

Future Prospects of Biologic Therapies for Immunologic Diseases



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KEYWORDS

- Asthma • Atopic dermatitis • Biologic • Churg-Strauss syndrome
- Hemophagocytic lymphohistiocytosis • Immune dysregulation • Immunodeficiency
- Mastocytosis

KEY POINTS

- Currently used or in-development biologic therapies have unexplored potential in treating various allergic and immunologic disorders.
- There is a substantial need for newer biologic therapies targeting specific disease pathways.
- Biologic therapies represent not only an innovative approach but also a substantial advance to disease management in the twenty-first century.

INTRODUCTION

Although biologic therapies like insulin have been used for nearly a century, improvements in recombinant technology and production techniques have led to an explosion of biologic therapies over the past 2 decades. Biologic therapies are currently used for

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treating many disease conditions in humans as either an adjunct to conventional therapy or a sole therapeutic intervention. Several of these biologic agents are available on the market in the United States and are approved by the US Food and Drug Administration (FDA) for specific indications.

Outside of approved indications, the use of certain biologics to treat immunologic disease is supported by case series or small studies. In other instances, potential therapeutic benefit may merely be inferred from animal studies or knowledge of the mechanisms of action. The goal of this review is to explore future potential therapeutic use for currently available biologic therapies, based solely on the mechanism of action of the specific agent considered. The pathophysiologic targets and disease states described herein do not represent an exhaustive list. Rather, they represent a selection of potential therapies that may prove useful for the treatment of specific conditions in the near future.

THERAPIES TARGETING CYTOKINES OR CYTOKINE RECEPTORS

Cytokines are soluble low-molecular-weight proteins that mediate communication between immune cells. As such, they are critically linked to the pathophysiology of immunologic disease.¹ Although there is some degree of overlap in the function of certain cytokines, in general, these proteins function in a predefined circuit. That is, release of given cytokine from a specific cell source will trigger a specific effector function by the receiving cell (Table 1). This makes cytokines an attractive target for therapeutic intervention, for neutralization of a particular cytokine may, in theory, abate a specific disease process without causing wholesale immunosuppression.^{1,2}

Tocilizumab: Anti-Interleukin-6 Receptor Antibody

Interleukin-6 (IL-6) and the IL-6 receptor (IL-6R) were discovered by Tadamitsu Kishimoto in Japan in the 1980s. IL-6 binds to and forms a complex with IL-6R and another cell membrane protein, gp130. Formation of this complex results in the activation of the Jak/STAT pathway through gp130. Two forms of the IL-6R subunit can be found—membrane bound (mIL-6R) and soluble (sIL-6R).^{3–5} Membrane anchoring of the IL-6R subunit is not required for signaling, and indeed signaling can occur when IL-6 forms a complex with sIL-6R and gp130. Signaling through soluble receptor is termed trans-signaling and may result in different functional outcomes.^{3,5} Understanding of the role of these molecules in various inflammatory pathways has led to numerous clinical trials with therapeutic agents that interfere with their mechanism of action.

Tocilizumab (Actemra) is a recombinant humanized anti-human IL-6R monoclonal antibody of the immunoglobulin G1 (IgG1) subclass. It is currently approved by the FDA for use in moderate to severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis.

Allergic asthma

IL-6 appears to play a role in allergic asthma. Patients with allergic asthma have high serum levels of sIL-6R at baseline, which is increased approximately 24 hours after an allergen challenge compared with controls.⁶ Allergen-induced airway inflammation, specifically with house dust mite and cockroach, has been shown to induce mixed granulocytic inflammation in the airway of mice.^{7,8} One may postulate that blockage of IL-6R would result in controlling mixed granulocytic inflammation in allergic asthma, potentially leading to clinical benefit. In a mouse model of allergen-induced asthma, cockroach-induced airway inflammation was shown to be attenuated by intranasal

