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Biologic Modulators in Allergic and Autoinflammatory Diseases

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Abstract

Purpose of review—The advent of molecular techniques has resulted in the ability to tailor medications to specific protein targets. This review will emphasize several biological therapies, specifically directed toward cytokine receptors and inhibitors, and their role in the treatment of atopic and autoinflammatory diseases.

Recent findings—Translational research and the identification of the molecular pathophysiology of diseases have led to more targeted treatment approaches. The biologic modulators, encompassing monoclonal antibodies as cytokine inhibitors, receptor blocking antibodies and new fusion receptors are now being applied to diseases beyond their original application.

Summary—The expanded use of biological therapies has experienced success in the treatment of numerous disorders, especially in subsets of patients with disease that has been refractory to conventional therapies.

Keywords

monoclonal antibodies; biologics; autoinflammatory; allergy

Introduction

The advent of molecular techniques has resulted in the ability to tailor medications to specific protein targets. Such therapies are known as biologic immunomodulators, or more commonly, biologics. Since their introduction, these therapies have been designed to specifically target the molecular pathways involved in the pathogenesis of various autoimmune and inflammatory disorders, as well as cancer. More recently, the use of monoclonal antibodies has been expanded to additional diseases, notably in patients with disease that has been unresponsive to conventional therapies. Several recent reviews have focused on the use of such agents in asthma [1] and other inflammatory conditions such as inflammatory bowel disease, lupus and rheumatoid arthritis [2, 3]. These disorders will not be discussed further here. In this review, we focus on the use of these novel therapies to treat diseases encountered by the allergist including allergic diseases, such as urticaria, allergic rhinitis, food allergy, hypereosinophilia syndromes, idiopathic anaphylaxis, and the autoinflammatory syndromes.

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Receptor Blocking Agents

Anakinra, is a recombinant form of the naturally occurring IL-1 receptor antagonist. It functions as a competitive inhibitor of IL-1 α and IL-1 β binding to the IL-1 receptor (IL-1R), by binding to the same receptors without transducing signals. Initially approved for the treatment of rheumatoid arthritis, significant literature establishes the use of anakinra in a multitude of autoinflammatory syndromes which are driven by IL-1 [4**].

In autoinflammatory disorders, anakinra has been most extensively studied in cryopyrin-associated periodic syndromes (CAPS), a continuum of rare autoinflammatory disorders, specifically familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multi-system inflammatory disorder (NOMID) [5**]. While these syndromes are of varying severity, the basis for their inflammatory pathology lies in IL-1 β , and the blockade of IL-1 by anakinra has met with dramatic success in patients with CAPS, with reduction of symptoms, reduction of inflammatory markers and improvement in quality of life [4**]. Additional studies with anakinra have demonstrated improvement or resolution in patients with more progressive and long-term complications of CAPS, including hearing loss and renal disease due to amyloidosis [6, 7]. These benefits have led to the use of anakinra as standard of care in severe cases, namely NOMID, although the FDA approval remains restricted to rheumatoid arthritis.

More recently, a number of case reports and two small series have demonstrated the efficacy and safety of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), a rare, autosomal dominant autoinflammatory disease, characterized by recurrent episodes of fever, myalgia, arthralgia, migrating rash and serositis [8]. The goals of treatment are prevention of acute attacks, limiting corticosteroid use, and controlling chronic inflammation to prevent amyloidosis. Despite its name, the use of TNF-blockers has not been met with the success initially anticipated, and other biological modifiers are under investigation. Obici et al. recently reported a series of 7 patients with TRAPS with persistent symptoms despite treatment with either daily prednisone or treatment with etanercept. In all patients, initiation of therapy with daily subcutaneous anakinra led to resolution of symptoms and normalization of CRP and serum amyloid A within the first month of treatment. Only one patient experienced breakthrough attacks requiring low dose prednisone. With an average of 22 months of follow-up, the remaining patients continued to maintain complete clinical response, with resolution of proteinuria and stabilization of renal function. All patients tolerated the daily injections well [9**].

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, initially approved for the treatment of rheumatoid arthritis. As IL-6 is implicated in multiple immunologic disorders, the applicability of tocilizumab to other diseases has been under investigation. In a preliminary report of one patient with TRAPS, tocilizumab aborted an evolving attack and prevented further attacks of TRAPS during the 6-month treatment period. During anti-IL-6 therapy, the patient did not require corticosteroids and showed significant clinical improvement in symptoms and quality of life scores. Acute phase response reduced significantly with treatment [10]. Thrombocytopenia and neutropenia, along with elevations in lipoproteins and liver function tests are currently the most recognized side effects of tocilizumab.

