

Future Forms of Immunotherapy and Immunomodulators in Allergic Disease

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KEYWORDS

- Immunotherapy • Immunomodulator • Cytokine
- Allergic rhinitis • Asthma

Novel agents for treating allergic diseases are being developed based on our expanding knowledge of innate and adaptive responses of the immune system at the molecular level. Immunomodulators are agents that cause a decrease in the pathologic immune response, rather than necessarily a return to an immunologically naive, or unresponsive state. Allergen-specific subcutaneous immunotherapy (IT) is the only form of immunomodulator that has been shown to induce immune tolerance, that is, long-lasting therapeutic effects that persist after discontinuation of therapy. It may also prevent further progression to multiple aeroallergen sensitization. However, with the benefits of IT come rare but real risks of severe adverse reactions, including anaphylaxis and death. Several immunomodulators are being developed that may improve the immunogenicity of IT without increasing its allergenicity, thereby improving its risk/benefit profile and it is to be hoped improving quality of life (QOL) and reducing the burden of disease (**Fig. 1**).

This review discusses future forms of IT, specifically toll-like receptor (TLR) agonists as adjuvants, but also other immunomodulators of allergic disease, including cytokine blockers (oral, parenteral, subcutaneous, and inhaled), transcription factor inhibitors, synthesis inhibitors, anti-IgE monoclonal antibodies (mAbs), receptor antagonists, and

Disclosures of potential conflicts of interest: T.T. Nguyen has nothing to disclose; J.R. Stokes has received speaker's honoraria from the Advancing Respiratory Care Network subset of the Respiratory Allergic Disease Foundation and has received research support from Novartis, Genentech, Stallergenes, and Schering-Plough; T.B. Casale is on the Stallergenes advisory board, has received research support from Novartis, Genentech, Stallergenes, and Schering-Plough, and is Executive Vice President of the American Academy of Allergy, Asthma & Immunology. Department of Medicine, Division of Allergy and Immunology, Creighton University School of Medicine, 601 North 30th Street, Suite 3M100, Omaha, NE 68131, USA

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Immunol Allergy Clin N Am 31 (2011) 343–365

doi:[10.1016/j.iac.2011.02.003](https://doi.org/10.1016/j.iac.2011.02.003)

immunology.theclinics.com

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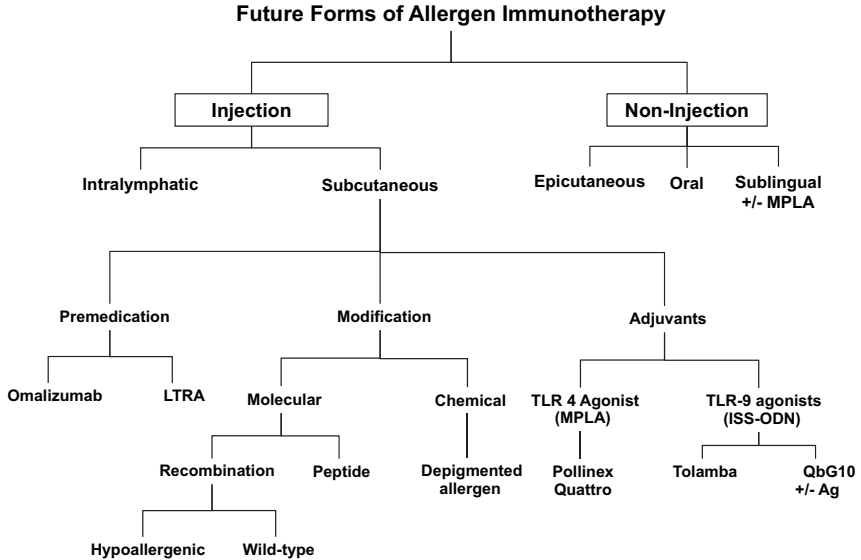


Fig. 1. Future forms of allergen immunotherapy under investigation in animal models and/or clinical trials. Toll-like receptor (TLR) agonists, particularly TLR-4 and TLR-9, are discussed in this article, whereas the other forms are addressed elsewhere in this issue. MPLA, mono-phosphoryl lipid A; QbG10, Q β protein G10; LTBA, leukotriene receptor antagonist.

other receptor modulators (Fig. 2). Rationale and preclinical in vitro and animal study data are reviewed for each agent but the focus is on presenting human clinical trial results on safety, tolerability, and efficacy that determine the risk/benefit profiles and likelihood of further development and usefulness in human allergic diseases.

Other promising forms of IT, including sublingual, peptide, recombinant, epicutaneous, and intralymphatic IT, and use of adjuvants other than TLRs are discussed in other sections with these respective themes (see Fig. 1).

TLRS

TLRs are cell surface or intracellular receptors that recognize pathogen-associated molecular patterns commonly conserved in bacteria, viruses, and some fungi. Binding of these TLRs activates antigen-presenting cells (APCs), such as macrophages and dendritic cells, to commence both innate and adaptive immune responses. Agents directed against TLRs may skew the cytokine balance from Th2 toward Th1, thereby affecting allergic diseases. Eleven TLRs have been identified in humans, and agonists for 4 TLRs (TLR-1, TLR-4, TLR-8, and TLR-9) have been studied in clinical trials for allergic diseases. Of these, ligands for TLR-4 and TLR-9 have been most studied and are the focus of the following discussion.

TLR-9 Agonists (Immunostimulatory Oligodeoxynucleotides)

TLR-9 (CD289) recognizes unmethylated CpG DNA motifs from bacteria that are engulfed by endosomes that are either exposed after proteolytic degradation or produced de novo if these pathogens persist intracellularly. In vertebrates, CpG sequences are often silenced by methylation. In humans, plasmacytoid dendritic cells (pDCs) and B cells express the highest concentrations of TLR-9. On TLR-9 activation,