Table 1
Selected cytokine targets for therapeutic intervention

Cytokine	Principal Sources	Acts on	Function	Therapeutic Agents ^a
IL-6	APCs MCs Th2 cells Multiple somatic cells	Activated T cells B cells MCs Multiple somatic cells	Promotes T cell & neutrophil recruitment Induces Th2 & Th17 differentiation Promotes B-cell survival & differentiation into plasma cells ↑ Histamine & FcεRI expression by MCs Triggers acute phase response	Tocilizumab
IL-12	APCs Neutrophils	Activated T cells NK cells	Induces Th1 differentiation ↑ Cytotoxicity of CD8+ T cells & NK cells	Ustekinumab
IL-18	APCs MCs Multiple somatic cells	Multiple immune cells Multiple somatic cells	Promotes T-cell activation ↑ T-cell cytokine production ↑ Cytotoxicity of CD8+ T cells & NK cells Promotes somatic cell cytokine, chemokine, and adhesion molecule production	<i>GSK1070806</i> <i>Tadekinig alfa</i>
IL-23	APCs Neutrophils	Activated T cells Memory T cells	↑ IL-17 production by Th17 cells Promotes survival of memory T cells	Ustekinumab
IFN γ	NK cells Th1 cell	Multiple immune cells Multiple somatic cells	↑ MHC class I & II expression ↑ IL-12 production by APCs Triggers antiviral responses in many cells Primes macrophages for activation Induces cell cycle arrest & apoptosis in many cells	<i>NI-0501</i>
TNF- α	Multiple immune cells Multiple somatic cells	Multiple immune cells Multiple somatic cells	↑ MHC class I & II expression Promotes activation of multiple immune cells ↑ Vascular permeability ↑ Cytokine, chemokine, and adhesion molecule expression by somatic cells Triggers acute phase response	Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab

^a Medications in italic are not yet FDA approved, but currently undergoing clinic trials.

treatment with anti-IL-6R antibody. This effect was also demonstrated in a small sample size human study.⁹

However, the heterogeneity of asthmatic patients presents a special challenge to this strategy. It is important to understand the concept of asthma endotypes¹⁰—if a specific group of asthma patients can be identified with high IL-6R levels in the sputum (ie, a “high IL-6” endotype), then it is reasonable to suspect that anti-IL-6R antibody would be a viable therapeutic option. However, endotypes may need to be refined even further given the differential responses noted with anti-IL-6R antibodies. For example, in murine models, activation of sIL-6R induces IL-17A production by $\gamma\delta$ T cells and downstream airway neutrophilia. This effect is not seen with classical (membrane-bound) IL-6R stimulation, which activates conventional $\alpha\beta$ T cells, leading to downstream airway eosinophilia.¹¹ The observation in murine studies that roach-induced airway inflammation was attenuated by anti-IL-6R antibody, while house dust mite allergen challenge induced an eosinophilic response in mice treated with anti-IL-6R antibody, has led to speculation regarding differential IL-6R activation (ie, soluble vs membrane bound) by different allergens.

There is already some evidence in murine systems that an anti-IL-6R antibody like tocilizumab is effective in specific models of allergic asthma. Further investigation may uncover a role for this biologic agent in a specific endotype of human asthma.

Atopic dermatitis

The pathogenesis of atopic dermatitis (AD) includes a mixed inflammatory infiltrate, with identification of both T helper 1 (Th1) and Th2 lymphocytes in normal and involved skin, respectively. CD4+ T cells have been shown to release IL-6 when activated, contributing to a proinflammatory state. Other cells like B lymphocytes, fibroblasts, and monocytes also secrete IL-6 and might play a role in the pathogenesis of AD.

Tocilizumab use would be expected to dampen the inflammatory state in AD and may be effective in the treatment of severe, refractory forms of the disease. Navarini and colleagues¹² reported improvement in the Eczema Area and Severity Index in a small number of subjects with AD after treatment with tocilizumab. However, they noted an increased incidence of bacterial skin infections. Further understanding of the heterogeneity of susceptibility to bacterial infections in subjects with AD may improve the prospects for the use of anti-IL-6 therapeutic regimens in these patients.

STAT3 gain-of-function mutations

Next-generation sequencing technologies have fostered an incredible expansion in the understanding of the genetic basis of immunodeficiency and immune dysregulatory disorders. One consequence has been the discovery of activating mutations in the transcription factor STAT3 causing a syndrome very similar to autoimmune lymphoproliferative syndrome (ALPS).^{13,14} These patients typically have notable autoimmune cytopenias and lymphoproliferation, with a tendency toward solid organ autoimmunity and recurrent or severe infections. Unlike patients with ALPS, who typically respond to standard immunosuppression with sirolimus, those with gain-of-function mutations in STAT3 may require substantial immunosuppression. In fact, many have failed multiple different immunosuppressive regimens.¹⁵

Mechanistic studies suggested that the mutations in these patients resulted in decreased dephosphorylation of STAT3, prolonging the activity of the transcription factor after stimulation through cytokine receptors. IL-6 is a major activator of STAT3 in immune cells, and therefore, it was theorized that blockade of IL-6 signaling could help to normalize the cumulative STAT3 activity in these patients.¹³ Trials of tocilizumab in several patients have been very encouraging—in all cases, an improvement

in their clinical status, especially with regards to solid organ autoimmunity, was observed.^{13,15} STAT3 gain-of-function mutations are relatively rare, although as additional patients are identified, tocilizumab may prove to be a cornerstone of treatment.