Lumiliximab is a primatized macaque/human anti-CD23 monoclonal antibody. CD23, the low-affinity IgE receptor (Fc ϵ R2), is expressed on a wide variety of cells and has been implicated in IgE-mediated immune responses, the regulation of IgE synthesis, and stimulation of production of pro-inflammatory mediators from multiple cell types. Existing in both membrane and soluble forms, CD23 is believed to play an important role in allergic

reactions. *In vitro* studies of peripheral blood mononuclear cells from patients with allergic rhinitis, and sensitization to cat and timothy grass, revealed a significant decrease in allergen mediated IL-5 secretion following treatment with lumiliximab [11]. An initial trial in allergic asthmatics demonstrated that lumiliximab had a favorable safety profile. Phase II trials in patients with allergic rhinitis are currently underway [12].

Cytokine Blocking Antibodies

Canakinumab is a human monoclonal antibody to IL-1 β with a half-life that permits dosing frequency to be spaced to every 8 weeks. In a nearly year-long, three-phase trial of 35 CAPS patients, Lachmann et al. demonstrated that administration of canakinumab resulted in reduction of symptoms within the first 24 hours of treatment and complete response within the first month. Patients receiving canakinumab during the double-blind withdrawal period remained in remission, compared to 81% of patients in the placebo group who flared during the withdrawal period. One patient did have an infection, leading the authors to caution that vigilance in monitoring for infections remains an important consideration during immunomodulatory therapy [13].

Mepolizumab is a humanized murine IgG1 monoclonal antibody which binds to and inactivates IL-5, a cytokine involved in development and maintenance of eosinophil populations, and thus implicated in the pathogenesis of asthma, eosinophilic esophagitis, hyper-IgE syndrome (HIES) and hypereosinophilia syndromes (HES) [14**]. Mepolizumab has been shown to effectively reduce eosinophils in the peripheral blood for several weeks after infusion and reduce their recruitment into the airways after allergen challenge [14**]. Initial clinical trials in eosinophilic esophagitis have further demonstrated tolerability of mepolizumab, with a significant decrease in peripheral and esophageal tissue eosinophils, but limited improvement in symptoms has been observed, with one study demonstrating only 2/5 patients reporting improvement in swallowing after 2 months of therapy, compared to 1 of 6 controls [15*]. Experience with this agent in asthma suggests that a prolonged course of therapy is necessary to substantially deplete tissue eosinophils.

Mepolizumab has been investigated in hypereosinophilia-related diseases other than eosinophilic esophagitis, specifically HIES and HES. Published data, including one randomized, double-blind, placebo-controlled trial of 85 patients with HES, describing the use of mepolizumab in HIES have shown a similar decrease in peripheral eosinophilia, despite concomitant corticosteroid therapy and a positive response in quality of life measurements, and studies are ongoing [16].

Additional monoclonal antibodies targeting IL-5 (Reslizumab) or the primary producer of IL-5, eosinophils (alemtuzumab) are also under investigation in HES [17]. Reslizumab is a humanized rat IgG4 monoclonal antibody to IL-5 that is currently in trials for the treatment of pediatric eosinophilic esophagitis, asthma and nasal polyps, although reports of rebound eosinophilia may limit its use [18]. Alemtuzumab is a monoclonal antibody targeting the CD52 receptor present on eosinophils and, in case reports, has shown success in the treatment of refractory HES [17, 19], although its approval at this time remains limited to therapy for chronic lymphocytic leukemia. While these studies show promise for the use of anti-IL-5 therapy in these syndromes, further trials are indicated to elucidate the full beneficial effects and adverse events profile.

Fusion receptors

Improved understanding of cytokine signaling, has led to the development of biologic modifiers which competitively inhibit the binding of cytokines to their specific receptor, leading to inhibition of downstream signaling. This class of therapeutics is known as fusion

receptors. Fusion receptors consist of two subsets of biologic modulators: protein-based cytokine inhibitors consisting of the cytokine receptor, and cytokine traps which consist of fusions between the Fc region of human IgG linked to the high affinity extracellular domains of two different cytokine receptor components involved in binding the cytokine [20].

Etanercept is a fusion protein between the type II TNF receptor and the Fc portion of human IgG which binds to and inhibits the action of TNF- α . Etanercept also binds TNF- β [21*]. It is the most widely studied anti-TNF therapy for TRAPS, but the results have been mixed [22]. Publications of multiple case reports and one small case series report some benefits in reducing steroid use in TRAPS patients but this response is highly variable and may not be sustained, as evidenced by a patient with progressive amyloidosis while on therapy [23]. Clearly the targeted therapies noted above appear to be more promising in this disorder.