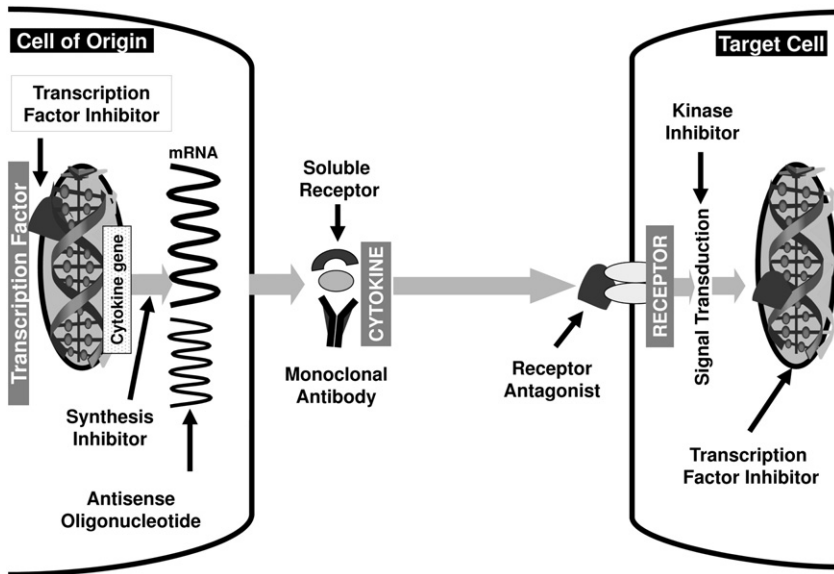


Fig. 2. Strategies to inhibit inflammatory pathways. Overview of different targets and mechanisms of action studied in inhibition of inflammatory pathways using drugs covered in this article. (Adapted from Casale TB, Stokes J. Immunomodulation for allergic respiratory disorders. *J Allergy Clin Immunol* 2008;121(2):294; with permission.)

pDCs produce interferon α (IFN- α), leading to secondary activation of neutrophils, monocytes, and natural killer T cells, whereas B cells produce interleukin 6 (IL-6) and IL-10 and induce B-cell differentiation into plasma cells and trigger IgG isotype switching and antibody production.¹ TLR-9 agonists act by these mechanisms to activate both innate and adaptive immune responses.

There are 3 known classes of immunostimulatory CpG oligodeoxynucleotides (ISS-ODNs): A, B, and C, which differ in length, motif, and which immune responses each elicits; A and B have been studied as adjuvants in allergen IT, and B and C in infectious diseases and malignancy.

Tolamba (Dynavax Technologies, Berkeley, CA, USA) is a B-type ISS-ODN, ISS-1018, covalently linked to the major ragweed allergen, *Amb a 1*. A phase 2 clinical trial was conducted in 25 adult patients with seasonal ragweed allergic rhinitis who were treated with 6 weekly subcutaneous injections of Tolamba or placebo before the ragweed season and then monitored for 2 ragweed seasons. Patients receiving Tolamba reported better QOL and rhinitis symptoms than the placebo group and had suppression of seasonal increases in *Amb a 1*-specific IgE, which persisted over both ragweed seasons.² A subsequent study reported reduction in IL-4 and IFN- γ mRNA-positive cells and also eosinophils from nasal biopsies in Tolamba-treated patients, but did not reproduce significant reductions in nasal symptoms.³ Questions about efficacy continued after the interim analysis of a large, multicenter phase 2 clinical trial, the Dynavax Allergic Rhinitis Tolamba Trial (DARTT), failed to meet its primary end point (difference in total nasal symptom score), possibly because symptom scores were too low in both study groups even during the ragweed season to detect a treatment effect.⁴ Further development of Tolamba has been placed on hold.

An inhaled form of ISS-1018 has been studied in atopic asthmatic patients.⁵ Although treatment significantly increased IFN- γ and IFN- γ -inducing genes, it did not attenuate early-phase or late-phase asthmatic responses to allergen challenge nor were there significant reductions in sputum eosinophils or Th2-related gene expression.

A-type ISS-ODNs, with and without conjugation to allergen, have also been studied in allergen IT. A-type ISS-ODNs are more potent inducers of IFN- γ than B-type ISS-ODNs but their unstable phosphodiester backbones made them less clinically useful until they were stabilized by association to viruslike particles such as the bacteriophage Q β coat protein. A single-center, open-label phase 1/2a study of 20 patients with perennial rhinitis with house dust mite (HDM) allergy reported that subcutaneous allergen IT of HDM extract conjugated to an A-type ISS-ODN (G10) and contained in Q β protein (Qb) over a 10-week period was well tolerated and still reduced symptoms and skin test responses at least 38 weeks after treatment completion.⁶ In a more recent phase 2 study, CYT003-QbG10 (Cytos Biotechnology, Zurich, Switzerland) was used without allergen in 80 patients with mild to moderate perennial allergic rhinoconjunctivitis to HDM and/or cat allergens. Patients received 6 weekly subcutaneous injections of CYT003-QbG10 or placebo; after 8 weeks the treatment group had significantly improved total rhinoconjunctivitis symptom scores, and median allergen tolerance on nasal allergen provocation improved 100-fold.⁷

In another phase 2 trial, 63 persistent allergic asthmatic patients on inhaled corticosteroids (ICS) received either 7 weekly subcutaneous injections of CYT003-QbG10 or placebo, and were monitored over a 12-week period. During the run-in period, all patients were stabilized on an ICS, beclomethasone, and then 4 weeks into the study, the ICS was reduced by 50%, and if possible, reduced to zero in another 4 weeks. From weeks 6 to 12, the treatment group had significantly better combined symptom and medication scores than placebo, and at 12 weeks, had stable forced expiratory volume after 1 second (FEV₁) compared with placebo. A subgroup analysis of patients who were able to come off ICS after week 8 suggests that CYT003-QbG10 may be as effective as an ICS in asthma.⁸

TLR-4 Agonists

TLR-4 (CD284) is expressed on the cell surface and, with the adaptor molecule CD14, binds lipopolysaccharide (LPS) found on gram-negative bacteria leading to proinflammatory Th1 responses. Monophosphoryl lipid A (MPLA) is derived from the active component of LPS of *Salmonella minnesota* R595. It has been used as an adjuvant in the anthrax vaccine used by the US Armed Forces and has been investigated in allergen rhinitis and allergen IT.

CRX-675, an intranasal formulation of MPLA, was administered in patients with ragweed allergic rhinitis at varying doses (2, 20, 100, and 200 μ g) 24 hours before ragweed intranasal challenge. It was tolerated well, but there was no inhibition of nasal allergen challenge responses compared with placebo; however, improvement in nasal symptom scores was observed at the 100- μ g dose.⁹

