Clinical reviews in allergy and immunology
(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

Immunomodulators for allergic respiratory disorders

Thomas B. Casale, MD, and Jeffrey R. Stokes, MD *Omaha, Neb*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: February 2008. Credit may be obtained for these courses until January 31, 2010.

Copyright Statement: Copyright © 2008-2010. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: *Authors:* Thomas B. Casale, MD, and Jeffrey R. Stokes, MD

Activity Objectives

1. To understand the role of immunomodulators in treating allergic diseases and their mechanisms of action.
2. To understand the efficacy of immunomodulators in allergic disease based on human clinical trials.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: Thomas B. Casale has consulting arrangements with Genentech, Novartis, OSI, Pharma, and Zymo/Genetics; has received research support from Dynavax, Novartis, Genentech, Amgen, and Schering; and is on the speakers' bureau for Merck, Genentech, and Novartis. Jeffrey R. Stokes is on the speakers' bureau for GlaxoSmithKline.

New knowledge about the pathogenesis of allergic and immunologic diseases has led to a variety of novel targeted therapeutic approaches. Many immunomodulators are currently under development for the therapy of asthma and allergic and immunologic diseases and are undergoing human clinical trials. The study of immunomodulators in human subjects is ultimately required to determine their therapeutic utility because several agents showing promise in *in vitro* and animal models have failed in human studies. Novel therapeutic approaches include Toll-like receptor 4 and 9 agonists, immunostimulatory oligodeoxynucleotides, oral and parenterally administered cytokine blockers, and specific cytokine receptor antagonists. Transcription factor modulators targeting syk kinase, peroxisome proliferator-activated receptor γ, and nuclear factor κB are also being evaluated for the treatment of allergic diseases, especially asthma. The anti-IgE mAb omalizumab is already used for the treatment of allergic asthma, but its potential role for other allergic diseases has yet to be clearly defined. Overall, the development of new agents that inhibit specific immunopathogenic mechanisms holds promise for beneficial outcomes for patients with the least amount of risk. However,agents that are too specific in their targets might not exhibit therapeutic benefits because of the redundancy of the immune system and the heterogeneity of diseases such as asthma. The goal of this review is to summarize the data from human clinical trials with immunomodulators, discussing the rationale for their use, efficacy results, and putative adverse events associated with them. (J Allergy Clin Immunol 2008;121:288-96.)

Key words: *Immunomodulators, monoclonal antibodies, transcription factors, cytokine blockers*

New knowledge about the pathogenesis of allergic and immunologic diseases, including the molecular mechanisms involved, has led to a variety of novel therapeutic approaches. This article reviews some of these new potential treatment modalities that are in human clinical trials. The importance of focusing on human clinical trials has become evident by the failure of treatments that have shown promise in animal models. Novel therapeutic approaches reviewed in this article include Toll-like receptor (TLR) agonists, oral and parenterally administered cytokine blockers, specific cytokine receptor antagonists, transcription factor modulators, and anti-IgE mAbs (Fig 1). The risk/benefit ratio of approaches aimed at certain immunologic processes will

From the Department of Medicine, Division of Allergy/Immunology, Creighton University.

Disclosure of potential conflict of interest: T. B. Casale has consulting arrangements with Genentech, Novartis, OSI, Pharma, and Zymo/Genetics; has received research support from Dynavax, Novartis, Genentech, Amgen, and Schering; and is on the speakers' bureau for Merck, Genentech, and Novartis. J. R. Stokes is on the speakers' bureau for GlaxoSmithKline.

Received for publication October 9, 2007; revised November 26, 2007; accepted for publication November 28, 2007.

Reprint requests: Thomas B. Casale, MD, Creighton University, Department of Internal Medicine, Division of Allergy/Immunology, 601 N 30 St, Suite 5850, Omaha, NE 68131. E-mail: tbcasale@creighton.edu.

0091-6749/$34.00

© 2008 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2007.11.040

Abbreviations used
BAFF: B-cell survival and maturation factor
hpf: High-power field
NF-κB: Nuclear factor κB
PPAR: Peroxisome proliferator-activated receptor
sIL-4R: Soluble IL-4 receptor
TLR: Toll-like receptor

also be reviewed. Ultimately, the goal for the therapy of allergic and immunologic diseases should be the induction of immune tolerance, a change in the immune response such that discontinuation of the therapy results in continued long-lasting therapeutic benefits without adverse consequences. The discussion of the economics involved in using some of these agents, especially mAbs, is not included. However, costs should be kept in mind because pharmacoeconomic data need to support the use of expensive medications, especially for disorders that are very common and have little or no mortality. Overall, the development of new agents that specifically inhibit key immunopathogenic mechanisms holds promise for beneficial outcomes for patients.

TLRs

TLRs play a key role in activating antigen-presenting cells for both innate and adaptive immune responses. Blocking or stimulating TLRs can modify the T_H1/T_H2 cytokine balance affecting allergic diseases. Eleven different TLRs have been identified. Agonists for TLR4 and TLR9 have been developed and used in clinical trials for the therapy of allergic respiratory diseases. TLR4 binds LPSs and endotoxins expressed on the cell surface. TLR9 binds CpG motifs most common in bacterial pathogens.[1]

TLR4 agonist

Lipid A, the active component of LPS, is a TLR4 agonist that induces T_H1 responses. An aqueous formulation of monophosphoryl lipid A, CRX-675, is a TLR4 agonist that has been evaluated as a potential therapy for seasonal allergic rhinitis.[2] Patients were treated with either placebo (n = 16) or CRX-675 (2, 20, 100, or 200 μg administered intranasally; n = 12 per arm) 24 hours before a ragweed intranasal challenge. The adverse event profile of CRX-675–treated patients was similar to that of placebo-treated patients, and no dose-related toxic effects were observed. There was no clear trend in the ability of CRX-675 to inhibit nasal allergen challenge responses, but improvement in nasal symptom scores was observed at 100 μg. Appropriate dosing and timing will ultimately define the potential therapeutic role of CRX-675 or other TLR4 agonists for allergies.

TLR9 agonists (immunostimulatory oligonucleotides)

Bacterial and viral genomes have immunostimulatory DNA sequences containing unmethylated CpG sequences that are suppressed and methylated in vertebrate genomes. TLR9 is the receptor for CpG DNA, which in human subjects is expressed in highest concentrations on B cells and plasmacytoid dendritic cells. TLR9-activated plasmacytoid dendritic cells produce IFN-α, leading to secondary activation of natural killer T cells, monocytes, and neutrophils. B cells activated by TLR9 produce IL-6 and IL-10 while inducing B-cell differentiation into plasma cells and triggering IgG isotype switching and antibody production.[1] TLR9 agonists activate both the innate and humoral immune system through these interactions.

