



Perspective

Biologics in allergic and immunologic diseases Promises and challenges in the era of personalized medicine

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Introduction

The discovery of new biologics offers promise in the treatment of chronic, refractory allergic and immunologic conditions. Emerging biologic therapies have ushered in an era of personalized medicine, also referred to as precision medicine, whereby physicians can choose targeted therapies based on disease phenotype. Undoubtedly, this has been a significant advance for patients with conditions such as severe asthma and offers hope for successful management of other allergic and immunologic conditions, such as severe atopic dermatitis and refractory chronic urticaria. Nonetheless, many questions and challenges exist when using biologics in clinical practice, beyond appropriate patient selection, including those surrounding agent selection and cost.

Biologic drugs are products, isolated from natural substances by biotechnology methods and other cutting-edge technologies, that target specific disease pathways. Such drugs have been at the forefront of recent biomedical research, providing treatment options for difficult-to-manage diseases in the fields of rheumatology, oncology, gastroenterology, and others, oftentimes with a favorable toxicity profile compared with the drugs available in the past.

When considering the use of biologic agents in asthma, chronic urticaria, or atopic dermatitis, clinicians are faced with added treatment considerations. These considerations include identifying patient phenotypes using biomarkers, selection of the targeted biologic, and consideration of adverse effects, costs, and alternative therapies.

Biologics for Asthma

Through cluster analysis, molecular phenotyping, and other study techniques, our knowledge of the mechanisms of severe asthma has increased significantly during the past decade. New understanding is emerging regarding the mechanisms of asthma phenotypes, biomarkers, and response to targeted therapy. The concept of type 2 (T₂) asthma vs non-T₂ asthma has emerged as a way to broadly categorize asthma. Asthma with T₂ inflammation involves prominent expression of the T_H2 cytokines interleukin (IL) 4, IL-5, and IL-13. T₂ innate lymphoid (ILC-2) cells, epithelial cells, and others have also emerged as key players in T₂ pathogenesis. T₂ inflammation is linked to increases in blood eosinophils, lung eosinophils, and exhaled nitric oxide, as well as other potential biomarkers under investigation, such as periostin and thymus and activation-regulated chemokine.

T₂ asthma likely encompasses many molecular phenotypes of asthma, which may involve the aforementioned inflammatory pathways in varied ways. Non-T₂ asthma includes patients who lack evidence of T₂ inflammation. Much less is known about the pathobiology of this phenotype, which may represent a neutrophilic or paucicellular process and is often associated with difficult-to-control asthma.

Asthma phenotypes are complex, and there are subphenotypes of disease, overlap among phenotypes, and the potential for instability of phenotypes over time. As our understanding of asthma phenotypes and integral cellular players and inflammatory cytokines increases, new treatment targets will continue to emerge. As such, agent choice will become more focused and complex.

As has been consistently reported, patients with uncontrolled asthma have greater health care use. These patients have an increase in hospitalizations, emergency department visits, history of intubation, and frequent use of steroid bursts and costly polypharmacy.¹ Biologics offer promise in improving clinical outcomes in these patients. Clinical trials of targeted monoclonal antibodies to IgE, IL-5, IL-5 receptor, IL-4 receptor α , and thymic

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stromal lymphopoietin (TSLP) have shown efficacy in reducing asthma exacerbations and, in some cases, small improvements in lung function.

Biologics currently available for asthma target IgE (omalizumab) and eosinophils (anti-IL-5 biologics). Omalizumab was the first biologic approved for the treatment of allergic asthma (in 2003) and inhibits IgE, leading to decreased expression of IgE receptors on mast cells. The main biomarker used in clinical practice to predict favorable response to omalizumab is serum IgE and blood or skin test positivity for a perennial allergen that is clinically implicated as an asthma trigger for the patient. However, more recent studies report that other T2 biomarkers (such as fractional exhaled nitric oxide, blood eosinophils, and serum periostin levels) or a composite of multiple biomarkers may be better indicators of efficacy.²

