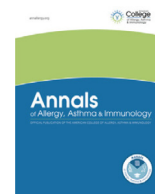




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Editorial

Biologic therapies in atopic diseases

How far have we come?



Our understanding of the role of type 2 inflammation in atopic disorders has made tremendous gains over the past 2 decades. Type 2 (interleukin [IL]-4, IL-5, and IL-13) and epithelial (thymic stromal lymphopoietin [TSLP], IL-25, and IL-33) cytokines and Janus kinases (JAK) have been found to be important therapeutic targets in some or all the atopic diseases including asthma, nasal polyposis, atopic dermatitis, and eosinophilic esophagitis.¹ Whereas type 2 biology seems to be responsible for disease activity in most patients with these disorders, a subgroup of patients do not have an elevation of biomarkers suggestive of type 2 inflammation, and the mechanisms of their disease are often uncertain. The collection of articles in this issue of the *Annals* explores these disease states and presents summaries of currently recommended treatments along with therapies that may be effective in the future.

Chupp et al² begin our issue with a review of the long-term efficacy and safety of biologic medications that are currently approved for uncontrolled asthma. Experience with these medications began nearly 2 decades ago with the approval of omalizumab for allergic asthma. Since that time, monoclonal antibodies (MAbs) that bind to IL-4, IL-5, IL-4 or IL-5 receptors, and most recently TSLP, have all been approved for patients with moderate-severe uncontrolled asthma. The Food and Drug Administration (FDA) approval of the anti-TSLP MAb tezepelumab was not limited to any specific asthma phenotype, indicating that it is appropriate for use in patients with both eosinophilic and noneosinophilic asthma. Whereas omalizumab has been associated with rare episodes of anaphylaxis, overall, biologic medications for asthma have had excellent safety records with no indication of increased susceptibility to infection or long-term organ system dysfunction. As the authors point out, these data are reassuring to physicians and patients, particularly because these drugs are used for extended periods.

Whereas the above perspective emphasizes lessons learned from biologic medications which largely treat eosinophilic, or type 2, asthma, Niessen et al³ review potential current and future biologic therapies for noneosinophilic asthma. While there remain major gaps in our understanding of the mechanisms involved in noneosinophilic airways disease, the authors highlight a number of targets with potential relevance to low type 2 asthma, including epithelial cytokines (ie, IL-25, IL-33, TSLP), tumor necrosis factor- α , granulocyte-macrophage colony-stimulating factor, IL-1- β , IL-6, IL-17, and IL-23. Whereas trials of tezepelumab included large numbers of patients with noneosinophilic asthma, most previous trials of other agents did not focus on this phenotype, making it difficult to determine their efficacy in these patients. Early-phase results with itepekimab (anti-IL-

33) also indicate possible use in patients with low blood eosinophil counts. Precise treatment of noneosinophilic asthma will require a fuller understanding of disease mechanisms in this pathogenetically diverse group and the development of biomarkers that accurately identify specific targets in individual patients.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is one of the most frequently encountered comorbidities in patients with eosinophilic asthma and contributes significantly to the burden of the disease. As a significant percentage of patients do not respond to medical therapy, sinus surgery is often recommended and may be followed by multiple revisional surgeries in a substantial portion of patients. Our appreciation of the role of type 2 inflammation in CRSwNP, along with therapeutic successes of inhibitors of type 2 cytokines and immunoglobulin E in other disease states, has prompted the investigation of these medications in patients with CRSwNP. The review by Borish et al⁴ summarizes the clinical trials of biologics in CRSwNP, which include dupilumab, omalizumab, mepolizumab, and benralizumab. The first 3 of these medications have received FDA approval for treating CRSwNP or NP alone, whereas data for benralizumab has been submitted to the FDA. The authors highlight the differences in baseline patient characteristics, study design, and outcome measures used in the respective trials. The authors end with an important discussion of the implications of future research in patients with CRSwNP. These issues are of particular relevance as we seek to determine the optimal agent to use in specific patients and design new trials comparing existing drugs and future drug candidates.

Appiah et al⁵ complete our issue by reviewing the evaluation and treatment of patients with atopic dermatitis (AD). The authors note that topical treatment (corticosteroids and calcineurin inhibitors) is most appropriate for most patients with localized skin lesions; new and effective options for mild-moderate disease now include crisaborole 2% ointment, a selective phosphodiesterase-4 inhibitor, and ruxolitinib 1.5% ointment, a JAK1 and JAK2 inhibitor. Patients with more severe, widespread diseases have historically relied on systemic corticosteroids or immunosuppressants, particularly cyclosporine A, which are associated with significant adverse events. Dupilumab, which inhibits functional activities of both IL-4 and IL-13, was the first biologic medication to be approved for AD and has revolutionized our approach to treating severe patients. MAbs that bind to IL-13 alone which have exhibited efficacy in moderate-severe AD include tralokinumab (recently approved by the FDA) and lebrikizumab (in phase 3 trials). The anti-IL-31 MAb nemolizumab is in late-stage development and has been found to significantly reduce pruritus but not other signs or symptoms of AD. Whereas inhibition of type 2 cytokines has proven beneficial in many patients with AD, some patients do not respond adequately. Two oral inhibitors of JAKs, upadacitinib and abrocitinib, are highly efficacious in AD and have been approved in moderate-

Disclosures: Research funding - Amgen, AstraZeneca, Novartis, Optinose Regeneron, Sanofi; Speakers bureau - AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi; Advisory boards - AstraZeneca, Novartis, Regeneron, Sanofi.

Funding: The author has no funding sources to report.

<https://doi.org/10.1016/j.anai.2022.06.002>

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severe AD; baricitinib is currently in development for this indication. Deciding which agent to initiate in a given patient will likely be based on the presence of comorbidities, such as asthma, and the potential for adverse events with specific medications.

As highlighted by the articles in this issue of the *Annals*, the identification of key molecular targets involved in atopic diseases has led to the development of specific treatments with increasingly high levels of efficacy and safety. Future studies should provide new and useful information regarding the optimal utilization of these medications in our patients who have these chronic diseases.

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