There are 3 classes of CpG molecules, A, B, and C, which are described in Table I. Both B- and C-class CpG oligodeoxynucleotides have been used in vaccine therapy for infectious diseases, cancer, or both.[1,3]

Murine models of allergic lung disease have demonstrated the effectiveness of CpG in the prevention and reduction of airway inflammation.[1,3-5] Conjugation of antigens or allergens to CpG can dramatically improve the efficacy of CpG motifs. Conjugation of Amb a 1 (the predominant ragweed allergen) to CpG induced Amb a 1–specific T_H1 immune responses and suppressed T_H2 responses in human subjects with ragweed allergy.[6] This response was associated with significant increases in IFN-α, CXCL9, and CXCL10 levels and decreases in IL-5, CCL17, and CCL22 levels.[7] The number of immunostimulatory DNA sequences containing CpG motifs bound to the Amb a 1 protein alters the immunogenicity and allergenicity of the response.[8]

Tolamba is an immunostimulatory oligonucleotide covalently linked to Amb a 1. In a ragweed seasonal allergic rhinitis trial, adult subjects with ragweed allergy were treated with 6 weekly injections of either Tolamba or placebo before the ragweed season and followed for 2 ragweed seasons.[9] Patients treated with Tolamba experienced a significant reduction in total nasal symptom scores from baseline during the 2-week peak pollen season compared with placebo-treated patients in both the first and second years of the ragweed season. The seasonal increase in Amb a 1–specific IgE levels was suppressed by Tolamba therapy in both years, whereas a transient increase in Amb a 1–specific IgG levels was noted in the first ragweed season. A second study found that nasal biopsy specimens from Tolamba-treated patients had a significantly reduced increase in eosinophils and IL-4 mRNA–positive cells and increased IFN-α mRNA–positive cells compared with those in placebo-treated patients after the ragweed season.[10] A large, multicenter, placebo-controlled trial of Tolamba for ragweed-induced seasonal allergic rhinitis showed no clinical benefit. However, the symptom scores were low, even in the placebo group, potentially making it difficult to discern a treatment effect.[11] Treatment with Tolamba is generally well tolerated.

Atopic asthmatic patients were treated with a CpG preparation through inhalation. Despite an increase in IFN-α gene expression, no effect was noted on allergen-induced eosinophils or T_H2-related gene expression.[12] Furthermore, no inhibition of airway responses was noted.

The application of TLR9 ligands is not limited to allergic disease. Human trials have demonstrated the effectiveness of CpG as either monotherapy or an adjunctive treatment in vaccines in a number of infectious diseases, such as hepatitis B, hepatitis C, anthrax, and influenza.[13] CpG is currently being studied in phase II and phase III human trials for cancer treatment, either alone or in combination with standard chemotherapy.[14]

Overall, the data suggest that TLR9 agonists could be valuable as adjuvants for the therapy of a variety of diseases, including allergic respiratory disorders. Indeed, the combination of CpG and allergens might prove more effective, with a better safety profile than allergen immunotherapy alone.

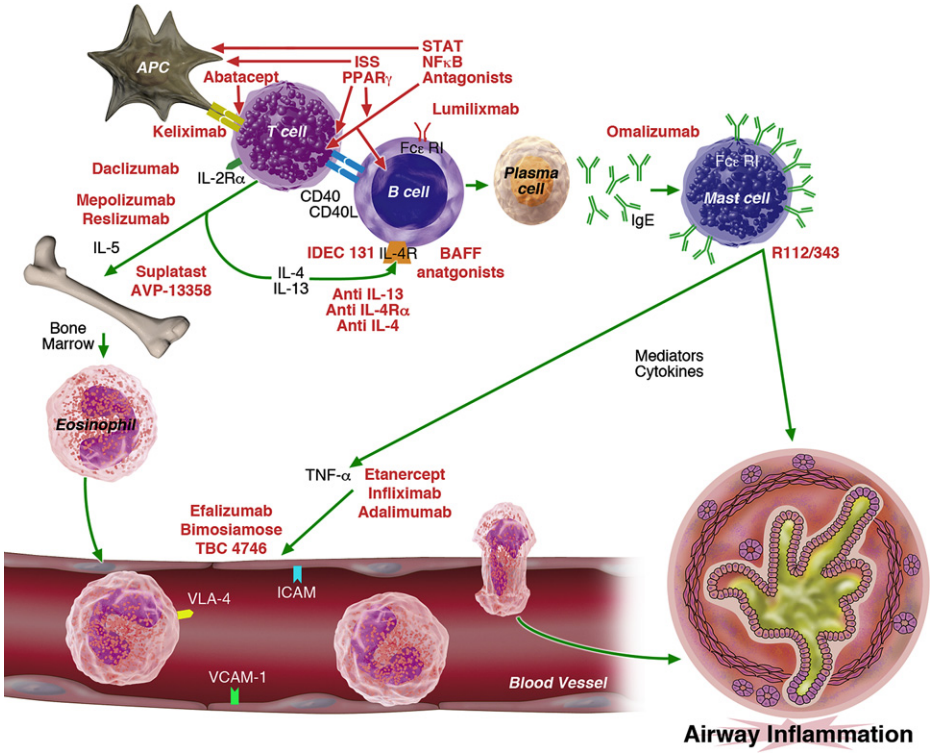


FIG 1. Immunomodulators for the treatment of allergic respiratory diseases. Novel therapeutic approaches include mAbs, cytokine blockers and receptor antagonists, and transcription factor modulators. *APC*, Antigen-presenting cell; *ISS*, immunostimulatory oligodeoxynucleotides; *STAT*, signal transducer and activator of transcription; *CD40L*, CD40 ligand; *BAFF*, B-cell survival and maturation factor; *VLA-4*, very late antigen 4; *ICAM*, intercellular adhesion molecule, *VCAM-1*, vascular cell adhesion molecule 1.