Pollinex Quattro (Allergy Therapeutics, West Sussex, UK) is an allergy vaccine that contains pollen extract (available with grass, tree, parietaria, or ragweed) that is chemically modified by glutaraldehyde and adsorbed onto an L-tyrosine depot with an MPLA adjuvant. It has been used in Europe and Canada as a preseasonal ultrashort-course IT consisting of 4 weekly subcutaneous injections. A large multicenter phase 3 study of G301 (Pollinex Quattro-Grass) that enrolled 1028 patients to receive ultrashort-course IT or placebo for 4 weeks reported significant improvement in symptom plus medication scores during the peak (12%) and entire pollen

season (13%) and improved QOL scores over placebo. Active treatment was well tolerated. A prospective study of 34 patients with seasonal grass pollen allergic rhinitis was conducted with Pollinex Quattro-G given over 2 seasons.¹⁰ Specific grass IgG and IgG4 levels increased slightly the first season but only significantly after the second season along with an increase in FoxP3+ regulatory T cells, suggesting that at least 2 seasonal IT courses are needed to establish tolerance. A controlled field study of 29 *Parietaria* seasonal allergic patients who underwent MPLA-adjuvanted IT compared with 28 who refused, showed persistent improvement in rhinoconjunctivitis and asthma symptoms, although no effect on lung function, after 3 years of IT and 5 years after discontinuation in the treated group.¹¹ Although Pollinex Quattro appeared to be well tolerated and effective in adults and children,¹² clinical trials in the United States were halted because of a reported serious adverse event of transverse myelitis in 1 patient. A recent study has reported the potential of using MPLA to augment the clinical and biologic responses to sublingual IT (SLIT) in grass allergic patients.¹³

CYTOKINE BLOCKERS

Th2 cytokines, particularly IL-4, IL-5, and IL-13, play essential roles in allergic diseases and have been targeted by immunomodulators such as mAbs directed against the cytokines themselves or their receptors. Other unique blocking strategies have been studied in phase 1 and 2 clinical trials. Therapies directed against other cytokines including IL-2, IL-9, and tumor necrosis factor α (TNF- α) have also been investigated for their roles in treating allergic diseases. Cytokine-blocking therapies must be evaluated carefully, because redundancy of effector mechanisms may render single cytokine-directed therapy ineffective, yet inhibition of pleiotropic cytokines may lead to undesired or unexpected side effects and risks that outweigh benefits in patients.

ORAL SYNTHESIS INHIBITORS

Two oral inhibitors of cytokine synthesis have undergone human clinical trials. Suplatast tosilate (IPD-1151T, Taiho Pharmaceutical, Tokyo, Japan) is an oral dimethylsulfonium compound that selectively inhibits Th2 type cytokine production and is taken 3 times daily but is available only in Japan. In murine models of asthma, suplatast reduced levels of IL-4, IL-5, IL-13, eotaxin-1, and transforming growth factor β (TGF- β) in bronchoalveolar lavage fluid and inhibited airway remodeling.¹⁴ Pretreatment with suplatast in rats and mice significantly suppressed allergen-induced nasal symptoms, mucus secretion, and nasal eosinophilia and blunted the increase in mRNA expression of histamine H₁ receptors and IL-4.^{15,16}

In human asthmatic patients, suplatast inhibited monocyte-derived dendritic cells in vitro from stimulating CD4+ T cells to produce IL-5 and IFN- γ .¹⁷ Suplatast administered during the first 6 months of IT in adults with perennial allergic rhinitis to HDM significantly decreased serum IL-4 and specific IgE compared with placebo and perhaps may improve efficacy and/or tolerability to IT.¹⁸ Moderate to severe asthmatic patients who received suplatast reported significantly better FEV₁, peak expiratory flow, and asthma symptom scores than placebo when their stable dose of ICS was reduced by half. Suplatast may be effective in mild asthmatic patients who do not respond to leukotriene receptor antagonist monotherapy.^{19,20} Suplatast has also been shown to improve lung eosinophilia and airway hyperresponsiveness (AHR).²¹⁻²³ Topical suplatast formulations inhibited expression of IL-4 and IL-5 in skin of a mouse model of atopic dermatitis, and may be effective as an adjunctive, sparing agent to topical calcineurin inhibitors in humans.^{24,25}

A phase 1 clinical trial with AVP-13,358, a novel, orally available 2-(substituted phenyl)benzimidazole derivative (Avanir Pharmaceuticals, Aliso Viejo, CA, USA) reported safety and tolerability at all tested doses in 54 healthy volunteers and was able to suppress antigen-stimulated IL-4 and IL-5 responses, but is not in development.

SOLUBLE RECEPTOR/MAB THERAPIES

Chemokine Receptor CCR3 and Common β Chain Antagonist

CCR3 is the chemokine receptor for eotaxin-3 and is involved in eosinophil trafficking. GM-CSF, IL-3, and IL-5 are critical to eosinophil development in the bone marrow. TPI-ASM8 (Pharmaxis, Frenchs Forest, Australia) is a nebulized drug containing 2 modified phosphorothioate antisense oligonucleotides: one targeting CCR3, the other targeting the common β chain of the receptors for GM-CSF, IL-3, and IL-5. In mild asthmatic patients, TPI-ASM8 attenuated allergen-induced increases in mRNA of the common β chain and CCR3 and also significantly reduced the early asthmatic response and sputum eosinophilia.²⁶ A subsequent study reported dose-response relationships for these effects, significant attenuation of the late asthmatic response, and tolerability at all tested doses.²⁷ In an asthmatic rat model, TPI-ASM8 added to nebulized budesonide showed a synergistic, dose-dependent reduction of eosinophil recruitment induced by allergen challenge and decreased bronchoalveolar lavage fluid levels of monocyte chemoattractant protein 1 and IL-13, suggesting that TPI-ASM8 may be an effective adjunctive treatment in asthma.²⁸ A phase 2 3-way crossover study of TPI-ASM8 in mild asthmatic patients started in late 2010.²⁹

Anti-IL-5 mAb

IL-5 is critical to the differentiation and maturation of eosinophils in the bone marrow and their subsequent egress to the circulation, and may be important in the pathogenesis of several allergic disorders, including certain asthma phenotypes, eosinophilic esophagitis, and hypereosinophilic syndrome. There are currently 2 anti-IL-5 mAbs in active development for allergic diseases: mepolizumab and reslizumab. Initial data from animal models had been promising, but clinical trials thus far have only been able to show decreases in eosinophilia with significant concurrent improvements in clinical outcomes only in subsets of patients.