Ustekinumab: Anti-Interleukin-12/23 p40 Antibody

Ustekinumab (Stelara) is a fully humanized monoclonal IgG1 antibody against the p40 subunit shared by IL-12 and -23. IL-12 is essential to the development of Th1 cells due to its ability to stimulate interferon gamma (IFN γ), and also increases the cytotoxic activity of CD8+ T cells and natural killer (NK) cells. On the other hand, IL-23 is involved in the development and proliferation of Th17 cells.^{16,17} Currently, this biologic agent is approved by the FDA for the treatment of plaque psoriasis or psoriatic arthritis in subjects ≥ 18 years old.

Asthma

A form of chronic asthma that is not responsive to conventional therapy can be conceptualized as a Th17-dominant disease, wherein neutrophils and eosinophils are recruited to the airways via IL-17-dependent pathways. In this subpopulation of neutrophil-predominant asthma, ustekinumab may be useful to control airway inflammation by limiting the proliferation of Th17 cells. Indeed, Amarnani and colleagues¹⁸ have described a patient with both psoriasis and asthma who was treated with ustekinumab. The patient's asthma improved to the extent that he was able to discontinue controller medication while on ustekinumab. Further studies are needed to replicate these results, but ustekinumab is an attractive therapy for the often difficult-to-treat neutrophilic asthma.

Atopic dermatitis

As previously discussed, ustekinumab inhibits Th1 and Th17 inflammatory pathways, and this results in a decrease in IFN γ and tumor necrosis factor-alpha (TNF- α) production. Although AD is typically considered to be a Th2-mediated disease, elevated levels of IL-17 have been demonstrated in the skin during acute eczema flares.¹⁹ Ustekinumab has been shown to be effective in decreasing symptoms of AD based on SCORAD and visual analogue scores in a few case reports.^{20,21} Clearly more data are required on the roles of Th1 and Th17 cells in AD, but ustekinumab may find a role as an adjuvant therapy in the disease.

Inflammatory gastrointestinal disorders

Th1 cells are essential to the pathology of multiple inflammatory gastrointestinal diseases. Almost 2 decades ago, researchers discovered increased IL-12 and a predominance of IFN γ -producing T-helper cells in the affected tissue of patients with Crohn disease.^{22–24} Research that is more recent has suggested an additional role for Th17 cells in the development of lesions in Crohn disease. With this in mind, several trials were conducted to evaluate the efficacy of ustekinumab in Crohn disease, and the results were positive, particularly in patients who had failed prior therapy with anti-TNF- α therapies.²⁵ These data have reportedly been submitted to the FDA in hopes of obtaining an indication in the treatment of Crohn disease.

Furthermore, a common theme in immune-mediated disorders of the gastrointestinal tract is the involvement of Th1 and/or Th17 cells. For example, enteropathy in patients with common variable immunodeficiency (CVID) is associated with increased production of IL-12, but not IL-17, by T lymphocytes.^{26,27} In contrast, patients with immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX), which is characterized by severe enteropathy, have increased numbers of Th17 cells and a relative reduction in Th1 cytokines.¹⁷ The fact that the IL-12/23

p40 subunit is shared in both pathways makes this an appealing target in these syndromes. To this end, a small study exploring the usefulness of ustekinumab in CVID enteropathy is currently underway.

GSK1070806: Anti-Interleukin-18 Antibody/Tadekinig Alfa: Recombinant Interleukin-18 Binding Protein

GSK1070806 is a humanized monoclonal antibody of the IgG1 isotype that binds to and neutralizes IL-18.²⁸ It is currently being evaluated as an adjunctive therapy for preventing solid organ graft rejection. Tadekinig alfa is a recombinant form of human IL-18 binding protein and is undergoing evaluation for use in adult-onset Still disease.

