

Targeted therapy for allergic diseases: At the intersection of cutting-edge science and clinical practice

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The seminal work of Köhler and Milstein,¹ which led to a Nobel Prize in 1984, ushered in a new era of biologic therapy. In the years since, we have witnessed the development of targeted therapies for a wide spectrum of diseases. Some biologics have revolutionized the treatment of certain diseases (eg, anakinra in patients with neonatal-onset multisystem inflammatory disease), whereas others remain innovative therapies in search of the right patient. In this issue of the *Journal*, we have timely reviews discussing the use of biologics in patients with asthma and allergic diseases, food allergy, and inflammatory skin diseases. Although each of these articles provides an overview of a distinct allergic disease, there is some overlap, which serves to reinforce the concept that allergic diseases are part of a spectrum of systemic immunologic diseases.

Fajt and Wenzel² present a comprehensive compendium of the biologics that have been studied in asthma and allergic diseases. They define important genetic and pathophysiologic concepts that have allowed for development of targeted therapies. Fig 1 in their review illustrates the complexity of the diseases that we treat, highlighting some of the key cells and pathways involved in asthma and allergic diseases, as well as therapeutic targets. They also stress the need to identify unique biomarkers to help clinicians with treatment choices in pursuit of personalized medical care, which increasingly is tied to economic constraints. Their detailed tables summarize the use of biologics in double-blind, placebo-controlled trials in asthma and allergic diseases to facilitate evidence-based decisions. Future studies will need to build on our current knowledge and address important gaps, such as developing specific treatments that reach beyond T_H2 immune characteristics and are designed for unique disease endotypes that will emerge from a better understanding of disease mechanisms and their relationship to disease triggers and duration of illness.

Bauer et al³ provide an informative review of IgE-mediated food allergy, addressing mechanisms of allergy and therapeutic

implications. Although the National Institutes of Health has recognized the increasing importance of food allergy,⁴ clinicians are all too aware that current management guidelines are limited to allergen avoidance and symptomatic treatment of acute reactions.⁵ Although some clinicians have introduced oral and sublingual allergen immunotherapy for food allergy into their practices, this approach needs significant further investigation before it can be recommended for routine clinical practice.^{6,7} A recent report in the *Journal* was encouraging in that approximately 50% of subjects showed sustained unresponsiveness after peanut oral immunotherapy,⁸ but for the most part, tolerance remains elusive, and novel approaches based on mechanistic insights need to be pursued. Indeed, optimization of immunotherapy will likely need to be done in combination with other targeted therapies that reduce the risk of anaphylactic reactions to allergens or enhance tolerance.

Finally, Noda et al⁹ discuss the use of biologics in patients with inflammatory skin diseases. They compare and contrast psoriasis and atopic dermatitis (AD), elucidating common and polarized immune abnormalities. The emergence of a more complex understanding of immune dysregulation in patients with psoriasis from a T_H1-dominant disease to a T_H1-T_H17/T_H22-skewed disease has led to a change in the treatment paradigm for psoriasis by using selective biologics against dysregulated cytokines and receptors. Although readers of the *Journal* are likely more interested in treatment directed at AD, insights into disease pathways in patients with psoriasis might provide valuable lessons in translational medicine for the development of therapeutic agents for AD.

Although lagging considerably behind psoriasis, a number of biologics are being investigated currently in patients with AD. Among the more exciting clinical advances was the report of successful trials in adult patients with moderate-to-severe AD using dupilumab, a human mAb directed at IL-4 receptor α .¹⁰ This study confirms the importance of T_H2 pathway activation in the majority of patients with moderate-to-severe AD. Subsequently, Hamilton et al¹¹ presented elegantly performed studies describing an AD “signature” or transcriptome that was improved by this novel biologic therapy. In practice, clinicians typically assess response to treatment of patients with AD based on the patient’s or caregiver’s subjective self-assessment and the clinician’s “global assessment.” Although SCORAD and the Eczema Area and Severity Index were both developed to assist the clinician, these scoring tools have been largely relegated to clinical research trials. Hamilton et al¹¹ advance the approach to evaluating the efficacy of this biologic by comparing clinical benefit (as assessed by using Eczema Area and Severity Index) with molecular changes noted in lesional and nonlesional skin in a subgroup of patients from one of the clinical trials. Although the number of patients studied in such a comprehensive manner was of necessity small, these patients might be representative of the larger cohort. However, before we can refer to a molecular