Mepolizumab

Mepolizumab (Bosatria, GlaxoSmithKline, Vienna, Austria) is a recombinant humanized anti-IL-5 mAb that has been studied in asthma, atopic dermatitis, and eosinophilic esophagitis. Two single intravenous infusions of mepolizumab 750 mg given 1 week apart were studied in patients with moderate to severe atopic dermatitis and resulted in significant decreases in peripheral blood eosinophilia but not clinically significant changes in symptoms.³⁰ In eosinophilic esophagitis, mepolizumab showed improved mean esophageal eosinophilia histologically and decreased TGF- β 1 expression, but resulted in limited improvement in clinical symptoms.³¹ In asthma, several initial clinical trials failed to show clinical outcome improvement despite reduction in sputum and blood eosinophilia. However, a recent clinical trial of 1 year's duration reported effectiveness of mepolizumab in reducing blood and sputum eosinophilia in patients with refractory eosinophilic asthma, and also in clinical parameters, namely exacerbations and asthma QOL scores.³² Another trial also reported improved FEV₁, asthma control, and reductions in sputum and serum eosinophils in asthmatic patients with persistent sputum eosinophilia despite prednisone treatment, over a 5-month treatment period and up to 8 weeks after the last infusion.³³

Reslizumab

Reslizumab (Cinquil [SCH55700] Ception Therapeutics Inc, Frazer, PA, USA) is a humanized IgG2 anti-IL-5 mAb that has been shown to block pulmonary eosinophilia induced by antigen challenge in monkeys and AHR and pulmonary eosinophilia in allergic guinea pigs.³⁴ A phase 2 clinical trial of patients with eosinophilic asthma receiving monthly intravenous reslizumab for 4 months was recently completed, but no results have been reported yet. Reslizumab has been granted orphan drug status by the US Food and Drug Administration (FDA) for treatment of pediatric eosinophilic esophagitis, and a phase 2/3 clinical trial was completed in early 2010.³⁵

Anti-IL-5R α mAb

Benralizumab (MEDI-563, Medimmune LLC, Gaithersburg, MD, USA) is a humanized anti-IL-5 receptor α (anti-IL-5R α) IgG1 mAb that induces apoptosis of eosinophils and basophils by antibody-dependent cell-mediated cytotoxicity.³⁶ A phase 1 trial of intravenous benralizumab reported acceptable safety and tolerability, and phase 2 trials in asthma are under way.^{36,37}

Anti-IL-9 mAb

IL-9 is implicated in asthma because it increases numbers of mast cells and Th2 lymphocytes in the lung, and leads to increased airway inflammation, AHR, and mucus production. Expression of IL-9 and its receptor are also higher in asthmatic airways, and the chromosomal region 5q31–33, where the IL-9 gene is located, has been linked to asthma in gene association studies. Murine models of asthma also show that IL-9 induces airway eosinophilia and IgE production.^{38,39} MEDI-528 (Medimmune LLC) is a humanized IgG1 anti-IL-9 mAb currently undergoing a phase 2b clinical study in uncontrolled adult asthmatic patients receiving either subcutaneous MEDI-528 or placebo biweekly for 24 weeks.⁴⁰ A recent pilot study reported that MEDI-528 may improve exercise-induced bronchospasm by reducing the maximum mean decrease in FEV₁ after exercise.⁴¹

IL-4 Antagonists

IL-4 induces immunoglobulin isotype switching to IgE and promotes differentiation of naive T lymphocytes to the Th2 lineage, leading to subsequent production of IL-4, IL-5, and IL-13. Altrakincept is a nebulized, soluble recombinant human IL-4 receptor (Amgen, Thousand Oaks, CA, USA) that binds IL-4 without mediating cellular activation because it only is the extracellular component. Although an initial study showed some promise, a subsequent study was not so favorable and this molecule is no longer under development for asthma.⁴²

Clinical trials of pascolizumab (SB 240,683), a fully humanized anti-IL-4 mAb, and a similar mAb made by PDL, had disappointing results and neither is being developed further. Targeting IL-4 alone may be ineffective because of redundant mechanisms shared with other cytokines, particularly IL-13.

Anti-IL-13 mAbs

Blockade of IL-13 may be an important strategy in treatment of allergic diseases, particularly asthma, because of the effects of IL-13 on IgE production, AHR, mucus production, and airway remodeling in animal and in vitro models. IL-13 blockade reduced lung inflammation in monkey and mouse studies.^{43,44} Several anti-IL-13 mAbs are undergoing or have completed phase 2 human clinical trials.

QAX576 (Novartis, Basel, Switzerland) is an intravenous anti-IL-13 mAb being developed for several allergic diseases. QAX576 failed to attenuate nasal symptoms and eosinophilia in patients undergoing nasal antigen challenge with Timothy grass pollen, though nasal IL-13 was inhibited.⁴⁵ A phase 2 study of QAX576 in moderate to severe atopic asthmatic patients was withdrawn because of complexity of the design and lack of enrollment.⁴⁶ An ongoing phase 2 trial is evaluating its effectiveness in eosinophilic esophagitis.⁴⁷

Anrukinzumab (IMA-638, Pfizer, New York, NY, USA) is a humanized anti-IL-13 mAb administered subcutaneously. Although an initial phase 2 trial in mild atopic asthmatic patients reported attenuation of postallergen early and late asthmatic responses, a subsequent trial of persistent asthmatic patients did not meet its end point in clinical efficacy and its development was halted in May 2009. However, Pfizer is developing another anti-IL-13 mAb, IMA-026, which completed a phase 2 asthma study in 2009.^{48–50}

Tralokinumab (CAT-354, MedImmune, Gaithersburg, MD, USA) is a humanized IgG4 anti-IL-13 mAb in development for asthma. Intraperitoneal injection of CAT-354 attenuated intratracheal human IL-13-induced AHR as well as airway and esophageal eosinophilia in a murine model of asthma.⁴⁴ Tolerability and safety have been reported in phase 1 studies.⁵¹ A phase 2 trial has been completed, but the results have not yet been published.⁵²

Lebrikizumab (Genentech, South San Francisco, CA, USA) is a humanized anti-IL-13 mAb undergoing phase 2 studies in asthmatic patients inadequately controlled on only ICS.⁵³

Anti-IL-4R α Antagonists

IL-4 has 2 receptors that are heterodimers consisting of 1 IL-4R α subunit and either the common γ chain (type I) or the IL-13R α 1 subunit (type II). Binding of the type II IL-4 receptor by either IL-4 or IL-13 results in common pleotropic effects, mediated via the JAK/STAT pathway, to promote Th2 cytokine production, eosinophil transmigration into tissue, and immunoglobulin class switching to IgE. Several therapies targeting IL-4R α in allergic diseases have been evaluated in clinical trials.

