and underappreciated[3] and may likely decrease health equity. In a recent report of omalizumab treatment patterns among patients with asthma in the US Medicare population, patient age, low-income subsidy status, and the fewer number of physician visits for evaluation and management were factors associated with omalizumab therapy discontinuation.[4] In addition, asthma biologic use is relatively infrequent. Inselman et al[1] recently evaluated asthma biologic use in 110 million commercially insured and Medicare Advantage enrollees, reporting that between 2003 and 2018, use of asthma biologics peaked in 2006 at 3 per 1000 individuals with asthma. Factors associated with asthma biologic use included middle age, higher income, commercial insurance, and specialist access. Could you reliably fit such requirements into your schedule, and what would the impact be of the choices you make to do so? Then imagine if you had fewer resources, relied on public transportation, or had poor job flexibility. The saying “Drugs don't work if you don't take them” is true, but it is worse if you cannot provide the best drug to the patient in most need.

Further research is needed to understand whether home access to biologics will improve adherence, given concerns that adherence may worsen without direct supervision, or whether more adverse events will occur because of loss of experienced nursing staff triage before injection (although this could be achieved with telehealth in cases of pressing concern). Given the high annual cost of asthma biologics, incorporating home adherence monitors may help provide valuable information regarding use.[3,4] Regardless, incorporating shared decision making into a conversation about the setting of biologic administration seems highly appropriate.[5]

Across the practice of allergy, asthma, and clinical immunology, we are learning that one size does not fit all. We need to be clinically nimble and willing to tailor and individualize management approaches. Our best intentions will always have unintended consequences, but we must be willing to change previous paradigms of care when data no longer justify their continuation. By partnering with patients and families in a transparent process to share information and evidence, facilitate knowledge translation, and enhance values clarification, we can help our patients optimize their treatment strategies to enhance cost-effective care delivery and provide the right care, in the right place, at the right time, every time.

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