TABLE I. Three major classes of CpG oligodeoxynucleotide

A class: Chimeric backbone
Examples: ODN 2216, 1583 (5′-G*G*G-T-C-A-A-C-G-T-T-G-A-G*G*G*G*G-3′)
Responses: High IFN-α, IFN-γ, T_H1 inducer, poor B-cell stimulator
Target cells: pDC, PBMC, NK
B class: Phosphorothioate backbone, linear
Examples: ODN PF-3512676, 1018, 1826 (5′-T*C*C*A*T*G*A*C*G*T*T*C*C*T*G*A*C*G*T*T-3′)
Responses: B-cell proliferation, pDC maturation, secrete IgG, high IgM, IP-10, IL-6
Target cells: pDC, monocyte, NK
Clinical use: Monotherapy, vaccines, in combination for allergies, CA, infectious diseases
C class: Phosphorothioate backbone, 3′ palindrome, can form duplexes
Examples: ODN CPG10101, 5393, 2395 (5′-T*C*GT*C*G*T*T*T*T*C*G*G*C*G*C*G*C*G*C*C*G)
Responses: Combined intermediate effects of A and B classes, high IFN-α, B-cell activation, strong T_H1 inducer
Target cells: B cell, pDC, NK cell, PBMC
Clinical use: Monotherapy for infectious diseases (hepatitis B)

pDC, Plasmacytoid dendritic cell; *NK*, natural killer; *ODN*, oligodeoxynucleotide; *CA*, cancer.

CYTOKINE BLOCKERS

Therapeutic agents targeting TLRs affect both the innate and humoral arms of the immune system through a multiplicity of action. However, with the potential broad-ranging effects of some agents on the immune system, there is a concern of a shift in the risk/benefit ratio. In contrast, strategies aimed at single or multiple related cytokines might provide a lower risk for adverse events. This must be balanced by the potential of a less-efficacious or nonefficacious therapy. As reviewed below, there are several examples of agents targeting a single cytokine not being effective, perhaps because of the redundancy of the immune system. Anticytokine therapies provide a way to discern the importance of individual molecules in the pathogenesis of human disease.

Because T_H2 responses are the drivers of allergic responses, agents aimed at blocking key T_H2 cytokines have been logical targets for the therapy of allergic diseases. Strategies aimed at blocking the effects of IL-4, IL-5, and IL-13 have been evaluated in several phase I and phase II trials.

Oral synthesis inhibitors

Two oral agents that inhibit cytokine synthesis are undergoing clinical trials. Suplatast tosilate has been shown to inhibit the production of IL-4 and IL-5. Clinical trials with suplatast have shown an improvement in airway inflammation, airway hyperresponsiveness, clinical symptoms, and peak expiratory flow rates. Suplatast has also been shown to decrease serum IgE levels.[15-17] AVP-13358 has been shown to suppress IgE, CD23, and T_H2 cytokine responses *ex vivo* and *in vitro* in mouse and human cell assays.[18] Avanir Pharmaceuticals has put a hold on clinical trials with this compound, but safety data were favorable.

Soluble receptor/mAb therapy

Anti–IL-4 strategies. IL-4 induces IgE isotype switching and promotes naive lymphocytes to differentiate into T_H2 cells with subsequent release of additional IL-4, IL-5, and IL-13. Two human studies evaluated the efficacy and safety of a recombinant human sIL-4R. sIL-4R was safe and well tolerated, with the serum half-life of an inhaled dose being 5 days. The first study enrolled adult atopic patients with moderate persistent asthma requiring daily inhaled corticosteroids.[19] Patients were dosed one time with nebulized sIL-4R of either 500 μg or 1500 μg or placebo. All inhaled corticosteroids were stopped 1 day prior. Only the patients receiving the 1500-μg dose of sIL-4R had significant improvement in asthma symptom scores, rescue β-agonist use, and exhaled nitric oxide levels compared with those receiving the placebo. The 1500-μg dose also resulted in a significant increase in FEV_1 at 4 days. A follow-up study with 62 asthmatic subjects requiring inhaled corticosteroids evaluated weekly dosing of sIL-4R for 12 weeks at 0.75 mg, 1.5 mg, or 3.0 mg and placebo.[20] Inhaled corticosteroids were discontinued at the start of the study. Only patients receiving 3.0 mg of soluble IL-4 receptor (sIL-4R) weekly through a nebulizer were able to maintain their lung functions. No significant improvements were noted in symptoms or asthma exacerbations. Similarly, an mAb against IL-4 had no proved efficacy, leading to the discontinuation of further exploration into anti-IL-4–specific therapies. This might in part be due to the redundancy in mechanisms between IL-4 and other cytokines, especially IL-13.

Anti–IL-5 mAbs. IL-5 is required for eosinophil differentiation and survival. Two humanized IL-5 mAbs have been studied in human subjects: reslizumab (SCH55700) and mepolizumab. A small study evaluated subjects with severe persistent asthma treated with one dose of reslizumab (0.03 mg/kg, 0.3 mg/kg, or 1.0 mg/kg) or placebo for 90 days.[21] A decrease in serum eosinophils was noted only in the high-dose (1.0 mg/kg) group 30 days after treatment. No significant sustained changes in FEV_1, asthma symptom scores, sputum eosinophils, or physician-evaluated overall condition were noted with any dose of reslizumab compared with placebo.

Mepolizumab suppressed serum eosinophils in asthmatic subjects without altering T-cell functions.[22] Studies in patients with mild atopic asthma noted that mepolizumab reduced extracellular matrix protein remodeling and airway eosinphils.[23,24] Treatment with mepolizumab decreased median serum eosinophils from baseline by 100%, whereas airway eosinophils only decreased by 55%, with decreases in serum eosinophils lasting up to 16 weeks and decreases in sputum eosinophils lasting for 4 weeks.[24,25] However, no effects on clinical measures of asthma, including airway hyperresponsiveness, FEV_1, and peak flow measures, were noted.[24,25]

In patients with atopic dermatitis, mepolizuamb was ineffective in improving physician-based global assessment and pruritis scoring.[26]

Nasal polyps are frequently associated with increased levels of IL-5. One dose of reslizumab (either 1 or 3 mg/kg) was compared with placebo in the treatment of severe nasal polyposis.[27] Only 50% of patients treated with reslizumab had improvement in their nasal polyps. The only marker to predict responsiveness to therapy was an increased level of nasal IL-5 (>40 pg/mL) at baseline.

Hypereosinophilic syndrome might be a disease more responsive to anti–IL-5. In a small study of patients with hypereosinophilic syndrome, one dose of 1.0 mg/kg reslizumab decreased eosinophil counts to the normal range, with marked improvement of clinical signs and symptoms in 2 of the 4 patients treated.[28] Eosinophils remained suppressed up to 12 weeks, but as eosinophilia returned, so did the signs and symptoms of hypereosinophilic syndrome. When the 2 responsive patients received further doses, the magnitude and duration of the improvement lessened with each subsequent dose. Mepolizumab has also been evaluated in 2 small studies for hypereosinophilic syndrome.[29,30] Treatment with mepolizumab decreased serum eosinophils to normal levels within 24 hours of administration, with marked symptomatic improvement. Two of the three patients treated remained asymptomatic after cessation of mepolizumab therapy.[29] Mepolizumab treatment might have a corticosteroid-sparing effect in patients with hypereosinophilic syndrome.[30] Overall, there are too few patients treated to determine whether anti–IL-5 mAb therapy will be a good treatment option, but further studies are warranted.