AMG 317 (Amgen, Thousand Oaks, CA, USA) is a fully human IgG2 anti-IL-4R α mAb being developed for allergic asthma. A phase 2 clinical trial of weekly subcutaneous AMG 317 in asthmatic patients did not significantly improve asthma control questionnaire scores, its primary end point, but did decrease frequency of and time to exacerbations in patients in the higher-dose groups. Patients with more asthma symptoms at baseline were more likely to respond to AMG 317, which was also well tolerated.⁵⁴

AIR 645 (Altair Therapeutics, San Diego, CA, USA) is a 2'-O-methoxyethyl 2-MOE Gapmer antisense oligonucleotide that targets the mRNA encoding IL-4R α . A phase 1 trial of nebulized AIR 645 in healthy volunteers reported low systemic absorption and no severe adverse events.⁵⁵ A phase 2a trial in mild allergic asthmatic patients was recently completed although no results have been reported yet.⁵⁶

Pitrakinra (Aerovant [also AER 001 or BAY 16-9996], Aerovance, Berkeley, CA, USA) is a recombinant IL-4 mutein that interferes with binding to IL-4-R α and is being developed for use in allergic asthma. Two phase 2a studies were conducted in atopic asthmatic patients receiving pitrakinra, either as daily subcutaneous injection or twice-daily nebulization versus placebo.⁵⁷ Late-phase asthmatic response after allergen challenge, measured by maximum percentage decrease in FEV₁, was decreased in both treatment groups, although statistically significant only in the nebulized pitrakinra group. There were significantly fewer adverse events related to asthma in the subcutaneous pitrakinra group compared with placebo. A phase 2b trial of an inhaled dry powder formulation is under way. Aerovance is also developing Aeroderm

(AER 003), a PEGylated mite of pitrakinra, as a weekly or every-2-weeks subcutaneous injection for severe eczema. A phase 2a study of patients with moderate to severe eczema receiving subcutaneous Aeroderm twice daily reported significant reductions in eczema symptom score at 28 days and also fewer exacerbations compared with placebo.⁵⁸

Anti-IL-2R mAb

IL-2 is critical to the proliferation of T and B cells and natural killer cells, and also enhances cytokine synthesis in T cells. Daclizumab (Hoffman-Roche, Basel, Switzerland) is a humanized IgG1 mAb directed against CD25, the α subunit of the high-affinity receptor for IL-2. Although currently approved for prophylaxis of renal allograft rejection, a phase 2 study of intravenous administration in moderate to severe persistent asthmatic patients demonstrated significantly improved lung function, reduced daytime symptoms and rescue inhaler use, and prolonged time to exacerbation.⁵⁹ Daclizumab was well tolerated, but caution must be taken in pursuing therapies against a pleiotropic cytokine such as IL-2.

TNF- α Inhibitors

TNF- α is a pleiotropic proinflammatory cytokine with biologic effects that may be important in refractory asthma, such as increased AHR and expression of chemokines and adhesion molecules that promote neutrophil recruitment. Small clinical trials reported promising results with TNF- α receptor antagonists, such as etanercept, which reduced AHR and improved asthma-related QOL scores.⁶⁰ However, larger trials have been disappointing. Golimumab (CNTO 148 or Simponi, Centocor, Horsham, PA, USA), a human anti-TNF- α mAb, was investigated in a phase 2 clinical trial of 309 subjects with severe persistent asthma; however, the study was terminated at its interim 24-week analysis because of an unfavorable risk/benefit profile, in which the treatment group failed to achieve significant improvement in FEV₁ or incidence of severe asthma exacerbations but had significantly more respiratory infections and an increase in malignancy.⁶¹ There are no further efforts to pursue this strategy in allergic disease, although it is approved for several rheumatologic conditions.

TRANSCRIPTION FACTOR INHIBITION

Transcription factors are proteins that bind to promoter regions of genes to stimulate or inhibit transcription, and regulate gene expression for proinflammatory cytokines and mediators; thus, they are attractive targets for immunomodulation of allergic disease.

Spleen Tyrosine Kinase Inhibitors

Spleen tyrosine kinase (Syk) is an intracellular enzyme that is activated after allergen cross-links IgE bound to the high-affinity IgE receptor (Fc ϵ RI) on mast cells and transduces signals leading to degranulation of preformed mediators such as histamine, production of proinflammatory cytokines such as TNF- α , and synthesis of lipid mediators including leukotriene C₄. R112 (Rigel Pharmaceuticals, South San Francisco, CA, USA) is a potent, rapid-onset, reversible Syk inhibitor discovered by a human mast cell culture screen to inhibit all mast cell reactions mediated by Fc ϵ RI cross-linking.⁶² A phase 2 study compared an intranasal formulation of R112 administered twice daily with placebo in patients with seasonal allergic rhinitis in a park setting over a 2-day period, reported significant symptomatic improvement with onset of action within 30 to 90 minutes, and was well tolerated.⁶³ However, in a subsequent phase 2 trial comparing intranasal R112 and beclomethasone with placebo over

a 7-day period in patients with allergic rhinitis, R112 did not significantly improve symptoms over placebo, although beclomethasone did.⁶⁴ Although the company has halted development of R112, it has brought R343, a dry powder inhaler formulation of R112, to phase 1 clinical trials for asthma.

Peroxisome Proliferator-activated Receptor- γ Agonists

GATA-3 is a key transcription factor of Th2 cytokines IL-4, IL-5, and IL-13, which are all involved in allergic diseases. Downregulation of GATA-3 using a dominant negative mutation in a murine model of asthma attenuated Th2-driven inflammatory responses including mucus production, airway eosinophilia, and cytokine and IgE synthesis.⁶⁵ Peroxisome proliferator-activated receptors (PPARs), particularly the α and γ subtypes, can also downregulate GATA-3 with similar effects but also inhibit *in vitro* chemotaxis of eosinophils and antibody-dependent cellular cytotoxicity.⁶⁶ Agonists of PPAR- γ include the thiazolidinediones rosiglitazone and pioglitazone, which are oral hypoglycemic agents used in noninsulin-dependent diabetes mellitus. PPAR- γ agonists can bind to and inhibit other transcription factors such as activated protein (AP)-1, signal transducer and activator of transcription 1 (STAT-1), nuclear factor κ B (NF- κ B), and nuclear factor of activated T cells, and attenuate production of reactive oxygen and nitrogen metabolites and cyclooxygenase 2 expression.^{67,68}

Bronchodilatory effects of rosiglitazone were studied in 46 mild to moderate asthmatic patients who were current smokers, and were randomized to either rosiglitazone 8 mg daily or inhaled beclomethasone dipropionate 200 μ g daily for 4 weeks. At 28 days, patients on rosiglitazone had significantly improved FEV₁, FEV₂₅₋₇₅, and forced vital capacity than those on beclomethasone, but no significant improvement in asthma symptoms.⁶⁹ Results of an open-label pilot study were recently reported in 14 steroid-naïve asthmatic patients given rosiglitazone 4 mg daily for 8 weeks then 8 mg daily for 4 additional weeks. Trends favored improvement in AHR and FEV₁ in a dose-dependent and time-dependent manner; however, incomplete data likely precluded statistically significant results.⁷⁰

Further studies of rosiglitazone in asthma are unlikely to take place because the modest potential for benefit is largely outweighed by association of increased adverse cardiovascular events in patients already taking this drug, which has prompted its withdrawal in Europe and severe restrictions in the United States for use only in diabetes not controlled on other medications. However, pioglitazone does not have such known associations and is being investigated in 2 phase 2 clinical trials for asthma.^{71,72}

NF- κ B Inhibition

NF- κ B is a key transcription factor that enhances expression of many genes involved in allergic diseases. Corticosteroids can suppress NF- κ B activity as part of their anti-inflammatory effects, but long-term use is associated with an undesirable side effect profile. One nonsteroidal strategy involves decoy oligonucleotides that mimic consensus binding sequences of the promoter region normally bound by NF- κ B to effectively silence transcription factor activity without altering its expression. Another strategy involves inhibiting the inhibitor of κ B kinase (IKK2/IKK β) to prevent release and activation of NF- κ B and its translocation to the cell nucleus.⁷³ No human trial data have been reported with either strategy in allergic diseases.