IL-5 regulates the proliferation, maturation, and effector functions of eosinophils and is therefore an important therapeutic target. Speaking to this, high blood eosinophil count correlates with asthma exacerbations.³ US Food and Drug Administration (FDA)–approved biologics that target the IL-5 pathway include mepolizumab and reslizumab (for patients with blood eosinophil counts $>150/\mu\text{L}$ and $400/\mu\text{L}$, respectively) and benralizumab.^{4–10} Benralizumab is a biologic that binds the IL-5 receptor α on eosinophils and basophils (unlike the other 2, which block IL-5); it was recently approved by the FDA for the treatment of patients 12 years and older with severe asthma and an eosinophilic phenotype. Clinical trials of anti-IL-5 agents have shown promising results, with a decrease in asthma exacerbation rates and a reduction in oral corticosteroid use.¹¹ For example, one phase 3 trial of 56 weeks of treatment with benralizumab as add-on therapy found a 36% reduction in their primary end point of annual exacerbation rates (4-week dosing) and a 28% reduction (8-week dosing) compared with placebo; another phase 3 trial with 48 weeks of benralizumab dosing found 45% and 51% reductions for the 4-week dosing and 8-week dosing regimens respectively, compared with placebo.^{12,13} A meta-analysis of anti-IL-5 agents by Wang et al¹⁴ of 13 trials (6,072 participants) reporting on asthma exacerbations found a significant reduction in exacerbations compared to placebo (relative risk, 0.66; 95% confidence interval, 0.59–0.73; $P < .001$). Other T2-targeted biologics are under investigation, such as those against IL-4, IL-13, and others. Dupilumab is a fully humanized anti-IL-4 receptor α antibody, essentially depleting both IL-4 and IL-13. It is approved for use in atopic dermatitis and shows promise as an emerging therapy for the treatment of asthma.¹⁵ Biologics that specifically target the IL-13 pathway are being studied as well. Lastly, a recent proof-of-concept trial using an anti-TSLP antibody by Corren et al¹⁶ has shown promising results. TSLP is an epithelial factor that may promote T2 inflammation. Anti-TSLP (tezepelumab) decreased exacerbations and symptoms and improved forced expiratory volume in 1 second in a recent phase 2 study. Epithelial cells secrete TSLP, highlighting the important role of this cell, perhaps upstream of other targets.

Although numerous treatment options are emerging for T2 asthma, there are still few targeted therapy options for patients with a lack of T2 inflammation. As mentioned earlier, non-T2 asthma is defined as the apparent absence of T2 biomarkers and is much less defined than T2 asthma. It is a phenotype associated with poor corticosteroid response and neutrophilic or paucicellular inflammation and can represent some of our most challenging patients. Other factors may influence this phenotype, including obesity, infection, and smoking. There are currently no biologics available that specifically target non-T2 asthma. The limited trials published to date that target this population have not shown favorable results. It is yet unclear, but some clinical trials, such as a phase 2 dupilumab trial, are beginning to show that T2 targeted drugs may have some efficacy, even for those patients without elevations of T2 biomarkers.¹⁷

Biologics for Nasal Polyposis

Chronic rhinosinusitis with nasal polyposis is a commonly seen comorbidity that can not only aggravate asthma but also prove refractory to medical therapy and require multiple surgical interventions. Newer treatment options should substantially benefit this group of patients, who face frequent operations, steroid use, and recurrent infections. Phenotyping of chronic rhinosinusitis has identified numerous phenotypes. Chronic rhinosinusitis with nasal polyposis is mostly an eosinophilic process, raising the question of whether emerging biologics may help treat this disease. Data indicate that biologics, such as dupilumab and mepolizumab, may be useful in the treatment of nasal polyposis.^{18,19} A trial using mepolizumab found that patients with severe nasal polyposis in the treatment arm were less likely to need sinus surgery than those in the placebo arm. Further study of therapeutic response, optimal dosing, and biomarkers is warranted.