Eosinophilic esophagitis is a chronic eosinophil-associated gastrointestinal disorder defined by high numbers of eosinophils in the esophagus (>20-24 eosinophils per high-power field [hpf]). In a study of 4 patients with dysphagia and eosinophilic strictures, mepolizumab decreased mean esophageal eosinophilia from 46/hpf to 6/hpf and maximal esophageal eosinophil levels from 153/hpf to 28/hpf. In addition, patients had improved quality of life and clinical outcomes.[31]

It is unclear whether monoclonal anti–IL-5 therapy for asthma or atopic dermatitis will be a good therapeutic option. This is likely due to the contribution of noneosinophilic cells, such as T_H2 lymphocytes, that remain unaffected by this therapy. However, promising results have been demonstrated in patients with hypereosinophilic syndrome and eosinophilic esophagitis. At this time, mepolizumab is currently undergoing further evaluation in eosinophilic esophagitis.

Anti–IL-13 mAb. Based on *in vitro* and murine data, IL-13 has a variety of biologic effects that could be important in the pathogenesis of asthma. IL-13 has been shown to induce airway hyperresponsiveness, mucus production, secretion of eotaxin, and changes in airway remodeling. In addition, IL-13 is important in the production of IgE. Thus strategies aimed at inhibiting the effects of IL-13 could be an important therapeutic avenue. Studies in mice and monkeys demonstrated reduction of lung inflammation in anti–IL-13–treated animals.[32,33] There are at least 3 different humanized mAbs under development that are specific for human IL-13. All 3 mAbs are either in phase I or phase II human clinical trials. A phase I clinical trial with CAT-354 showed that increasing single doses of intravenously administered anti–IL-13 mAb in 34 patients with mild asthma were well tolerated at all doses, and there were no identified safety concerns.[34]

IL-4Rα receptor antagonist. Both IL-4 and IL-13 bind to the IL-4Rα receptor subunit, which leads to a number of downstream signaling effects important for the biologic actions of both of these cytokines. AMG-317 is a fully human mAb antagonist to the IL-4Rα receptor subunit that is being developed by Amgen for the treatment of allergic asthma. Aerovant is an IL-4 mutein that inhibits the effects of both IL-4 and IL-13 through its ability to block IL-4Rα.[35] A phase IIa trial of inhaled Aerovant in asthmatic patients treated twice daily for 27 days resulted in a statistically significant 72% reduction in the late-phase asthmatic response caused by allergen inhalational challenge. Aerovant also decreased exhaled nitric oxide levels and improved pulmonary functions in this group of patients with asthma.

Aeroderm is the parenteral form of Aerovance's IL-4/IL-13 antagonist that has been used for the treatment of atopic dermatitis. This agent is currently in phase II clinical trials.[36]

IL-2 receptor antagonist. IL-2 increases cytokine synthesis in T cells and also has important biologic effects on regulatory T cells, natural killer cells, and B cells. Daclizumab is a humanized mAb approved for prevention of renal allograft rejection that binds to the α chain (CD25) of the IL-2 receptor on activated T cells. Daclizumab inhibited IL-2–induced proliferation and reduced T_H2 and T_H1 cytokines from activated T cells. Phase II study results in patients with moderate-to-severe asthma showed that daclizumab improved pulmonary functions, reduced asthma symptoms and rescue medication use, increased time to severe exacerbations, and reduced blood eosinophils and serum eosinophil cationic protein levels.[37] Daclizumab appeared to have greater positive therapeutic effects in patients with more refractory asthma. Daclizumab was fairly well tolerated in this study, but because of IL-2's pleiotropic effects, caution is warranted in targeting this key cytokine.

Anti–TNF-α strategies. TNF-α has a variety of biologic effects that could be important in asthma. TNF-α can induce increased airway responsiveness, the expression of key adhesion molecules on both epithelial and endothelial cells, the generation of chemoattractants from epithelial and endothelial cells, the synthesis and release of TGF-β, and chemokinesis of inflammatory cells. Blocking TNF-α improved lung function and asthma quality of life and reduced exacerbation frequency in patients with severe disease.[38] The therapeutic utility of this strategy has been reviewed by Brightling et al.[39] The results of recently completed large-scale clinical trials with blockers of TNF-α have been disappointing, and therefore it is unclear whether this strategy will be pursued.

B-CELL SURVIVAL AND MATURATION FACTOR RECEPTOR ANTAGONISTS

The TNF family ligands B-cell survival and maturation factor (BAFF) and APRIL regulate lymphocyte survival and activation. BAFF is important for costimulation of B cells and plays a role in immunoglobulin isotype switching to IgE. Therefore antagonists of BAFF, which are currently in clinical trials for a variety of autoimmune disorders, could potentially play a role in the therapy of respiratory diseases.

TRANSCRIPTION FACTOR INHIBITION

Gene expression for proinflammatory cytokines and mediators is regulated by transcription factors. Transcription factors are proteins that bind to promoter regions of genes and stimulate or inhibit their transcription into mRNA. Because of their central role in the synthesis of inflammatory mediators important for the pathogenesis of allergic diseases, transcription factors are potential targets for the development of immunomodulatory agents.

Syk kinase inhibitors

Syk kinase is an intracellular protein tyrosine kinase that plays an important role in both mast cell and basophil activation and the release of mast cell mediators, including important cytokines. Therefore inhibition of Syk kinase represents a potential therapeutic modality for allergic inflammation. R112, a Syk kinase inhibitor administered intranasally to patients with seasonal allergic rhinitis, demonstrated improvement in symptom scores over placebo with a duration of action exceeding 4 hours. No significant adverse events were reported.[40] R-343, a Syk kinase inhibitor, is under development for intrapulmonary delivery for the therapy of allergic asthma.