STAT-6 Inhibition

The biologic effects of IL-4 and IL-13 are mediated, in part, through STAT-6, leading to upregulation of proinflammatory genes, and thus STAT-6 may be an important target

in allergic disease. AS1517499 is a STAT-6 inhibitor found to inhibit allergen-induced bronchial hyperresponsiveness in mice and also blunts upregulation of RhoA, a protein involved in airway smooth-muscle contraction.⁷⁴ This may be a novel strategy in treating allergic diseases, especially asthma.

RGS2

G-protein coupled receptor (GPCR) signaling pathways are involved in airway contraction, and GPCR agonists and antagonists are used in treatment of asthma. Some regulators of G-protein signaling (RGS) proteins inhibit GPCRs and may be important in asthma pathophysiology. Nguyen and colleagues found that RGS2 knockout mice have increased AHR, equivalent to allergen sensitization (Nguyen TT and colleagues, unpublished data, 2011).⁷⁵ Nguyen and colleagues recently completed a pilot study examining whether RGS2 expression is lower in human asthmatic patients and if the degree of AHR was related to RGS2 expression using isolated monocytes as a model. Fifteen nonatopic, nonasthmatic patients and 15 treatment-naive atopic mild to moderate asthmatic patients underwent methacholine challenge to determine the degree of AHR, measured by PD20. Peripheral blood mononuclear cells (PBMCs) from these patients were analyzed for RGS2 mRNA and protein expression. RGS2 mRNA expression and protein levels were lower in asthmatic patients than normal patients, and amongst asthmatic patients, there is a statistically significant correlation between lower AHR and higher RGS2 mRNA expression.⁷⁵ Future studies aimed at elucidating the exact role of RGS2 in asthma could lead to new therapeutic opportunities.

ENDOTHELIAL ADHESION RECEPTOR ANTAGONISTS

Extravasation of leukocytes plays a central role in chronic inflammation seen in asthma. Animal models have shown that P-selectins, E-selectins, and L-selectins, are involved in rolling, adhesion, and transmigration, respectively, of leukocytes from bloodstream into peribronchial tissue. Preventing entry of these cells by blocking key adhesion molecules may inhibit inflammation.

Panselectin Antagonists

Panselectin antagonists including bimosiamose (TBC1269, Revotar Biopharmaceuticals AG, Germany) target all 3 selectins. An inhaled formulation of bimosiamose administered twice daily in 12 mild atopic asthmatic patients showed significant attenuation of late asthmatic reactions after allergen challenge although it had no significant effect on early asthmatic response, AHR, or exhaled nitric oxide.⁷⁶ Bimosiamose has also undergone phase 2 studies for chronic obstructive pulmonary disease (COPD) and for psoriasis and atopic dermatitis, as a topical microemulsion cream.^{77–79}

Very Late Antigen 4 Antagonists

Very late antigen 4 (VLA-4, $\alpha 4\beta 1$) is upregulated by IL-4 and IL-13 and binds to vascular cell adhesion molecule 1, which halts rolling of eosinophils and mononuclear cells and promotes their extravasation and accumulation, which may contribute to airway inflammation in asthma. IVL745 (Sanofi-Aventis, Bridgeport, NJ, USA) is a VLA-4 antagonist that was administered via dry powder inhaler to mild to moderate asthmatic patients and resulted in modest reduction in sputum eosinophils but after allergen challenge failed to show a significant difference in early or late asthmatic response, AHR, or peak expiratory flow.⁸⁰

Vascular Adhesion Protein 1 Antagonists

Vascular adhesion protein 1 (VAP-1), also known as human semicarbazide-sensitive amine oxidase, is an inflammation-inducible endothelial cell adhesion molecule that mediates interaction between leukocytes and activated endothelial cells. LJP 1207 (La Jolla Pharmaceuticals, La Jolla, CA, USA) is an oral VAP-1 inhibitor that reduced mortality in murine models of ulcerative colitis and levels of TNF- α and IL-6 in LPS-challenged mice.⁸¹ LJP 1207 also reduced adhesion and infiltration of leukocytes in cerebral vessels in animal models of stroke.⁸² VAP-1 is expressed at higher levels in the serum and skin of patients with atopic dermatitis compared with healthy controls, and decreases after treatment of eczema.⁸³ Although there are no known plans to develop LJP 1207 for allergic diseases, another VAP-1 inhibitor, PXS4159 (Pharmaxis, Frenchs Forest, Australia), is undergoing review for phase 1 trials for asthma treatment.

ANTI-IGE MABS

Omalizumab

Omalizumab (Xolair, Genentech, South San Francisco, CA, USA) is a 95% humanized mAb that forms soluble immune complexes with free IgE at the same site, which normally binds the high-affinity IgE receptor, Fc ϵ RI, thus preventing cross-linking of Fc ϵ RI and subsequent basophil and mast cell activation. Omalizumab can reduce serum free IgE levels by 99% within 2 hours of administration, and within 2 weeks of therapy initiation can reduce nasal allergen challenge responses.⁸⁴ Omalizumab also induces downregulation of Fc ϵ RI on basophils, dendritic cells, and monocytes within 7 days.^{84,85} In patients with allergic rhinitis, omalizumab reduced serum eosinophils. In asthmatic patients, omalizumab reduced serum, tissue, and sputum eosinophilia and cells positive for Fc ϵ RI and CD4+ lymphocytes.⁸⁶

Several studies have established the safety and efficacy of omalizumab, including 3 phase 3 clinical trials conducted on a total of 1405 patients with moderate to severe persistent allergic asthma.^{87–89} All 3 studies reported that omalizumab, compared with placebo, reduced asthma exacerbations and had a corticosteroid-sparing effect. Significantly more omalizumab-treated patients were able to reduce their ICS dose by 50% and also to discontinue ICS, compared with placebo (39.1% vs 19.1%, $P < .01$).⁸⁷ Omalizumab was also associated with decreased rescue medication use, fewer asthma symptoms, and improved QOL scores. Small but significant improvements in peak expiratory flow and FEV₁ were observed in adolescent and adult patients on omalizumab.⁸⁹ Omalizumab-treated patients have also sought significantly fewer unscheduled outpatient visits and emergency department visits, and required fewer hospitalizations.⁹⁰

In light of the supporting evidence for omalizumab, the FDA has approved it for the treatment of moderate to severe persistent allergic asthma in patients 12 years of age and older. Recent expert panel guidelines recommend consideration of omalizumab as adjunctive therapy in perennial allergic asthmatic patients who fail to achieve adequate control on medium-dose ICS in conjunction with a long-acting β agonist. Patients with greater disease severity seem to benefit more from therapeutic addition of omalizumab, although cost-benefit analysis is not favorable for all severe asthmatic patients.⁹¹ Omalizumab is administered subcutaneously every 2 to 4 weeks, with initial dosing determined by 2 factors: pretreatment serum total IgE, up to 700 IU/mL, and patient weight, up to 150 kg.

