

Are Biotherapeutics Revolutionizing Treatment of “Allergic” Diseases?



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What do hypereosinophilic syndromes (HES), chronic sinusitis with nasal polyps, chronic urticaria, and severe atopic dermatitis have in common? They are in the purview of allergy/immunology diseases, frequently do not have identifiable causes, are persistent, and, perhaps most importantly to both the health care provider and affected patient, are largely unresponsive to currently considered treatments. Thus, they provide a major unmet therapeutic need for the allergy/immunology community.

In this issue of *JACI: In Practice*, this unmet clinical need is addressed with new information on how the use of biotherapeutics is leading to more effective approaches to treatment (Figure 1). These evolving changes in treatment with biotherapeutics have come, principally, from major advances in our understanding of immune-associated diseases and a more precise identification of their underlying immunological mechanisms.¹ With this new knowledge, key molecules, inflammatory pathways, and regulatory processes have been discovered as well as clues to potential therapeutic targets. With this development and subsequent regulatory approval of biotherapeutics, we have begun to see a clinical and therapeutic revolution in the treatment of atopic dermatitis, chronic urticaria, chronic sinusitis with polyps, and HES as these agents are replacing the existing broad spectrum therapeutic approaches, often associated with major risks for significant adverse events.

The application of biotherapeutics, or biologics, to allergic diseases has largely come from studies in asthma.² Collectively, such research efforts have provided an expanded picture into the complex immune networks and mechanisms that contribute to airway inflammation, particularly the Type (T)2-type inflammatory profile and its associated clinical phenotypes and endotypes. Biologics are now available to modify T2 inflammation by blocking IgE and cytokines like IL-4, IL-5, and IL-13. The clinical use of omalizumab, mepolizumab, and reslizumab

in asthma has not only provided effective treatment options for patients with severe asthma but also lessons on disease mechanisms.

The application of biotherapeutics to chronic urticaria, chronic rhinosinusitis with polyps, severe atopic dermatitis, and HES is another example of how biologics are leading to major breakthroughs in patient care. Although each of these diseases has distinctive immunopathobiology, striking benefit has followed the use of T2-type antagonists in well-defined patient populations. In some situations, the beneficial results were anticipated, that is, anti-IL-5 treatment for eosinophilic asthma,³⁻⁵ yet, in others, that is, chronic idiopathic urticaria, the striking benefit with omalizumab was to many surprising as classical IgE-dependent causes of chronic urticaria are an exception rather than the rule.⁶ The composite message from these 4 articles is that a rational and informed application of biologics may not only be a safe and effective therapeutic option in these diseases, but their use can also overcome the ineffectiveness of current treatments and minimize the risk for side effects found with present approaches.

In chronic idiopathic urticaria, antihistamines are first-line treatment. However, when antihistamines alone are not effective, which is often the case, treatment choices for the next level of care are not strongly evidence based and include systemic corticosteroids, cyclosporine, and others. Treatment effectiveness with these medications is unpredictable, but their potential for side effects is frequent. As detailed by Joshi and Khan,⁷ omalizumab offers an effective alternative. For many, the benefit with omalizumab is rapid and dramatic, but not “curative” as relapses commonly occur when omalizumab is withdrawn. The effectiveness of omalizumab is surprising as classical allergic reactions, that is, IgE-allergen interactions, are infrequently identified. The mechanisms of action of omalizumab in chronic urticaria are not established but point to an IgE response element. Data would suggest that when antihistamines are not beneficial in chronic idiopathic urticaria, omalizumab has become the next line of treatment.

Atopic dermatitis is an equally complex immune dysfunctional response of the skin that includes T2 pathways as well as Th1, Th22, and IL-17/IL-23 and a major defect in the epithelial barrier.⁸ As discussed by Boguniewicz,⁹ the use of the IL-4/IL-13 pathway antagonist, dupilumab, has led to striking improvements in chronic atopic dermatitis in adults. Microarray analyses of skin biopsies have identified numerous genetic pathways that are dysregulated in both involved and noninvolved skin sites.¹⁰ When treatment with dupilumab leads to control of atopic dermatitis, these dysregulated pathways revert to “normal” indicating that a clinically effective treatment may also correct the defects in immune pathways of this disease. The use of biotherapeutics in severe atopic dermatitis is another example of precision medicine with minimal side effects and an avoidance