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“AD signature,” we would need to study a much larger cross-section of the population with AD and compare patients of different ages, ethnic groups, symptom severities, and clinical phenotypes. Nevertheless, the authors were able to identify consistently upregulated and downregulated genes involved in predominantly immune and, to a lesser extent, skin barrier abnormalities. Over a relatively short period of time, they showed important molecular changes in a dose-dependent manner and observed lesional skin reverting to a nonlesional “epidermal phenotype.”

It is important for the clinician to recognize that normal-appearing skin in patients with AD is not normal and in fact has more in common with acutely involved skin than it does with normal non-AD skin.¹²

Another molecular concept with important therapeutic implications for clinicians to be familiar with is that of the residual genomic signature of AD.¹² Even with systemic therapies, such as cyclosporine, patients with AD are prone to relapse because of these residual abnormalities. “Next-generation” therapeutics will need to address such abnormalities to prevent relapses. Alternatively, combination therapies will be needed to completely eliminate all relevant immune pathways leading to AD and its propensity to relapse. Meanwhile, it would be extremely useful to clinicians caring for patients with recalcitrant AD to see whether molecular signatures could prove discriminatory when assigning patients to a particular treatment or predicting disease relapse.

Readers of the *Journal* are likely aware that a number of original articles describing trials with biologic therapies have been published in the recent past. Perusal of the *Journal*'s table of contents for the previous 2 years identifies citations demonstrating utility of mAb therapy in clinically relevant diseases. Importantly, although most of these studies focus on the therapeutic aspects of these novel therapies, several advance our understanding of the mechanisms of disease with insights gained from targeting unique pathways using this class of therapeutics. The majority of these studies address asthma, a significant global health problem and one in which a subgroup of patients have suboptimal response to standard therapies. Benralizumab, a humanized mAb targeting IL-5 receptor α , was shown to reduce eosinophil counts in sputum, airway mucosa, and submucosa, as well as suppressing bone marrow and peripheral eosinophils, in adults with eosinophilic asthma.¹³ However, additional studies are needed to demonstrate consistent clinical benefit. The failure of GSK679586, a humanized anti-IL-13 mAb, to benefit patients with severe asthma refractory to maximally indicated doses of inhaled steroids illustrates the need to better characterize which patients to select for a specific therapy.¹⁴ A number of studies have previously reported on mepolizumab in asthmatic patients,^{2,15} describing changes occurring after patients completed a 12-month trial. The quick increase in eosinophil counts and recurrence of asthma exacerbations point to the need for continued suppression of eosinophil-driven inflammation.

Thymic stromal lymphopoietin (TSLP) has been identified as a key driver of allergic inflammation and represents a potential important therapeutic target in asthmatic patients. Cheng et al¹⁶ used a cynomolgus monkey model of asthma to study allergic lung inflammation using gene expression profiling and TSLP receptor blockade with an mAb against human TSLP receptor. Animals treated with the mAb showed reduced numbers of eosinophils and IL-13 cytokine levels in bronchoalveolar lavage fluid, as well as reduced airway resistance in response to allergen

challenge, compared with vehicle-treated animals. Expression profiling of bronchoalveolar lavage fluid cells collected before and after challenge identified a group of genes upregulated by allergen challenge that overlapped with genes upregulated in dendritic cells (DCs) when the latter were stimulated *in vitro* by TSLP (ie, a TSLP-DC gene signature). The number of genes differentially expressed in response to allergen challenge was reduced in mAb- versus vehicle-treated animals. Importantly, the TSLP-DC gene signature was also significantly reduced in the mAb-treated animals. The TSLP-DC signature could potentially serve as a novel clinical marker in induced sputum in asthmatic patients in trials targeting TSLP.