Peroxisome proliferator-activated receptor γ agonists

GATA-3 is thought to be a key transcription factor in the expression of T_H2 cytokines in allergic respiratory diseases. GATA-3 expression is increased in the airways of patients with asthma, and segmental allergen challenges lead to enhanced expression. In murine asthma models downregulation of GATA-3 resulted in decreased lung inflammation and reduced expression and production of T_H2 cytokines and IgE.[41] Although there are no current synthetic inhibitors of GATA-3, peroxisome proliferator-activated receptor (PPAR) γ agonists have been shown to inhibit GATA-3 expression and T_H2-driven inflammatory responses in murine models. Thiazolidinediones are PPAR-γ agonists that are currently approved for the treatment of non–insulin-dependent diabetes in human subjects. PPAR-γ agonists have a number of potential anti-inflammatory effects in addition to the inhibition of GATA-3 levels that could be beneficial for the treatment of allergic diseases.[42] PPAR-γ agonists can bind to other transcription factors, such as nuclear factor κB (NF-κB), signal transducer and activator of transcription, nuclear factor of activated T cells, and activator protein 1, preventing their association with DNA sequences. PPAR-γ agonists have also been reported to stabilize inflammatory transcription factor suppressor molecules. There are several small clinical trials ongoing examining the effects of PPAR-γ agonists for the therapy of allergic respiratory diseases, but results have not been published. Anecdotally, diabetic patients with asthma started taking thiazolidinediones for the therapy of diabetes had improvement in asthma manifested by decreased symptoms and improved pulmonary function values.[43]

NF-κB inhibition

NF-κB is a transcription factor that plays a key role in the expression of a multitude of inflammatory genes important for allergic respiratory disorders. Corticosteroids exert their anti-inflammatory effects in part through repression of NF-κB activity. Persistent activation of the NF-κB signaling pathway has been demonstrated in patients with severe uncontrolled asthma.[44] Therefore agents other than corticosteroids that inhibit the activity of NF-κB could provide new therapeutic avenues for the treatment of respiratory diseases and inflammation in general. There have been a number of decoy oligonucleotides developed that specifically target NF-κB. Although there are no data at present using these agents for the therapy of allergic respiratory diseases, decoy oligonucleotides targeting transcription factors have been in human trials for the treatment of other disorders, such as vein graft failure.[45]

MISCELLANEOUS AGENTS

Table II lists a number of other agents that are currently in human trials for the treatment of inflammatory diseases. A review of all of these agents is beyond the scope of this article. The mechanisms that are thought to be a part of their potential therapeutic effects are illustrated in Table II and Figs 1 and 2.

ANTI-IgE mAbs

Omalizumab is a 95% humanized mAb that recognizes and binds to the Fc portion of the IgE molecule. The binding of omalizumab to IgE results in the formation of soluble immune

complexes that are subsequently cleared by the reticuloendothelial system. Because omalizumab binds to the same site that IgE molecules use to attach to FcεRI, it cannot cross-link cell surface–expressed IgE.[46] The amount of cell-bound IgE decreases over the course of omalizumab treatment because of the decreased free IgE available.

Administration of omalizumab results in a rapid and substantial decrease in free IgE levels in serum and decreased expression of FcεRI on several cell types.[47-50] A 99% reduction in free serum IgE levels has been noted within 2 hours of omalizumab administration. Within 3 months of therapy, human basophil responsiveness (histamine releasability) was reduced by 90%.[48] Omalizumab administration results in reductions in expression of FcεRI on basophils, dendritic cells, and monocytes within 7 days.[48] Omalizumab might therefore have a significant effect on the sensitization phase of the allergic response through regulation of FcεRI expression on dendritic cells and monocytes. The mechanisms of action of omalizumab are summarized in Fig 3.

Omalizumab treatment reduced blood eosinophil levels in patients with seasonal allergic rhinitis and asthma and sputum eosinophils in asthmatic patients. In patients with mild asthma, omalizumab reduced tissue eosinophils; cells positive for FcεRI; $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes; B lymphocytes; and cells staining positive for IL-4. However, it did not improve airway hyperresponsiveness to methacholine.[51-53] Indeed, omalizumab has been shown to have inconsistent effects on airway hyperresponsiveness.

A number of studies have established the efficacy and safety of omalizumab, leading to the US Food and Drug Administration's approval of omalizumab for the treatment of moderate-to-severe persistent allergic asthma in patients 12 years and older. Three phase III trials were conducted on a total of 1405 patients with moderate-to-severe allergic asthma.[54-56] In all 3 studies, when compared with placebo, omalizumab reduced asthma exacerbations and had a corticosteroid-sparing effect. A significant number of omalizumab-treated patients were able to decrease or, in many cases, discontinue inhaled corticosteroids. Twice as many individuals treated with omalizumab successfully discontinued corticosteroids compared with those treated with placebo. In addition, fewer asthma symptoms, less rescue medication use, and improved quality-of-life scores were noted in the omalizumab-treated patients. In the adolescent and adult studies, omalizumab resulted in small but statistically significant improvements in peak expiratory flow and FEV_1 values.[56] Significantly fewer unscheduled outpatient visits, emergency department visits, and hospitalizations were observed in the omalizumab-treated patients compared with those in the placebo-treated patients.[57] Patients with features suggestive of greater disease severity appeared to obtain the most benefit from the addition of omalizumab to their therapeutic regimens. Recent expert guidelines suggest omalizumab as a therapeutic option for patients 12 years and older with perennial allergic asthma whose symptoms are not well controlled by a medium-dose inhaled corticosteroid and a long-acting β-agonist.[58]

In patients with seasonal allergic rhinitis, omalizumab therapy significantly decreased nasal symptoms scores, improved rhinitis quality-of-life scores, and reduced rescue antihistamine use and days missed from work or school when compared with placebo.[59,60] The use of omalizumab has also been shown to be effective in the treatment of perennial allergic rhinitis.[61] In patients with allergic rhinitis, omalizumab therapy significantly decreased responses to allergen challenge within 7 to 14 days and decreased nasal challenge symptom scores and markers of inflammation.[48,62]

TABLE II. Immunomodulators and putative targets

Target	Agents
IL-2	Daclizumab (IL-2rα)
IL-4	Anti-IL-4 mAb
	sIL-4r
IL-4/IL-5	Suplatast
	AVP-13358
IL-5	Mepolizumab
	Reslizumab
IL-13	CAT 354 (mAb)
	IMA 638 (mAb)
	QAX 576 (mAb)
IL-4/IL-13	AER 001 (mutein)
	AMG 317 (mAb)
CD4	Keliximab
CD11a	Efalizumab
CD23	Lumiliximab
CD40L	IDEC-131 (mAb)
BAFF	Various
NF-κB	Decoy oligos
Selectins	Bimosiamose
	TBC 4746 (VLA-4)
Syk kinase	R112 R343 (inhaled)
STAT1	AVT-01 (ds oligo decoy, inhaled)
T_H2	ISS DNA alone
	ISS with Ag (eg, Tolamba)
	PPAR-γ agonists
TNF-α	Infliximab
	Etanercept
	Adalimumab

Not all agents listed are specifically under development for allergic respiratory diseases.
CD40L, CD40 ligand; *BAFF*, B-cell survival and maturation factor; *VLA-4*, very late antigen 4; *STAT1*, signal transducer and activator of transcription 1; *ISS*, immunostimulatory oligodeoxynucleotides; *Ag*, antigen.