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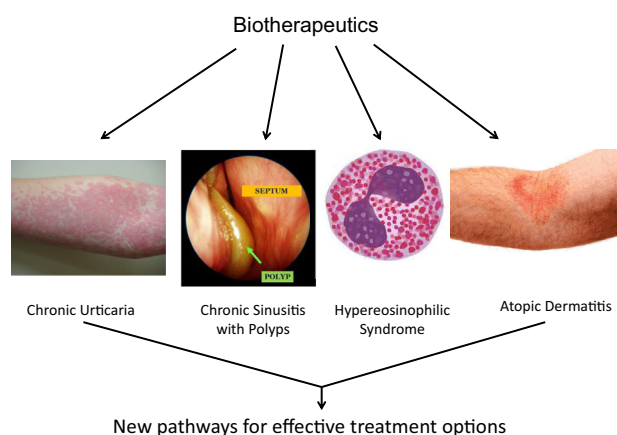


FIGURE 1. Biotherapeutics in the treatment of allergic/immunologic diseases.

of risks with antibiotics, systemic corticosteroids, and cytotoxic agents. Dupilumab is approved for use in adult patients with atopic dermatitis. Studies in children are underway.

Bachert et al review the data on the use of biologics in chronic rhinosinusitis with nasal polyps (CRSwNP).¹¹ CRSwNP has high morbidity, significant health care costs, a frequent use of surgery, and often the coexistence of uncontrolled asthma. Treatment benefit in CRSwNP has been seen with omalizumab, mepolizumab, and now dupilumab. A published pilot study in CRSwNP with dupilumab has found a reduction in polyp size, improved asthma control, and diminished sinusitis.¹² The results of large trials will determine if these biologics will become “treatments” of choice for patients with recurrent CRSwNP.

Kuang and Klion¹³ have had extensive experience with HES at the National Institutes of Health and discuss the subsets of HES and their treatment. Of interest has been their other experiences of treatment of patients with platelet-derived growth factor mutation-negative HES. Currently, systemic corticosteroids, hydroxyurea, and IFN- α offer benefit in HES, but either side effects or loss of effectiveness often occurs. IL-5 is a key cytokine in eosinophil production and inflammatory biology. The experience of anti-IL-5 monoclonal antibodies, particularly mepolizumab, in HES¹⁴ and now chronic granulomatosis with polyangiitis (previously known as Churg Strauss) has shown long-term disease regulation and reduction in the need for systemic corticosteroids.¹⁵ Other eosinophil directed biotherapeutics are emerging, and with these approaches has come more predictable responsiveness and a reduced risk for side effects from the long-term use of systemic corticosteroids.

Why is there such interest in biotherapeutics in allergic and immunologic diseases? The enthusiasm for these new therapeutics can be seen from the expanding experience in asthma, which at present is largely focused on T2-type pathway monoclonal antibodies. For patients with severe asthma, well-identified patient populations are achieving disease control with biologics when even large doses of standard treatment lack effectiveness. Second, monoclonal antibodies provide disease pathway “knockouts” and from these observations have come the identification that IgE and eosinophils play key roles in asthma exacerbations, but more limited effects on airflow obstruction—not exactly the original

concept on how these pathway blockades would work. Third, in the use of monoclonal antibodies, the safety profile continues to be reassuring. Finally, the experience and direction from asthma is now extending to other diseases in the broad area of allergic and immunologic diseases as detailed in this issue.

From my perspective, the emergence and application of biotherapeutics is opening a new era of treatment for patients with chronic, severe diseases found in our specialty. The use of biotherapeutics for these diseases is immunologically rational, targets pathways expressed in the resulting immunopathophysiology, and, consequently, promises greater precision and effectiveness. For this perspective to be achieved, many steps remain to be taken, but research is addressing these questions. For our specialty to move into this new era of treatment, expertise in selecting the most effective biotherapeutic for individual patients or patient groups is needed. Also, it will be necessary for caregivers to have sophisticated knowledge on the various biotherapeutics, their mechanisms of action, and eventual treatment paradigms. The articles in this issue of *JACI: In Practice* have begun to lay the needed groundwork for this journey to continue to move forward.

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