Patients with seasonal allergic rhinitis also show improvement on omalizumab, including improved rhinitis QOL scores, reduced nasal symptom scores, and antihistamine use, compared with placebo.⁹² Omalizumab was effective in attenuating

responses to nasal allergen challenge in patients with allergic rhinitis and has been shown to be effective in treating perennial allergic rhinitis in adults and adolescents.^{93,94} Several phase 2 trials are under way investigating the effects of omalizumab on chronic rhinosinusitis.^{95,96}

Omalizumab as adjunctive therapy to subcutaneous IT in children allergic to birch tree and grass was shown to reduce seasonal allergic rhinitis symptoms, rescue medication use, and symptom load.⁹⁷ Omalizumab has also been shown to reduce systemic reactions from and improve tolerability to traditional and accelerated schedules of subcutaneous IT.^{98,99} This use of omalizumab as premedication for IT is discussed elsewhere in this issue.

Omalizumab is also being investigated as a novel immunomodulator in several other allergic disorders in which IgE may play a key role in pathophysiology, including eosinophilic esophagitis, allergic bronchopulmonary aspergillosis, hyper-IgE syndrome, idiopathic anaphylaxis, and peanut allergy.^{100–105} There have been few case reports of omalizumab used with varying success in atopic dermatitis and chronic urticaria, which also has an ongoing phase 2 trial.^{106–108}

Omalizumab is generally well tolerated, with the most common adverse events noted as local reactions at the injection site. There was a higher rate of malignancy in omalizumab-treated patients reported during initial clinical trials compared with controls, but causal association is unclear and is being closely monitored during post-marketing surveillance, including the phase 4 prospective observational cohort study, Xolair to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma (EXCELS). The EXCELS study has also identified the potential association between omalizumab and cardiovascular events, but final conclusions await adjudication of events in relationship to patient characteristics. In 2007, the FDA ordered a black-box warning to be placed on omalizumab because of possible association with increased risk of anaphylaxis. A review of data from approximately 57,000 patients treated with omalizumab has indicated that anaphylaxis can occur at any dose and there can be delayed onset of symptoms beyond 2 hours and also a protracted course, with signs and symptoms lasting many hours.¹⁰⁹ Mechanisms of omalizumab-associated anaphylaxis and predisposing risk factors have yet to be elucidated. Current recommendations are to observe patients for 2 hours after each of their first 3 injections, and then for 30 minutes after each subsequent injection, which would have captured 75% of anaphylactic reactions that were reviewed by the Joint Task Force of the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma and Immunology.¹¹⁰ There may also be an association with Churg-Strauss syndrome and omalizumab, although causation is questionable because this effect may result from reduction of oral steroids that unmask the underlying disease.¹¹¹

Genentech, which manufactures and markets omalizumab under the trade name Xolair, is also developing a phase 1 trial in asthma for anti-M1 prime, a humanized mAb that binds to the M1 prime segment of membrane IgE and targets B lymphocytes before they produce IgE, rather than neutralizing existing IgE.

CD23

CD23 is the low-affinity receptor for IgE (FcεRII) and its expression on monocytes, alveolar macrophages, and B lymphocytes is increased in allergic patients. In vitro studies have shown that cross-linking CD23 downregulates IgE synthesis. Lumiliximab (IDEC-152, Biogen Idec Pharmaceuticals, Westin, MA, USA) is a primate, IgG1, anti-CD23 mAb that was studied in PBMCs of atopic patients and shown to reduce allergen-induced PBMC proliferation and levels of proinflammatory cytokines

such as IL-1 β , IL-5, and TNF- α .¹¹² Anti-CD23 mAb has not been shown to be effective for allergic rhinitis or asthma despite a significant effect on IgE levels, albeit much less than omalizumab.^{113,114} No additional clinical trials have been planned for lumiliximab in allergic diseases, but it has been investigated for chronic lymphocytic leukemia.

OTHER IMMUNOMODULATORS

OX40L mAbs

OX40L is expressed on APCs such as macrophages, dendritic cells, and endothelial cells, and also B and T lymphocytes. In the absence of IL-12, dendritic cells activated by thymic stromal lymphopoietin upregulate OX40L, which binds to OX40, and leads to Th2 cell differentiation and expansion of Th2 memory cells.¹¹⁵ OX40L-deficient transgenic mice had attenuated asthmatic responses to allergen challenge compared with wild-type, and administration of an OX40L antibody to wild-type mice during sensitization also prevented asthmatic responses.¹¹⁶ R0498991 (Hoffman-Roche Pharmaceuticals, Basel, Switzerland) is a humanized anti-OX40L mAb. Phase 2 trials of R0498991 are under way to assess safety of a subcutaneous formulation in patients with allergic rhinitis and efficacy of an intravenous formulation to attenuate allergen-induced responses in asthmatic patients.^{117,118}

Chemoattractant Receptor-homologous Molecule Expressed on Th2 Lymphocytes Antagonists

Prostaglandin D₂ (PGD₂) is a potent prostanoid released on mast cell activation linking early-phase and late-phase allergen responses. Chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTh2) is the biologically relevant GPCR for PGD₂ and its metabolites, as is the D prostanoid receptor, DP1.¹¹⁹ Several CRTh2 antagonists are in active development and have completed or are undergoing clinical trials.