Allergic rhinitis and asthma frequently coexist. Poor control of rhinitis might exert a detrimental effect on asthma. In 405 patients with moderate-to-severe asthma receiving stable therapy who also had persistent allergic rhinitis, treatment with omalizumab improved both asthma and rhinitis quality-of-life indices (57.7% vs 40.6% for placebo).[63] Fewer asthma exacerbations were observed in the omalizumab-treated patients than in the placebo-treated patients (20.6% vs 30.1%).[63]

The addition of omalizumab to standard maintenance dose immunotherapy was evaluated in children allergic to birch and grass.[64] The combination of immunotherapy plus omalizumab versus immunotherapy alone produced a further reduction in seasonal allergic rhinitis symptoms of 35% for the birch group and 45% for the grass immunotherapy group, respectively; rescue medication scores of 78% for the birch group and 81% the for grass immunotherapy group; and seasonal allergic rhinitis symptom load of 40% for both the grass and birch groups. Furthermore, the safety profile was at least as good as that of immunotherapy alone.

The effects of pretreatment of patients with ragweed-induced allergic rhinitis with omalizumab before rush immunotherapy were recently published.[65] The average daily allergy severity scores were significantly better in the omalizumab plus immunotherapy group versus the immunotherapy-only group. Furthermore, in protocol-correct patients the combination of omalizumab plus immunotherapy was better than omalizumab alone, immunotherapy

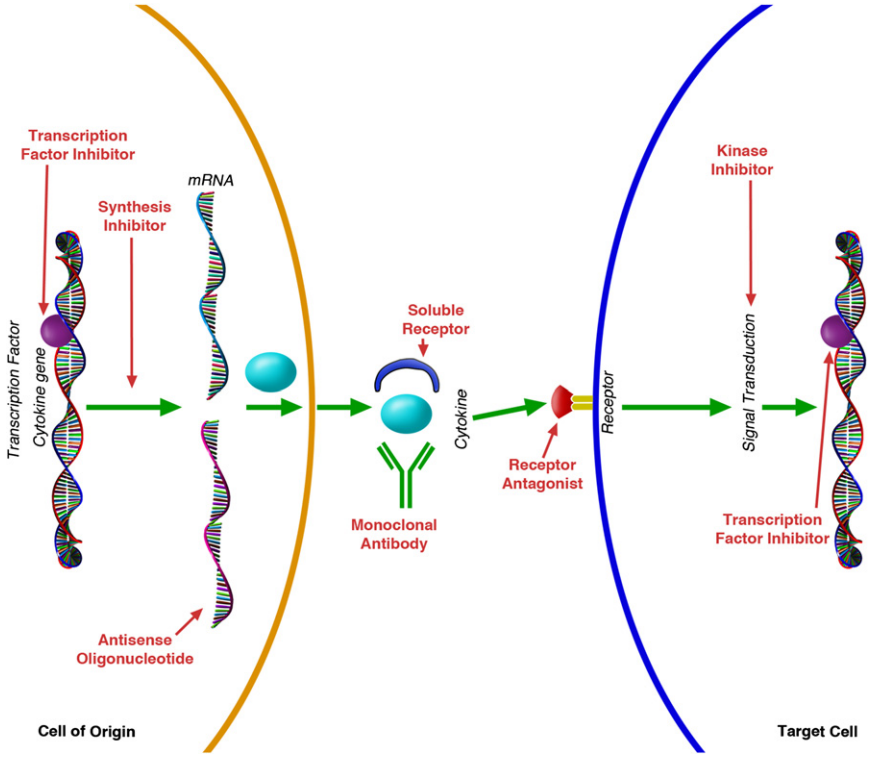


FIG 2. Mechanistic strategies to inhibit cytokine-induced effects.

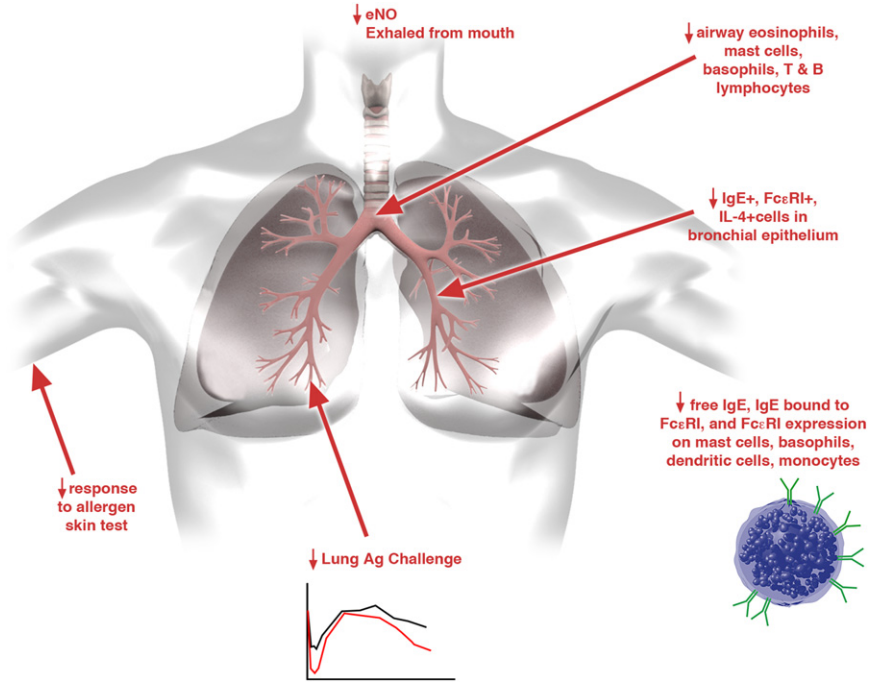


FIG 3. Mechanisms of action of omalizumab. *eNO*, Exhaled nitric oxide; *Ag*, antigen.

alone, or placebo alone. Patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone. *Post hoc* analysis of groups receiving immunotherapy demonstrated that the addition of omalizumab resulted in a 5-fold decrease in the risk of anaphylaxis caused by rush immunotherapy. Thus combined therapy with omalizumab and allergen immunotherapy might be an effective strategy to permit more rapid and higher doses of allergen immunotherapy to be given more safely and with greater efficacy to patients with allergic diseases.[65]

Another humanized IgG1 mAb against IgE, TNX-901, was evaluated in patients with peanut allergy. A double-blind, placebo-controlled, randomized trial in 84 patients with proved peanut hypersensitivity evaluated 3 doses of TNX-901 given every 4 weeks for 16 weeks.[66] The mean baseline threshold of sensitivity to peanut flour was 178 to 436 mg. By the end of treatment, the high-dose TNX-901 group had a significant improvement from a threshold dose of 178 mg (half of a peanut) to 2805 mg (nearly 9 peanuts). However, 25% of the patients had no improvement.