IL-18 is a member of the IL-1 family and, like IL-1, is produced as a protein precursor that must be processed by caspases after activation of the inflammasome complex. The full functions of IL-18 are still being elucidated, but it is known to play a role in inflammation and increases the production of other cytokines, such as IFN and IL-17, by immune cells.²⁹

Cryopyrin-associated periodic syndromes

The cryopyrin-associated periodic syndromes (CAPS) comprise a spectrum of disorders, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. All are characterized by recurrent fevers and tissue inflammation in the absence of an infectious or autoimmune source. CAPS is caused by activating mutations in NLRP3, also known as cryopyrin, which is a component of the inflammasome complex. Autoactivation of the inflammasome leads to unregulated production of cytokines like IL-1 and IL-18.³⁰

The mainstay of therapy for CAPS is blockade of IL-1, and several medications are currently approved for this. In many cases, treatment is very effective.^{30,31} However, in certain cases, typically those presenting at a very young age or with very severe features, continual upward titration of the dose is required. One theorized cause for this phenomenon is the effect of excess IL-18, which is not neutralized with current treatments. Data from animal models of CAPS suggest that IL-1 and IL-18 contribute differently to the overall inflammatory phenotype and may be responsible for different stages of the disease process.³¹ It is tempting to speculate that when used together with IL-1 blockade, IL-18 antagonists could improve disease control and long-term outcomes in patients with difficult-to-control CAPS.

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by overwhelming inflammation and cytokine release and can be viewed as the most severe incarnation of the cytokine storm.³² The causes of HLH are diverse and include both inheritable and environmental factors—thus, the syndromes can be classified as familial or reactive. Treatment has centered on removal of the inciting stimulus (in the case of reactive HLH) and potent immunosuppression to control the runaway inflammation.^{33,34}

One of the first functions ascribed to IL-18 was its ability to augment dramatically the production of IFN γ by Th1 cells after stimulation with IL-12.³⁵ Knowing the importance of IFN γ in the pathology of HLH (see later discussion), it is hence easy to expect a role for IL-18 in the disease. Indeed, IL-18 is highly elevated in persons with HLH, and levels correlate better with symptoms in humans than do IL-12 or TNF- α .³⁶ Furthermore, in murine models of HLH, animals treated with IL-18 binding protein showed significant improvement in multiple disease parameters.³⁷ Consequently, IL-18 blockade may represent another avenue of therapy for this potentially lethal disease.

NI-0501: Anti-Interferon γ Antibody

IFN γ is the quintessential Th1 cytokine but also has diverse roles in the immune response. It is a type II IFN produced by NK cells, cytotoxic T cells, and Th1 cells. IFN γ functions to prime macrophages, increase major histocompatibility complex (MHC) class I expression on somatic cells, increase MHC class II on antigen-presenting cells (APCs), boost the activity of NK cells and cytotoxic T cells, and promote the differentiation of Th1 cells.³⁸ NI-0501 is a fully human monoclonal antibody that neutralizes IFN γ . It was granted orphan drug status by the FDA and European Medicines Agency in 2010.

Hemophagocytic lymphohistiocytosis

Animal models of the disease revealed a unique role for IFN γ in the initiation and maintenance of the inflammatory cascade in HLH. In fact, blockade of IFN γ , but not several other cytokines, leads to complete resolution of the syndrome in animal models.³⁹ Accordingly, IFN γ has been an interesting target to treat the disorder in humans. Early results from phase 1 and 2 studies of NI-0501 in patients with familial HLH have been promising, combining improvements in clinical status with fewer side effects than the typical regimens.^{40,41} Because of this, the FDA has designated NI-0501 a Breakthrough Therapy, which may help to shorten the time to the drug's final approval. Based on its mechanism of action, it is reasonable to suspect that the medication will be similarly effective in reactive HLH. If the efficacy is confirmed with additional subjects, NI-0501 could soon become a primary therapy for all forms of HLH.

Adalimumab/Certolizumab/Golimumab/Infliximab: Anti-Tumor Necrosis Factor- α Antibody

TNF- α is generated by multiple cell types early in the inflammatory process, and as such, is part of a first line of defense against tissue injury and foreign antigens.⁴² TNF- α has also been shown to cause dysregulation of the immune response in asthmatics. Adalimumab (Humira) is a humanized monoclonal antibody that blocks the binding of TNF- α to its receptors. Its use in rheumatologic conditions and inflammatory bowel disease is well established. Other biologics with similar mechanisms include certolizumab pegol (Cimzia), golimumab (Simponi; Simponi Aria), and infliximab (Remicade).