Rilonacept is a fusion protein consisting of the extracellular portions of IL-1R and IL-1R accessory protein linked to the Fc portion of human IgG1, resulting in inhibition of IL-1 β signaling. Additionally, rilonacept acts as a soluble decoy receptor that binds IL-1 β , thereby preventing its interaction with cell surface receptors. Rilonacept also binds IL-1 α and IL-1 receptor antagonist with reduced affinity [4**, 24]. Rilonacept was initially approved in 2008 for the treatment of CAPS, and notably, its pharmacologic profile permits reduction of the frequency of administration to weekly, in comparison to the daily dosing necessary for anakinra. In two Phase III, randomized, double-blind, placebo-controlled trials, Hoffman et al. demonstrated that weekly subcutaneous injections of rilonacept led to dramatic improvements in symptom scores and serum inflammatory markers in 44 patients with FCAS or MWS [25]. Rilonacept is currently under investigation for FMF.

Anti-Immunoglobulin-E

Omalizumab is a humanized, recombinant IgG1 antibody which binds to the Fc portion of circulating IgE. Treatment with omalizumab reduces cell surface levels of IgE and reduces the number of high affinity IgE receptors or Fc ϵ RI on the cell surface [26]. It was initially tested and approved for the treatment of allergic asthma, but it has subsequently been applied to the treatment of multiple atopic disorders.

Allergic rhinitis is clearly a target for anti-IgE therapy, and the efficacy of omalizumab has been investigated in several large clinical trials for both seasonal and perennial allergic rhinitis. These trials have demonstrated an improvement in daily symptoms, antihistamine use and in quality of life scores compared to placebo [27, 28]. Notably in one trial of 289 patients with long-standing symptoms of perennial allergic rhinitis, treatment with omalizumab led to improvement following the first dose, resulting in a two-fold improvement in quality of life scores over placebo. Over a 16-week trial, omalizumab was found to be well tolerated without serious adverse events [27]. It was also found to be safe in trials with patients simultaneously receiving subcutaneous immunotherapy [29] and some have advocated its use during the buildup phase of immunotherapy to diminish the risk of allergen-mediated anaphylaxis.

The ability of omalizumab to reduce the number of Fc ϵ R1 surface receptors has been exploited to expand its use to patients with urticaria. Several small studies have demonstrated a significant reduction in scores of pruritus, the number of hives and hive size, and reduction in antihistamine use by four weeks of therapy [30]. The successful use of omalizumab has been reported in other cases of urticaria on an individual basis including pressure urticaria [31], heat urticaria [32], cold urticaria and solar urticaria [33], but results in cholinergic urticaria have been variable [34]. This latter failure is to be expected as, in contrast to the other urticarial disorders, is not IgE mediated.

The use of omalizumab has also been investigated in steroid-dependent idiopathic anaphylaxis and systemic mastocytosis, each of which is characterized by recurrent episodes of anaphylaxis. Although the mechanism is unclear, it is postulated that the down regulation of FcεRI by omalizumab may prevent IgE cross-linking on mast cells and basophils, as well as binding free IgE. Several case reports have now demonstrated efficacy in reducing the number of anaphylactic episodes and minimizing steroid use in idiopathic anaphylaxis [28, 35]. In systemic mastocytosis, omalizumab has been shown to reduce the frequency of anaphylactic events [36]. Caution must be used, however, as there is a risk of anaphylaxis associated with the use of omalizumab itself which has led to a black-box warning from the FDA regarding its use [37]. The effect of omalizumab on food allergy symptoms has been observed in patients under treatment for moderate to severe persistent asthma [38]. On average in one study, by the sixth dose of omalizumab, all 22 patients reported an improvement in food-induced urticaria, food-induced rhinitis or food-induced angioedema. It must be emphasized, however, that these observations were made during an open label study during which the amount of allergic food intake was not strictly controlled. Double-blind, placebo-controlled trials are necessary before specific use of omalizumab can be recommended for treatment of food allergy.

Leung et al., investigated the utility of a second anti-IgE antibody, TNX-901, in patients with peanut allergy [39]. TNX-901 is a humanized monoclonal, IgG1 antibody which binds the C3 domain of IgE as well as circulating IgE [40]. In a double blind, placebo-controlled randomized, dose-based trial of 82 patients with confirmed immediate hypersensitivity to peanut, they demonstrated that the high level dose of TNX-901 significantly increased threshold sensitivity to peanut protein as determined by oral food challenge. They concluded that this increase, from approximately 0.5 to nearly 9 peanuts, would lead to partial protection against accidental ingestion. At the current time, TNX-901 remains experimental and future studies are needed to determine the role and feasibility of anti-IgE monoclonal antibody treatment of food allergies.

