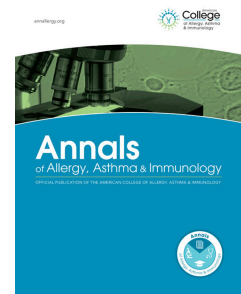


Journal Pre-proof

Perspective: Keeping Risk in Context While Rethinking the Setting of Asthma Biologics in Patient-Centered Care

Matthew Greenhawt, MD, MBA, MSc, Marcus Shaker, MD, MSc



PII: S1081-1206(20)30392-6

DOI: <https://doi.org/10.1016/j.anai.2020.05.029>

Reference: ANAI 3266

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 12 March 2020

Revised Date: 24 May 2020

Accepted Date: 25 May 2020

Please cite this article as: Greenhawt M, Shaker M, Perspective: Keeping Risk in Context While Rethinking the Setting of Asthma Biologics in Patient-Centered Care, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2020.05.029>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Perspective: Keeping Risk in Context While Rethinking the Setting of Asthma Biologics in

Patient-Centered Care

Matthew Greenhawt, MD, MBA, MSc¹

Marcus Shaker, MD, MSc^{2,3}

¹Children's Hospital Colorado, University of Colorado School of Medicine, Section of Allergy and Immunology, Food Challenge and Research Unit, Aurora, CO

²Dartmouth-Hitchcock Medical Center, Section of Allergy and Immunology, Lebanon, NH

³Dartmouth Geisel School of Medicine, Hanover, NH

Corresponding Author:

Matthew Greenhawt, MD, MBA, MSc

Associate Professor of Pediatrics

Section of Allergy/Immunology

Children's Hospital Colorado

13123 E. 16th Ave

Aurora, CO 80045

Phone: 720-777-2575 Fax: 720-777-7247

Funding Source: Agency for Healthcare Research and Quality #5K08HS024599-02 to Dr. Greenhawt

Word count: 1200

Clinical Trials Registration: Not Applicable

Abbreviations: Food and Drug administration (FDA)

Keywords: omalizumab; mepolizumab; asthma; biologic therapy

Conflicts of Interest:

Marcus Shaker has a family member who is CEO of Altrix Medical, and is a member of the Joint Taskforce on Allergy Practice Parameters.

Matthew Greenhawt is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian

Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, Allergenics, Aravax, Glaxo Smith Kline, Protalix, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters.

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

7 In 2003, omalizumab became the first Food and Drug administration (FDA)-approved
8 asthma biologic.(2) Because omalizumab was associated with a low rate of anaphylaxis,
9 medical observation post-injection was recommended in the original prescribing information,
10 and a boxed warning added in 2007. The Omalizumab Joint Task Force also established a series
11 of recommendations regarding length of medical observation post-administration.(3)
12 Omalizumab remained the only FDA approved biologic available for patients with severe
13 asthma until 2015, when mepolizumab was approved for patients with severe eosinophilic
14 asthma. Despite no association with anaphylaxis, the mepolizumab prescribing information
15 also recommended it be administered by a healthcare professional, with post-injection
16 monitoring. In 2019, with approval of a prefilled syringe, home-administration of mepolizumab
17 became an option, joining dupilumab, approved for home use in 2017. In the past year,
18 benralizumab was also approved for home use in the United States, and in Europe an
19 omalizumab pre-filled syringe is approved for home use from the fourth dose onward.(3) In
20 2020, the US Food and Drug Administration issued a letter to healthcare providers allowing for
21 temporary self-administration of omalizumab during the COVID-19 pandemic for select patients
22 with moderate to severe asthma. These collective actions imply safety of home biologic use.

For the allergist, this would represent a fundamental evolution in using asthma biologics, albeit one that may alter in-office revenue streams. For the patient, this 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/observation, which prioritizes additional safety over potential logistical inconvenience and access for many patients who needed an asthma biologic. The bigger question is if the risk of anaphylaxis remains truly great enough to justify such 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 considering patient values and preferences, while also erecting barriers to care. Such barriers may have inadvertently worsened both 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. While 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 examine 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/mepolizumab administration, taking the unique

approach of incorporating travel distance to primary care and allergy offices versus at home administration. The analysis demonstrated 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 clinic (1.18 per 100,000,000 vehicle miles) to have observed administration of a biologic with a very, very low risk of fatal anaphylaxis. This became highly apparent at total driving distances >24 miles. When considering a tertiary care allergy clinic in Northern New England, the average one-way travel distance greatly exceeded that of local primary care (49 miles vs 12 miles). Clinic-observed omalizumab administration was still not cost-effective even if given at a primary care office 12 miles from home, with costs exceeding \$500 million per death prevented. This 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 discontinuation.(4) In addition, asthma biologic use is relatively infrequent. Inselman and colleagues recently evaluated asthma biologic use in 110 million commercially insured and Medicare Advantage enrollees, reporting that between 2003 and 2018, asthma biologics use peaked in 2006 at 3 per 1000 individuals with asthma.(1) Factors associated with asthma biologic use included middle age, higher income, commercial insurance, and specialist access. Could you, yourself 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 less resources, relied on public transportation, or had poor job flexibility. “Drugs don’t work if you don’t take them” has absolute truth, but it is worse if you cannot provide the best drug to the patient in most need.

Further research is needed to understand if home biologics access will improve adherence, given concerns that adherence may worsen without direct supervision, or if more adverse events will occur attributable to loss of experienced nursing staff triage prior to injection (though this could be achieved with telehealth if there was 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, willing to tailor and individualize

management approaches. Our best intentions will always have unintended consequences, but we must be willing to evolve previous paradigms of care when data no longer justify their continuation. By partnering with patients/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.

References:

1. Inselman JW, Jeffery MM, Maddux JT, Shah ND, Rank MA. Trends and Disparities in Asthma Biologic Use in the United States. *J Allergy Clin Immunol Pract*. 2020;8(2):549-54 e1.
2. Manka LA, Wechsler ME. Selecting the right biologic for your patients with severe asthma. *Ann Allergy Asthma Immunol*. 2018;121(4):406-13.
3. Shaker M, Briggs A, Dbouk A, Dutille E, Oppenheimer J, Greenhawt M. Estimation of Health and Economic Benefits of Clinic Versus Home Administration of Omalizumab and Mepolizumab. *J Allergy Clin Immunol Pract*. 2020;8(2):565-72.
4. Li P, Kavati A, Puckett JT, Jahnke J, Busse P, Hanania NA, et al. Omalizumab Treatment Patterns Among Patients with Asthma in the US Medicare Population. *J Allergy Clin Immunol Pract*. 2020;8(2):507-15 e10.
5. Shaker M, Hsu-Blatman K, E MA. Engaging Patient Partners In State of the Art Allergy Care: Finding Balance When Discussing Risk. *Ann Allergy Asthma Immunol*. 2020, (2020), doi: <https://doi.org/10.1016/j.anai.2020.01.029>