Small case studies of omalizumab therapy for atopic dermatitis have demonstrated conflicting results.[67-69] In patients with extremely increased serum IgE levels, even high-dose omalizumab did not decrease levels sufficiently to effect clinical improvement. However, in patients with lower IgE levels and body weights, such that omalizumab dosing was closer to recommended values, some improvements were noted.

In 3 patients with refractory chronic urticaria, omalizumab therapy cleared their urticaria within 1 week for 2 patients and within 6 weeks for the third patient.[70] Omalizumab is more likely to be of therapeutic benefit in patients with chronic urticaria with autoantibodies to IgE or FcεRI.

Omalizumab is generally well tolerated. The most common adverse events are local reactions at the injection sites. However, in 2007 the US Food and Drug Administration was alerted to the possibility of increased frequency of anaphylaxis with omalizumab administration.[71] Anaphylaxis was reported after administration of omalizumab in clinical trials (0.1% frequency) and was therefore discussed in the initial product labeling.[72] Data from approximately 57,000 patients treated with omalizumab after approval have indicated that anaphylaxis can occur with any dose, there is a delayed onset of symptoms beyond 2 hours, and there is a protracted course, with signs and symptoms lasting many hours.[73] The mechanisms involved in omalizumab-associated anaphylaxis have not been delineated, nor have any specific predictive risk factors. These findings have led to new recommendations for the administration of omalizumab.[74] Nonetheless, the development of a selective anti-IgE humanized mAb represents a novel and important therapeutic option for severe allergic asthma and other allergic diseases.

CONCLUSION

As discussed in this review, many immunomodulators are currently under development for the therapy of asthma and allergic and immunologic diseases. As we learn more about the molecular mechanisms involved in the pathogenesis of allergic and immunologic diseases, additional specific pathway inhibitors that are novel will likely make their way into clinical trials. These approaches will help to better define the pathogenesis of disease processes and the utility of inhibiting specific mediators, cytokines, or molecular pathways (Fig 1). It is likely that agents that are specific for a particular molecule might not be effective in all patients because of the redundancy in the immune system and the heterogeneity of the diseases. Immunomodulators that have a broader spectrum of effects because of their actions upstream might have more therapeutic utility but higher risks for adverse events. The study of immunomodulators in human subjects will ultimately be required to determine their therapeutic utility because agents showing promise in *in vitro* and animal models have failed in human studies. Because many of the agents reviewed are in early phases of clinical trials, their utility in the therapy of allergic diseases will await long-term, multicenter clinical trials accurately assessing their risks and benefits.

REFERENCES

1. Krieg AM. Therapeutic potential of Toll-like receptor 9 activation. Nat Rev Drug Discov 2006;5:471-84.
2. Casale TB, Kessler J, Romero FA. Safety of the intranasal toll-like receptor 4 agonist CRX-675 in allergic rhinitis. Ann Allergy Asthma Immunol 2006;97:454-6.
3. Bhattacharjee RN, Akira S. Modifying toll-like receptor 9 signaling for therapeutic use. Mini Rev Med Chem 2006;6:287-91.
4. Hayashi R, Raz E. TLR9-based immunotherapy for allergic disease. Am J Med 2006;119:897, e1-6.
5. Kline JN. Eat dirt CpG DNA and immunomodulation of asthma. Proc Am Thorac Soc 2007;4:283-8.
6. Marshall JD, Abtahi S, Eiden JJ, Tuck S, Milley R, Haycock F, et al. Immunostimulatory sequence DNA linked to Amb a 1 allergen promotes TH1 cytokine expression while downregulating TH2 cytokine expression in PBMCs from human patients with ragweed allergy. J Allergy Clin Immunol 2001;108:191-7.
7. Simons FER, Shiykishima Y, Van Nest G, Eiden JJ, HayGlass KT. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. J Allergy Clin Immunol 2004;113:1144-51.
8. Higgins D, Rodriquez R, Milley R, Marshall J, Abbate C, Cruz TD, et al. Modulation of immunogenicity and allergenicity by controlling the number of immunostimulatory oligonucleotides linked to Amb a 1. J Allergy Clin Immunol 2006;118:504-10.
9. Creticos PS, Shroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R, et al. Immunotherapy with ragweed-toll-like receptor agonist vaccine for allergic rhinitis. N Engl J Med 2006;355:1445-55.
10. Tulic MK, Fiset PO, Christodoulopoulos P, Vaillancourt P, Desrosiers M, Lavigne F, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. J Allergy Clin Immunol 2004;113:235-41.
11. Bernstein DI, Segall N, Nayak A, Casale T, Korenblatt P, Martins E. Safety and efficacy of the novel vaccine Tolamba in ragweed allergic adults, a dose finding study. J Allergy Clin Immunol 2007;119(suppl):S78-9.
12. Guavreau GM, Hessel EM, Boulet LP, Coffman RL, O'Byrne PM. Immunostimulatory sequences regulate interferon-inducible genes but not allergic airway responses. Am J Respir Crit Care Med 2006;174:15-20.
13. Krieg AM. Antiinfective applications of toll-like receptor 9 agonists. Proc Am Thorac Soc 2007;4:289-94.
14. Krieg AM. Development of TLR9 agonists for cancer therapy. J Clin Invest 2007;117:1184-94.
15. Tamaoki J, Kondo M, Sakai N, Aoshiba K, Tagaya E, Nakata J, et al. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. Lancet 2000;356:273-8.
16. Horiguchi T, Tachikawa S, Handa M, Hanazono K, Kondo R, Ishibashi A, et al. Effects of suplatast tosilate on airway inflammation and airway hyperresponsiveness. J Asthma 2001;38:331-6.
17. Yoshida M, Aizawa H, Inoue H, Matsumoto K, Koto H, Komori M, et al. Effect of suplatast tosilate on airway hyperresponsiveness and inflammation in asthma patients. J Asthma 2002;39:545-52.
18. Richards ML, Lio SC, Sinha A, Tieu KK, Sircar JC. Novel 2-(substituted phenyl) benzimidazole derivatives with potent activity against IgE, cytokines, and CD23 for the treatment of allergy and asthma. J Med Chem 2004;47:6451-4.
19. Borish LC, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti JM, et al. Interleukin-4 Receptor in Moderate Atopic Asthma: a phase I/II randomized, placebo-controlled trial. Am J Respir Crit Car Med 1999;160:1816-23.
20. Borish LC, Nelson HS, Corren J, Bensch G, Busse WW, Whitmore JB, et al. Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. J Allergy Clin Immunol 2001;107:963-70.
21. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HAM, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med 2003;167:1655-9.
22. Büttner C, Lun A, Splettstoesser T, Kunkel G, Renz H. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell function. Eur Respir J 2003;21:799-803.
23. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest 2003;112:1029-36.
24. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 2003;167:199-204.