Limitations in the use of biologics

The increased and expanded use of monoclonal antibodies has met with new observations of adverse reactions that would not be unexpected from modulation of the immune system. The most commonly described adverse effects range from mild, such as infusion reactions for which prophylactic management is available and effective, to the more severe, including reactivation of latent tuberculosis, increased frequency of infection, blood dyscrasias and development of autoantibodies (Table 1). Given the difficulty in predicting these reactions, any use of immune system modulators should be performed with appropriate prudence. While this review exemplifies the breadth of possibilities for biologics in the treatment of human disease, many of the described uses are in preliminary stages and require additional evaluation. Larger studies are necessary to further elucidate the benefit versus risk ratio before recommending the use of monoclonal antibodies in more generalized treatment of allergic disease. Unfortunately, this field has been littered with agents demonstrating initial efficacy that have failed on further testing, further underscoring caution in this rapidly emerging area.

Conclusions

The ability to screen for mutations in inflammatory syndromes has led to a greater understanding of the pathophysiology behind symptoms and offered opportunities for new therapeutics. Treatment of the CAPS family of diseases is a primary example of progression from phenotypic description of patients to identification of genetic mutations and protein products which were amenable to drug targeting. Further advances in genetic engineering

and the modification to humanize antibodies has led to increased serum half-lives of the agents and thus reduced frequency of injections, in addition to decreasing their potential immunogenicity by decreasing the content of foreign material [41]. One would anticipate that continued expansion of our understanding of the human genome and the desire for individualized treatments will lead to the development of additional immunomodulatory therapies, and to novel uses for currently available agents. Ultimately, although the use of monoclonal antibodies has experienced success in the treatment of numerous disorders, especially in patients with disease that has been refractory to conventional therapies, one must remain cautious due to the potential adverse effects from modulation of the immune system.

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Abbreviations

CAPS	cypropyrin-associated periodic syndromes
CRP	C-reactive protein
FCAS	familial cold autoinflammatory syndrome
FMF	Familial Mediterranean Fever
HES	hypereosinophilia syndrome
HIES	hyper IgE syndrome
IL	interleukin
JIA	juvenile idiopathic arthritis
LFTs	liver function tests
MWS	Muckle-Wells syndrome
NOMID	neonatal onset multi-system inflammatory disorder
TNF	tumor necrosis factor
TRAPS	tumor necrosis factor receptor-associated periodic syndrome

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Key Points

- The ability to screen for mutations in inflammatory syndromes has led to a greater understanding of the pathophysiology behind symptoms and offered opportunities for new therapeutics which specifically target the mediators of disease.
- The use of existing biologic modulators has been successfully expanded to the treatment of other allergic and inflammatory diseases.
- More widespread and prolonged use of immunomodulatory treatments may raise new safety concerns, and caution should be used when employing these therapeutic agents.

Table 1

Summary of biologic immunomodulators under investigation for allergic diseases and autoinflammatory syndromes

Therapeutic agent	Approved indications	Under investigation	Serious adverse effects
Anakinra (necombinant IL-1 Ra)	Rheumatoid arthritis	CAPS, TRAPS	Injection site reactions, increased risk of infection [4,9**]
Tocilizumab (anti-IL-6R)	Rheumatoid arthritis	TRAPS, systemic onset JIA	Thrombocytopenia, elevations in LFTs and lipoproteins [10]
Lumiliximab (anti-CD23/FcεRII)	Not FDA approved	Allergic rhinitis, asthma	No serious adverse effects reported to date [11,12]
Canakinumab (anti-IL-1β)	CAPS	Gout	Increased risk of infection, one reported episode of vertigo with acute glaucoma (complication of CAPS) [13]
Mepolizumab (anti-IL-5)	Not FDA approved	Eosinophilic esophagitis, HIES, HES	No serious adverse effects reported to date [17]
Reslizumab (anti-IL-5)	Not FDA approved	Eosinophilic esophagitis, asthma, nasal polyps	Rebound eosinophilia [18]
Alemtuzumab (anti-CD52)	B-cell chronic lymphocyte leukemia	HES	Infusion reactions, cytopenias, cytomegalovirus reactivation and lymphoma have been reported in treatment of leukemia [19]
Etanercept (anti-TNF-α)	Rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis	TRAPS	Infection, active tuberculosis, malignancy [21*]
Rilonacept (IL-1 trap)	CAPS	FMF	Injection site reactions [25]
Omalizumab (anti-IgE)	Moderate to severe persistent asthma	Allergic rhinitis, urticaria, food allergy, mastocytosis idiopathic anaphylaxis	Anaphylaxis, injection site reaction, viral/upper respiratory tract infection, Churg–Strauss syndrome [37]
TNX-901 (anti-IgE)	Not FDA approved	Food allergy	Gastrointestinal symptoms, food allergy (to any food, patient-reported, not related to oral food challenges) [39]

CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; HES, hypereosinophilia syndrome; HIES, hyper IgE syndrome; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; TNF, tumor necrosis factor; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.