Omalizumab continues to be evaluated in patients with allergic moderate-to-severe asthma whose symptoms were not adequately controlled with inhaled corticosteroids. In a subgroup analysis Busse et al¹⁷ found that eosinophil counts could be a useful biomarker in identifying patients with normal lung function but ongoing symptoms who might benefit from this biologic. Given the concerns raised by rare reports of malignancy in patients treated with omalizumab, there were reassuring results from a prospective observational cohort study (EXCELS) in patients 12 years or older with moderate-to-severe allergic asthma, which found no association of omalizumab therapy with increased risk for malignancy over a median follow-up period of approximately 5 years.¹⁸ Of interest, omalizumab was found to be effective in the treatment of nasal polyps in both allergic and nonallergic patients with concomitant asthma.¹⁹ The benefit in nonallergic patients suggests possible effect on local tissue IgE levels. For clinicians who know all too well that patients with chronic rhinosinusitis with nasal polyps present a therapeutic challenge, omalizumab therapy might prove to be a useful addition to the treatment armamentarium.

One of the most eagerly awaited therapeutic advances in the recent past was the US Food and Drug Administration's approval of omalizumab for chronic urticaria in patients in whom standard therapy failed. Kaplan et al²⁰ reported the results from a phase III study in patients with chronic urticaria randomized to monthly injections of either 300 mg of omalizumab or placebo for 6 months followed by a 16-week observation period with a number of safety and efficacy end points evaluated at weeks 12 and 24. The safety profile was consistent with that seen in patients with allergic asthma treated with omalizumab. Omalizumab was well tolerated and reduced the signs and symptoms of chronic urticaria in patients whose symptoms were not controlled by high-dose antihistamines combined with H₂-blockers, leukotriene receptor antagonists, or both. Somewhat disappointing, although not completely unexpected, after discontinuation of omalizumab, symptoms were reported to recur over a period of approximately 10 weeks to levels similar to those observed with placebo. In another study adding to the practical utility of omalizumab, Schneider et al²¹ showed that omalizumab added before and during oral peanut desensitization allowed high-risk children with peanut allergy to be rapidly desensitized.

Mepolizumab, a fully humanized mAb specific for human IL-5, has previously been shown to be safe and effective as a corticosteroid-sparing agent in adults with FIP1L1/PDGFRA-negative hypereosinophilic syndromes.² Given the chronic nature of hypereosinophilic syndromes, Roufosse et al²² demonstrated the safety of this biologic when administered for a mean of 251 weeks. Mepolizumab has also been reported to reduce eosinophil counts in both adults and children with eosinophilic esophagitis, a disease with an increasing prevalence and a considerable

management challenge to clinicians.³ In addition, several studies published in the *Journal* have pointed to a role for mast cells and identified a specific mast cell gene signature in both pediatric and adult patients with eosinophilic esophagitis. Otani et al²³ investigated the effects of mepolizumab on esophageal mast cells and showed that the majority of patients had decreased numbers of mast cells after treatment with anti-IL-5. Because esophageal eosinophils were found to be the primary source of the mast cell growth factor IL-9 and mast cells in turn can activate eosinophils, the authors suggest a complex dynamic between eosinophils, mast cells, and IL-9 in patients with eosinophilic esophagitis that requires further elucidation.

Readers of the *Journal* can anticipate many more translational research articles with clinical implications and likely breakthroughs in the area of biologic therapy in the not too distant future. This makes for an exciting time in the field of allergic disorders for both translational research and patient management.

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