Asthma

After allergen challenge, lung mast cells (MCs) and macrophages release TNF- α .⁴³ Further evidence for the role of TNF- α in asthma includes the observations that TNF- α is elevated in the airway of asthmatics,⁴⁴ and, when administered to normal mice via inhalation, causes airway hyperresponsiveness (AHR). Hence, blockade of TNF- α by adalimumab has been shown in clinical studies to reduce asthma exacerbations and AHR and to improve asthma quality of life, albeit inconsistently. One reason for the variability in response may be due to polymorphisms in the TNF- α receptor (eg, TNF-308G/A⁴⁵). These and other factors need to be considered when designing future studies to test TNF- α blockade in asthmatics. Regardless, adalimumab may prove to have a role in a subpopulation of asthmatics with refractory symptoms.

THERAPIES TARGETING CELLULAR ACTIVATION OR FUNCTION

Many immunologic diseases arise from a failure to properly regulate potent immune effector functions. As the knowledge of this immune dysregulation has grown, treatment strategies have shifted from nonspecific immunosuppression toward restoring the correct balance between effector and regulatory elements. Current approaches

include elimination of the APCs that generate effector cells, inhibiting the activation of effectors, and enhancing the function of natural regulatory cells (Fig. 1).

Abatacept and Belatacept: CTLA-4-hlgG1-Fc Fusion Proteins

Costimulation is necessary for optimal T-cell responses, and this is usually provided via the binding of CD28 on T cells to CD80 or CD86 on APCs. Absence or inhibition of costimulation during T-cell activation can lead to anergy or self-tolerance. CTLA-4 is preferentially expressed on activated T cells and regulatory T cells (Tregs) and binds to CD80 and CD86 with much higher affinity than CD28, competing for the costimulatory molecules on the APCs.⁴⁶ In addition, CTLA-4 contains an inhibitory signaling motif, in contrast to the activating motif on CD28.^{47,48}

Abatacept (Orencia) and belatacept (Nulojix) are fusion proteins containing the extracellular domain of CTLA-4 with the Fc portion of human IgG1. The molecules are designed such that the Fc portion of the molecule is unable to fix complement or mediate antibody-dependent cellular cytotoxicity. These drugs are FDA approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis (abatacept) and for the prevention of allograft rejection (belatacept).

Allergen-specific immunotherapy adjuvant

Allergen-specific immunotherapy (SIT) is a very effective therapy aimed at inducing tolerance to an allergen over a period of time. The mechanisms by which this therapy works are only partially understood, but seem to involve the preferential development of allergen-specific Tregs.⁴⁹ CTLA-4 signaling has been shown to increase the proliferation and suppressive activity of Tregs as well as to induce anergy in effector T cells.

In an experimental murine model, administration of a CTLA-4-Fc fusion protein concomitantly with allergen-specific SIT was shown to result in an increased number of Tregs, inhibition of activated T cells, and improved induction of tolerance to that allergen. Other effects included decreased airway hyperreactivity and airway eosinophilia in treated mice.⁵⁰ One clinical benefit of CTLA-4-Fc fusion proteins as an

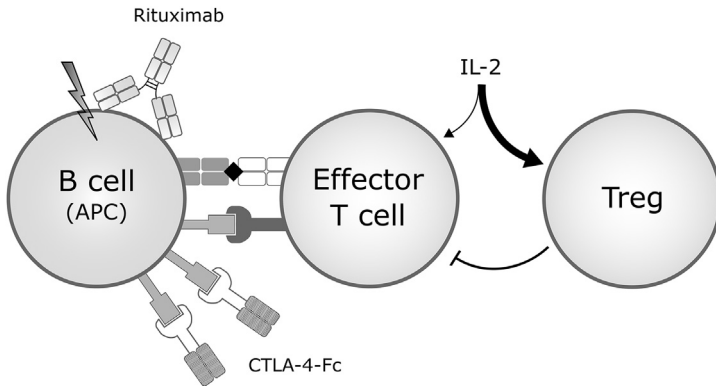


Fig. 1. Mechanisms for inhibiting cellular effector function. The regulation of cellular effectors may be manipulated at several points during the immune response. The use of rituximab may prevent T activation by the elimination of self-reactive B cells that can present self-antigens in germinal centers. CTLA-4-Fc fusion proteins bind to the costimulatory molecules CD80 and CD86, present on APCs. The therapeutic effect is likely due to competitive inhibition of T-cell co-stimulation through CD28. Low-dose IL-2 preferentially stimulates Tregs, which in turn are able to control the activation and proliferation of effector T cells.

adjuvant for SIT would be the ability to use lower doses of the allergen, with the potential for a decrease in systemic hypersensitivity reactions, while maintaining an excellent and possibly improved tolerogenic effect.