Biologics for Urticaria

Omalizumab has been approved for use in patients with refractory chronic idiopathic urticaria in whom high doses of antihistamines have failed since 2014. Clinical trials of omalizumab in patients with poorly controlled chronic urticaria despite treatment with existing medications demonstrated significant reductions in itch severity score and improvements in urticaria activity from baseline, weekly number of hives, and Dermatology Life Quality Index.²⁰ A phase 3 trial of omalizumab, 300 mg monthly, in patients with refractory chronic urticaria found that, at 12 weeks, 34% of patients in the treatment arm were completely itch and hive free compared with 5% in the placebo arm.²¹

Interestingly, there is no biomarker proven to correlate with treatment response to omalizumab in chronic idiopathic urticaria, as there is in asthma. Given that chronic urticaria spontaneously resolves in many cases, most clinicians will attempt to discontinue treatment after some period of disease inactivity; however, there are no firm guidelines on how to do this.

Biologics for Atopic Dermatitis

Until recently, the treatment of atopic dermatitis largely consisted of topical steroids, calcineurin inhibitors, and off-label use of oral medications. Now with the approval of dupilumab, patients with moderate-to-severe atopic dermatitis have a biologic treatment option. Two phase 3 trials of identical design (Study of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis 1 and 2) randomly assigned individuals in a 1:1:1 ratio to receive subcutaneous dupilumab weekly, placebo weekly, or dupilumab alternating with placebo weekly.²² The trial demonstrated that treatment with dupilumab improved signs and symptoms of atopic dermatitis, pruritus, symptoms of anxiety and depression, and quality of life. The primary outcome (proportion of patients with a score of 0 or 1 on the Investigator's Global Assessment and reduction of ≥ 2 points in that score from baseline) was met in 36% to 38% of patients receiving dupilumab weekly or every 2 weeks compared with 10% in the placebo arm ($P < 0.001$). The rates of conjunctivitis were noted to be higher in the dupilumab groups compared with the placebo groups.

It is likely that allergic skin diseases will see an expansion in biologic treatment options in the decade to come. It will be important to better understand the underlying mechanisms of phenotypes of disease, following the trend seen in asthma, as discussed in a recent publication by Bieber et al.²³ Steps are already being taken in this direction, as evidenced by a recent publication by Thijs et al.²⁴ This study used cluster analysis and identified 4 distinct phenotypes of

atopic dermatitis: severe disease, T2 high; mild disease, T2 high; severe disease, T2 low; and mild disease, T2 low. Further explorations of biologic-responsive phenotypes may allow us to maximize likelihood of efficacy when using these costly medications.

Use of Biologics: Many Unanswered Questions

What is My Patient's Phenotype?

Choosing the right biologic agent involves identification of a patient's clinical phenotype using noninvasive biomarkers. Although a trial-and-error approach to using asthma medications in the past may have been standard of care (eg, choosing between a long-acting β -agonist and a leukotriene modifier as an add-on therapy to inhaled corticosteroids), with these expensive biologics, it will be critical to identify biomarkers and find ways to use these drugs judiciously in patients with the highest likelihood of efficacy. Eosinophils seem to be a good biomarker for anti-IL-5 therapy. Enthusiasm is waning for IgE as the sole predictor of treatment response to omalizumab. As of yet, the "best" biomarkers for proposed phenotypes are not known and may in fact be a composite of biomarkers. Phenotypes are best studied in asthma to date, but we may see a similar explosion of study in atopic dermatitis as noted above.²⁴

Which Biologic Should I Choose?

Head-to-head clinical trials would help us answer this question; however, such trials are expensive and would require large numbers of patients and therefore have not been performed. Clinicians are still left with multiple choices and little guidance on treatment selection. This is becoming more evident as more drugs that target the same or a similar pathway become available. If we are able to subphenotype asthma with greater precision in the future, it is hoped that we can better use specific agents for a particular patient and in so doing see the dream of personalized medicine be achieved.

Should I Use a Biologic Alone or as an Add-on to Other Therapies?

There are no data to date regarding combinatorial therapy with 2 biologics. It is possible that patients may have multiple pathways involved, and medications against upstream targets (such as anti-TSLP) may prove useful in such patients. Treatment with biologics reduces the need for oral steroids. The optimal use of biologics in conjunction with standard first-line therapies is not known but is being investigated.

When Should Treatment Response be Evaluated?