25. Leckie MJ, Brinke AT, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. Lancet 2000;356:2144-8.
26. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005;60:693-6.
27. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol 2006;118:1133-41.
28. Klion AD, Law MA, Noel P, Kim YJ, Haverty TP, Nutman TB. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. Blood 2004;103:2939-41.
29. Plötz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med 2003;349:2334-9.
30. Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 2004;113:115-9.
31. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. J Allergy Clin Immunol 2006;118:1312-9.
32. Bree A, Schlerman FJ, Wadanoli M, Tchistiakova L, Marquette K, Tan XY, et al. IL-13 blockade reduces lung inflammation after *Ascaris suum* challenge in cynomolgus monkeys. J Allergy Clin Immunol 2007;119:1251-7.
33. Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). Clin Exp Allergy 2005;35:1096-103.
34. Available at: http://www.cambridgeantibody.com/data/assets/pdf_file/11030/CAT-354_Mar07.pdf. Accessed January 11, 2008.
35. Available at: http://www.aerovance.com/press_132007.html. Accessed January 11, 2008.
36. Available at: http://www.aerovance.com/aeroderm.html. Accessed September 27, 2007.
37. Nelson HS, Busse WW, Israel E, Baker JW, Charous BL, Kim KT, et al. Daclizumab improves asthma control in patients with refractory asthma. J Allergy Clin Immunol 2005;115(suppl):S134.
38. Berry M, Brightling C, Pavord I, Wardlaw AJ. TNF-alpha in asthma. Curr Opin Pharmacol 2007;7:279-82.
39. Brightling C, Berry M, Amrani Y. Targeting TNF-α a novel therapeutic approach for asthma. J Allergy Clin Immunol 2008;121:5-10.
40. Meltzer EO, Berkowitz RB, Grossbard EB. An intranasal Syk-kinase inhibitor (R112) improves the symptoms of seasonal allergic rhinitis in a park environment. J Allergy Clin Immunol 2005;115:791-6.
41. Zhang DH, Yang L, Cohn L, Parkyn L, Homer R, Ray P, et al. Inhibition of allergic inflammation in a murine model of asthma by expression of a dominant-negative mutant of GATA-3. Immunity 1999;11:473-82.
42. Spears M, McSharry C, Thomson NC. Peroxisome proliferator-activated receptor-gamma agonists as potential anti-inflammatory agents in asthma and chronic obstructive pulmonary disease. Clin Exp Allergy 2006;36:1494-504.
43. Hashimoto Y, Nakahara K. Improvement of asthma after administration of pioglitazone. Diabetes Care 2002;25:401.
44. Gagliardo R, Chanez P, Mathieu M, Bruno A, Constanzo G, Gougat C, et al. Persistent activation of nuclear factor-kappaB signaling pathway in severe uncontrolled asthma. Am J Respir Crit Care Med 2003;168:1190-8.
45. Conte MS, Lorenz TJ, Bandyk DF, Clowes AW, Moneta GL, Seely BL. Design and rationale of the PREVENT III clinical trial: edifoligide for the prevention of infrainguinal vein graft failure. Vasc Endovasc Surg 2005;39:15-23.
46. Easthope S, Jarvis B. Omalizumab. Drugs 2001;61:253-60.
47. MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
48. Lin H, Boesel K, Griffith D, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. J Allergy Clin Immunol 2004;113:297-302.
49. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεRI expression. J Allergy Clin Immunol 2003;112:1147-54.
50. Beck LA, Marcotte GV, MacGlashan D Jr, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. J Allergy Clin Immunol 2004;114:527-30.
51. Plewako H, Arvidsson M, Petruson K, Oancea I, Holmberg K, Ädelroth E, et al. The effect of omalizumab on nasal allergic inflammation. J Allergy Clin Immunol 2002;110:68-71.
52. Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthma following treatment with omalizumab. Int Arch Allergy Immunol 2003;131:46-52.
53. Djukanović R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 2004;170:583-93.
54. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-90.
55. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;108:e36.
56. Solér M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-61.
57. Corren J, Casale TB, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003;111:87-90.
58. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: expert panel report 3. Bethesda (MD): National Institutes of Health/National Heart, Lung, and Blood Institute; 2007. Publication no. 08-4051. Available at: www.nhlbi.nih.gov/guildelines/asthma/asthgdln.htm. Accessed September 27, 2007.
59. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956-67.
60. Ädelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000;106:253-9.
61. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2003;91:160-7.
62. Hanf G, Noga O, O'Connor A, Kunkel G. Omalizumab inhibits allergen challenge-induced nasal response. Eur Respir J 2004;23:414-8.
63. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004;59:709-17.
64. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.
65. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117:134-40.
66. Leung DYM, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003;348:986-93.
67. Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ. Treatment of recalcitrant atopic dermatitis with omalizumab. J Am Acad Dermatol 2006;54:68-72.
68. Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I. Efficacy of anti-IgE therapy in patients with atopic dermatitis. J Am Acad Dermatol 2006;55:168-70.
69. Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. J Am Acad Dermatol 2005;53:338-40.
70. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol 2007;99:190-3.
71. US Food and Drug Administration statement. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/omalizumabHCP.htm. Accessed September 27, 2007.
72. Prescribing information: summary of product characteristics. Available at: http://www.xolair.com. Accessed September 27, 2007.
73. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J Allergy Clin Immunol 2007;120:1378-81.
74. Cox L, Platts-Mills TAE, Finegold I, Schwartz LB, Simons FER, Wallace DV. AAAAI/ACAAI Joint Task force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol 2007;120:1373-7.