OC000459 (Oxagen Ltd, Oxfordshire, UK), an oral CRTH2 antagonist, was evaluated in 132 moderate to persistent asthmatic patients randomized to receive OC000459 twice daily or placebo for 28 days. The treatment group had significant improvement in FEV₁ (7.4%) compared with placebo, which continued to improve even at the study end point. QOL significantly improved on OC000459 and there was a significant reduction in total serum IgE and trend toward reduced sputum eosinophilia.¹²⁰ OC000459 has now completed phase 2 studies in both asthma and allergic rhinitis with enrollment of more than 600 patients and has been well tolerated. In addition, a phase 2 proof-of-concept clinical trial for use in eosinophilic esophagitis is under way.¹²¹ AMG 853 (Amgen Pharmaceuticals, Thousand Oaks, CA, USA) is an oral CRTH2 and DP1 antagonist that was tolerated well in a phase 1 study and is currently being evaluated in a phase 2 study in patients with inadequately controlled asthma.¹²² ACT-129,968 (Actelion Pharmaceuticals, South San Francisco, CA, USA) is another oral CRTH2 antagonist scheduled to undergo phase 2 clinical trials in both asthma and allergic rhinitis. In a recently completed 28-day phase 2 study in patients with mild to moderate asthma ACT-129,968 improved AHR by 1 to 1.5 doubling doses, FEV₁ by 10% to 14%, and asthma QOF questionnaire scores by 0.7 and decreased in sputum eosinophils and IgE.

ARRY-005 (Array BioPharma, Boulder, CO, USA) is an oral CRTh2 antagonist shown to dose-dependently inhibit early-phase and late-phase responses in a murine model of allergic rhinitis and improve clinical scores and inhibit scratching behavior in a murine model of atopic dermatitis. ARRY-006, another candidate CRTh2 antagonist developed

by Array BioPharma, inhibited airway hyperreactivity and cellular infiltration in bronchoalveolar lavage fluid after allergen challenge in ovalbumin-sensitized BALB/c mice.¹²³

Phosphodiesterase 4 Inhibitors

Phosphodiesterase (PDE) is a major cyclic adenosine monophosphate metabolizing enzyme, and 1 type, PDE-4, is upregulated in inflammatory cells in asthma and COPD. Theophylline, a nonselective PDE inhibitor, has been used to treat asthma or COPD; however, selective PDE inhibitors may provide better benefit-to-risk ratios. PDE4 inhibitors have shown antiinflammatory activity in murine models of asthma and COPD.

Roflumilast (Daxas, Forest Laboratories, New York, NY, USA) is an oral once-daily PDE4 inhibitor currently approved in Europe for COPD, but has been evaluated for both asthma and allergic rhinitis. A phase 2/3 clinical trial of roflumilast was conducted in asthmatic patients over a 12-week period and showed significant improvement in FEV₁ amongst all tested doses.¹²⁴ Roflumilast, given for 9 days in atopic patients, improved nasal airflow and subjective obstruction scores compared with placebo on intranasal allergen provocation.¹²⁵ In mild atopic asthmatic patients, roflumilast attenuated both early and late asthmatic reactions to allergen challenge.¹²⁶ Roflumilast, compared with inhaled beclomethasone dipropionate, was similar in improving FEV₁ and asthma symptoms and in reducing medication use in a study of 499 asthmatic patients over a 12-week period.¹²⁷ Promising results of phase 3 trials in which roflumilast was added to patients with COPD already treated with salmeterol or tiotropium included significant mean improvement in baseline FEV₁, (0.49 L, 0.8 L, respectively) and health-related QOL scores over a 24-week period.¹²⁸ However, this same study reported increased incidence of suicide and suicide attempts and malignancy in the

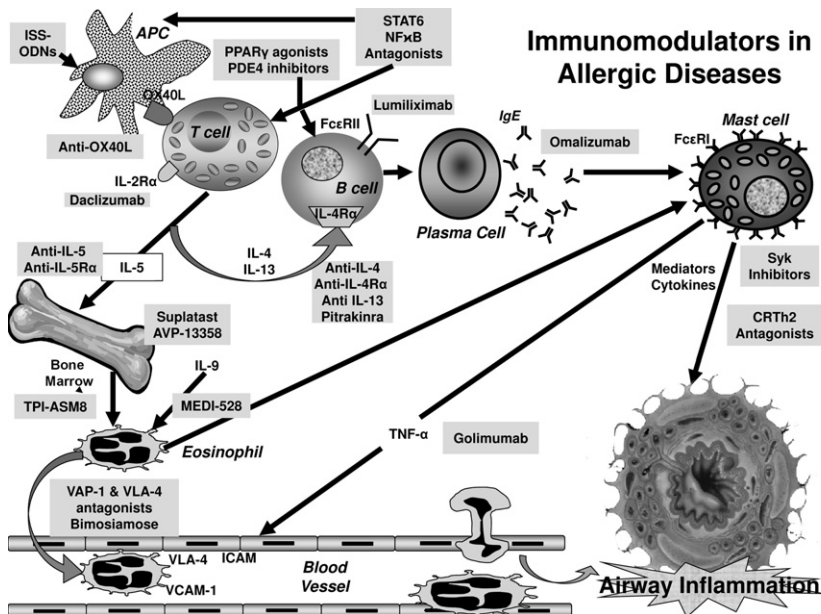


Fig. 3. Summary of immunomodulators in allergic diseases discussed in this article and their sites of action. (Adapted from Casale TB, Stokes J. Immunomodulation for allergic respiratory disorders. *J Allergy Clin Immunol* 2008;121(2):290; with permission.)

treatment group, prompting an FDA panel to vote against its use for COPD in the United States, and likely precluding use in asthma and other allergic diseases.

An inhaled PDE4 inhibitor, GSK256066 (GlaxoSmithKline, Vienna, Austria) given over a 7-day period to 24 steroid-naïve atopic asthmatic patients was shown to attenuate early-phase and late-phase allergic responses to allergen challenge compared with placebo.¹²⁹ An intranasal formulation of GSK256066 has been evaluated in 2 crossover clinical trials, comparing it with fluticasone propionate and also with azelastine hydrochloride in patients with seasonal allergic rhinitis over an 8-day period, although results have not yet been released.^{130,131}

SUMMARY

Many immunomodulators are on the horizon for treatment of allergic diseases, especially TLRs as potent adjuvants for allergen IT or perhaps as allergen-free IT themselves. (Fig. 3) Many therapies began with promising outlooks after initial in vitro or animal studies only to fail to translate into successful human clinical trials. Despite these disappointments, many important lessons have been learned about the pleiotropic effects of cytokines and the redundancies of their effector mechanisms, and also of the heterogeneity of allergic disease phenotypes. Several immunomodulators that have failed or been abandoned for development in allergic diseases live on in active clinical trials or have been approved for diseases common to other disciplines, including pulmonology, rheumatology, oncology, dermatology, and infectious diseases. Clinical studies with immunomodulators have helped define asthma pathogenesis. The goals for new immunomodulator therapies are to provide better therapeutic options by decreasing symptoms and improving QOL, preventing and favorably altering disease course, and having a good risk/benefit ratio with a cost-effective profile.

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