Immunodeficiencies with autoimmune features

CVID is a heterologous disease. Although all patients by definition have immune deficiency, some exhibit additional features of autoimmune disease and lymphoproliferation. Next-generation sequencing is slowly identifying individual genetic mutations that make up the group of diseases labeled as CVID. Within the past couple of years, investigators have identified mutations in *CTLA4* and *LRBA* that result in immunodeficiency with striking autoimmune elements.^{51–53}

Studies of these patients have revealed decreased CTLA-4 expression on T cells in both disorders. Moreover, in both disorders, the numbers and suppressive function of Tregs are significantly reduced. Based on the pathophysiology, it was theorized that treatment with CTLA-4-Fc fusion protein would help offset the lack of T-cell inhibition. In vitro studies confirmed a beneficial effect of the medication, and its use in a small number of patients was extremely promising.^{52,54,55}

Rituximab: Anti-CD20 Antibody

Rituximab (Rituxan) is a chimeric monoclonal anti-CD20 antibody that targets B cells for elimination via antibody-dependent cellular cytotoxicity, complement-dependent toxicity, and apoptosis.⁵⁶ CD20 is expressed on pre-B cells and mature B cells but not plasma cells. Hence, rituximab therapy preserves the function of pre-existing plasma cells.⁵⁷ This biologic drug is currently approved by the FDA for use in B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

Atopic dermatitis

There is clear evidence for the role of both B and T cells in the pathogenesis of atopic eczema.^{58,59} B-cell involvement is reflected in higher total and allergen-specific IgE in AD patients than controls.⁶⁰ Suppression of B cells with rituximab leads to a decrease in T-cell stimulation, total and specific IgE levels, and chemo-attraction of other immune cells. These effects are likely due to a reduction in antigen presentation and other immunomodulatory functions by B cells rather than antibody reduction.⁶¹ Rituximab has been shown to be effective in the treatment of severe AD resistant to conventional therapy in a few case reports and case series.⁶² However, immune suppression following the use of rituximab can be prolonged and severe. Thus, as with any other therapeutic modality, the use of this drug should follow a careful analysis of the risk/benefit ratio and should be reserved for the most severe cases, either refractory to treatment or steroid dependent.

Anticytokine autoantibody syndromes

Clinicians are increasingly identifying persons with features that mimic inherited immunodeficiencies but develop relatively late in life. In many cases, these patients lack genetic mutations in recognized pathways, but rather they acquire autoantibodies that interfere with specific inflammatory pathways.⁶³ For example, persons with neutralizing autoantibodies to IL-12 or IFN γ develop susceptibility to invasive mycobacterial infections, whereas those with autoantibodies to IL-17 may develop recurrent fungal infections and those with autoantibodies to granulocyte-monocyte colony stimulating factor develop pulmonary alveolar proteinosis. In fact, the International Union of Immunological Societies created a new category that includes these disorders in their most recent classification scheme—phenocopies of primary immunodeficiencies.⁶⁴

Despite the fact that rituximab spares plasma cells, it carries an FDA indication for the treatment of rheumatoid arthritis and is an effective therapy for multiple autoimmune conditions characterized by autoantibody production. As mentioned above, this may reflect the pathogenic roles of self-reactive B cells other than antibody production, including interactions with self-reactive T cells, for example, Rituximab's effect in these disorders makes it a logical choice for the treatment of anticytokine autoantibody syndromes. Several groups have reported successes in a small number of patients which has prompted a more rigorous phase 1 trial, currently being conducted by the National Institutes of Health.⁶⁵⁻⁶⁷

Aldesleukin: Recombinant Interleukin-2 Protein

Aldesleukin (Proleukin) is a recombinant form of human IL-2. This cytokine signals through a receptor complex consisting of a high-affinity α chain (also called CD25), a β chain, and a common γ chain that is shared with the receptor complexes for IL-4, IL-7, IL-9, IL-15, and IL-21.⁶⁸ CD25 is expressed at a modest level on activated T cells and is highly expressed on Tregs. Signaling through this receptor complex promotes cellular survival and activation. Aldesleukin is currently approved by the FDA for the treatment of metastatic renal cell carcinoma and metastatic melanoma.