For omalizumab, data suggest that 4 months is the appropriate time to evaluate whether a patient is a responder or nonresponder, using a global physician evaluation.²⁵ However, for the new anti-IL-5 biologics no such stopping rules exist that are supported by strong data. A recent publication in the *European Respiratory Journal* by Bousquet et al²⁶ proposes 12 months as the time to assess treatment response for mepolizumab, for example, using outcomes of exacerbation rate and reduction in steroid use. Further research regarding the optimal time to assess treatment response with biologics is needed, as well as further investigation of the best clinical outcome measures to track in a real-world setting. From a cost perspective, it is important that we identify nonresponders early. The trials of newer biologic agents for asthma have been of a short treatment period, with limited information on duration of treatment and sustained response. Given that chronic idiopathic urticaria frequently spontaneously remits, most clinicians will attempt to discontinue

omalizumab treatment for this condition after a period of good symptom control.

What are the Adverse Effects?

Overall published studies suggest a favorable medication toxicity profile. That said, long-term use of the newer biologics has not been studied, except for omalizumab in the treatment of allergic asthma.²⁷ Both omalizumab and reslizumab have black box warnings, and individuals should be made aware of a small risk of anaphylaxis. There are also concerns about compromised defenses against parasitic infections. Dupilumab had higher rates of conjunctivitis than placebo, with an unclear mechanism of this.

Biologics and High Value Care

An important consideration in treatment choice is cost. Biologics are very expensive medications. That said, studies have found significant reductions in asthma exacerbations, emergency department visits, and hospitalizations, all of which are the most expensive clinical outcomes. A recent real-world study in the *Annals* (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) reported variability in severity and biomarker profiles of patients chosen to begin treatment with omalizumab.²⁸ This finding highlights the importance of understanding biomarkers and their optimal use to help us identify patients most likely to respond to a specific target biologic. Limiting use of these expensive medications to responders should translate to improved cost-effectiveness. In a study by Whittington et al²⁹ that evaluated the cost-effectiveness of adding mepolizumab to standard of care for severe uncontrolled asthma, the authors found that mepolizumab provided clinical benefits but exceeded commonly used thresholds that are used in evaluating cost-effectiveness. This finding could be improved on by a significant reduction in medication cost or by limiting use of mepolizumab to likely responders. Likewise, as previously mentioned, from a cost perspective it will be important to obtain data on when to discontinue use of these agents in nonresponders.

In addition, these medications should not be used to compensate for lack of adherence with standard accepted therapies (ie, inhaled corticosteroids for asthma). A recent publication by Barnes³⁰ in *Chest* astutely notes that nonadherence with inhaled corticosteroid therapy is high in patients with asthma and that use of these biologics as a substitute for regular inhaled corticosteroid therapy will impose an "enormous financial burden." This burden would be seen on a societal level and reinforces the importance of better adherence monitoring important in the future. Government, regulatory, and insurance companies are increasingly demanding high-value care in which practices can show that they are choosing the best and most cost-effective treatments for their patients. Furthermore, with improved manufacturing capabilities and the development of biosimilar and biobetter agents, it is hoped that someday these agents could be delivered at a more reasonable cost. Decreased frequency of administration (eg, dosing of biologics at ≥ 8 -week intervals) or intermittent use (such as preseasonal use of omalizumab) may further improve cost-efficacy.³¹ Such approaches require further investigation but could also help with our present concerns of failure due to nonadherence.

Conclusion

Biologics offer a novel and effective treatment option for asthma, urticaria, and now atopic dermatitis. Numerous clinical trials have demonstrated their efficacy, mostly with a favorable safety profile.

Although this represents a big step forward, many questions remain about how to optimize use of these medications for our patients. This knowledge may very well unfold as these medications are used in clinical practice. In addition, in all likelihood, new biologics will emerge on the market in the next decade. We will be tasked with not only choosing the right drug for the right patient but also improving outcomes in a cost-effective manner. Given high costs associated with these medications, identifying nonresponders and those with remission of disease early will be important in reducing treatment expense. Fine-tuning our skills in personalized medicine is imperative to achieve this goal, and we must all be prepared to implement this because it will become standard of care.

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