Immunodeficiencies with autoimmune features

Studies examining the causes of inherited syndromes of immune dysregulation have revealed the importance of Tregs in controlling autoimmunity. Disorders such as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, CTLA-4 deficiency, IPEX, and LRBA deficiency are all associated with reduced numbers and function of Tregs.^{51-53,69,70} In addition, in studies of subjects with CVID for whom a genetic cause was not known, a similar trend was evident,⁷¹⁻⁷³ although it should be noted that these studies were performed before several genetic causes (ie, LRBA and CTLA-4) had been identified.

Initial trials with recombinant IL-2 focused on activating effector T cells to help fight cancer.⁷⁴ Although efficacy was demonstrated, this treatment also famously leads to severe side effects such as capillary leak syndrome. A renewed interest in recombinant IL-2 was generated after it was postulated that Tregs, with their high level of CD25 expression, might be preferentially activated by low doses of IL-2. Small case series and a large volume of mechanistic studies have demonstrated positive responses in treating autoimmunity.⁷⁵ Further trials in immunodeficiencies and immune dysregulatory disorders are certainly needed, but recombinant IL-2 may represent an ideal treatment wherein autoimmunity can be controlled without nonspecific immunosuppression—a boon for individuals who are already immunocompromised.

THERAPIES TARGETING IMMUNOGLOBULIN E

Many allergic and immunologic conditions are IgE mediated. Soluble IgE is found in peripheral blood and in the interstitial space, whereas membrane-bound IgE (mIgE) is present on IgE-expressing B lymphoblasts and memory B cells as part of the B-cell antigen receptor complex. IgE also binds to the high-affinity IgE receptor (Fc ϵ RI) present on the surface of basophils and MCs. Cross-linking of IgE-bound Fc ϵ RI by an antigen causes stimulation and degranulation of these cells. The pharmacologic mediators released are responsible for many allergic and immunologic symptoms. Targeting the IgE pathway can therefore lead to alteration of disease related pathomechanisms.

Quilizumab: Anti-CemX Antibody/Omalizumab: Anti-Immunoglobulin E Antibody

Anti-CemX is a newer biologic undergoing clinical trials for the treatment of IgE-mediated disease. CemX is a 52-amino-acid residue located between the CH4 domain and the C-terminal membrane anchor peptide of the ϵ chain of mIgE on human B cells. Binding of anti-CemX antibody to this unique domain has been shown to cause apoptosis of IgE class-switched B cells due to a lack of costimulatory signaling. However, it may secondarily cause antibody-dependent cellular cytotoxicity with destruction of the IgE-bearing B cell which ultimately prevents the generation of IgE-secreting plasma cells, resulting in decreased production of IgE.^{76,77} As the CemX protein is highly conserved, a high degree of specificity and safety is seen with this drug. This treatment does not target free IgE in the serum, and hence, its effectiveness does not depend on the concentration of IgE in the blood. Quilizumab has been proposed for use in patients with very high serum IgE levels who do not qualify other therapies.

Omalizumab (Xolair) is a humanized monoclonal IgG1 antibody to IgE, which binds to free serum IgE. Binding by this monoclonal antibody occludes the Fc ϵ RI binding site, therefore preventing the IgE from binding to receptors on MCs and basophils. In turn, this leads to downregulation of cell-surface FcER1 on these cells.⁷⁸ Omalizumab is currently approved by the FDA for treatment of allergic asthma and chronic spontaneous urticaria.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a syndrome characterized by an exaggerated Th2 response to fungi of the genus *Aspergillus* (most commonly *Aspergillus fumigatus*) in the lower airways. This Th2 immune response to the fungi can, in turn, lead to an acute or subacute worsening of asthma control. In addition to worsening severity of asthma symptoms, patients display elevated total and aspergillus-specific serum IgE levels as well as positive skin prick tests to aspergillus allergens.⁷⁹ The elevated total serum IgE level is thought to play a role in the pathogenesis of this condition.

Various treatment options have been tried, including antifungal therapy, systemic corticosteroids, and others. In recalcitrant cases, treatment with Omalizumab resulted in a reduced number of asthma exacerbations, decreased fractional exhaled nitric oxide levels, and decreased night awakenings.⁸⁰ Immunologic studies in omalizumab-treated patients demonstrated a decrease in basophil sensitivity, defined as the amount of allergen required to induce 50% maximal basophil reactivity as measured by CD63 expression on basophils. One can postulate that Omalizumab therapy in patients with ABPA would potentially prevent disease progression and might eventually result in a decreased incidence of progression to bronchiectasis.⁸¹

Churg-Strauss syndrome

Churg-Strauss syndrome, also known as eosinophilic granulomatosis with polyangiitis (EGPA), is a small-vessel vasculitis associated with blood and tissue eosinophilia.⁸² Up to 30% to 40% of patients are positive for serum antineutrophil cytoplasmic antibodies. The pathogenesis of this disorder is still unknown, but marked elevations of IgE and IgG4 are reported in this condition.^{83,84} If one postulates that the increased IgE levels play a role in the pathogenesis of this disease, or at least the secondary atopic symptoms associated with it, it would be reasonable to assume that treatment with IgE-targeted therapy may result in clinical benefit in affected patients.

Unfortunately, several cases were reported of Churg-Strauss syndrome developing in asthmatic patients treated with omalizumab.^{85,86} A causative relationship between

the disorder and drug has largely been disproven, and the association is thought to be due to an unmasking effect after reduction of the steroid dose while on omalizumab therapy.

EGPA remains a therapeutic challenge for most patients, because conventional therapy is not always effective. Omalizumab is a safe biologic therapy that has shown promise in inducing partial or full-treatment response and can also be used as a corticosteroid-sparing agent in EGPA with atopic symptoms such as asthma or sinusitis.⁸⁷

Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with nasal polyps (CRS w/NP) is a complex inflammatory condition. Treatment with conventional therapy such as topical corticosteroids has proven to be frustratingly ineffective, with a lack of improvement in most patients. Nasal polyps show significant eosinophilic infiltration on histologic examination, and Th2-type inflammation with evidence for local IgE production and increased IgE levels has been observed within the polyp tissue.⁸⁸ The increase in local IgE production is possibly due to stimulation by superantigens such as staphylococcal enterotoxins and is likely to be polyclonal. Furthermore, because the IgE is produced locally within the polyp tissue, it may not always be evident in the serum.⁸⁹ In patients with CRS w/ NP and concomitant asthma, there appears to be further increases in local IgE production. This IgE has been demonstrated to play a role in perpetuating the chronic inflammation in these tissues.⁹⁰ Thus, inhibiting IgE-induced chronic inflammation is a potential therapeutic target in this condition.

In double-blind placebo-controlled trials conducted in patients with CRS w/NP and comorbid asthma, omalizumab has been shown to improve total polyp score as well as quality of life as measured by the Asthma Quality of Life Questionnaire and Short Form-36 Health Survey validated questionnaires.⁹¹ This beneficial effect did not differ between patients with and without allergic rhinitis. As a consequence, IgE-targeted therapies are attractive as add-on therapy for patients with CRS w/NP and comorbid asthma, not controlled with conventional therapy.

Mastocytosis

Mastocytosis is a disorder characterized by an increased MC burden within the tissues. This increase in MC number can be associated with an increase in the total amount of FcεRI and/or a decrease in the activation threshold of the MCs. One of the more serious symptoms of MC disorders is recurrent anaphylaxis, either idiopathic or due to hypersensitivity to allergens such as foods or insect venoms.⁹² No large-scale studies have examined the use of IgE-targeted therapy in mastocytosis, but several case reports have highlighted a reduction in the number of further anaphylactic episodes, the severity of the reactions, baseline serum tryptase levels, and total serum IgE levels.^{93,94} Omalizumab has been successfully used as an adjunct therapy in patients with mastocytosis undergoing immunotherapy for venom hypersensitivity reactions; this strategy has been especially beneficial in patients undergoing rush protocols.

Although the exact mechanism of action of omalizumab in the treatment of mastocytosis is not definitively known, it is thought that by preventing free IgE from binding to FcεRI, treatment leads to a reduction in the surface FcεRI expression MCs, leading to an increase in the activation threshold. However, the effect of omalizumab for the treatment of chronic idiopathic urticaria, another disorder of spontaneous MC activation, does not appear to depend on the serum IgE level. Accordingly, omalizumab may affect MC activation through other mechanisms, and it is unclear if other IgE-target therapies will have similar effects in these patients. Further studies are needed.

SUMMARY

The promise of precision or personalized medicine has been evident for nearly a decade.⁹⁵ Although the promise has yet to be wholly fulfilled, the field of medicine has made fantastic strides toward this goal. Biologics, due to their inherent specificity, have led the charge in many disciplines and will likely continue to do so in the future. The medicines described above represent a sample of therapies “just in front of us”—ones that physicians may see in their practices in the near future. As the understanding of the pathophysiology of immunologic and allergic diseases expands, and additional therapeutic targets are identified (eg, IL-33 in Th2-predominant disorders), undoubtedly progressively more biologics approved for broader indications will be seen in the decades to come.

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