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Immunomodulation of Allergic Disease

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Annu. Rev. Med. 2009. 60:279–91

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi:
10.1146/annurev.med.60.041807.123524

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0066-4219/09/0218-0279\$20.00

Key Words

sublingual immunotherapy, subcutaneous immunotherapy, anti-IL-5, TLR-9, tolerance

Abstract

This review focuses on sublingual immunotherapy (SLIT), toll-like receptor-9 (TLR-9) vaccines using cytosine phosphorothioate guanosine (CpG)–allergen conjugates, and anti-IL-5 as novel immunomodulating therapies in allergy. At present, all three approaches are investigational in the United States and require further study to determine their safety and effectiveness. SLIT provides a novel oral route of administering an allergen to induce tolerance to inhaled allergens. Studies of SLIT in allergic rhinitis demonstrate that it reduces symptoms and medication use and is associated with a low incidence of systemic allergic reactions. Initial phase II studies with TLR-9 vaccines conjugated to a ragweed allergen demonstrate that they reduce symptoms of allergic rhinitis during the ragweed season. Anti-IL-5 is effective as a corticosteroid-sparing agent in the hypereosinophilic syndrome. It has not shown benefit in moderate asthmatics with persistent symptoms but may reduce aspects of airway remodeling in asthma.

SLIT: sublingual immunotherapy

CpG: cytosine phosphorothioate guanosine

SCIT: subcutaneous immunotherapy

Amb a 1: *Ambrosia artemisiifolia* (short ragweed) 1

INTRODUCTION

Allergic diseases are very common, affecting ~20% of the population of the United States (1, 2). Allergic diseases mediated by immunoglobulin E (IgE) range from potentially life-threatening allergic reactions (e.g., anaphylaxis or severe asthma) to chronic allergic diseases associated with significantly reduced quality of life (e.g., eczema or allergic rhinitis). Allergic diseases are the sixth leading cause of chronic disease in the United States (2). The development of allergy frequently starts in early childhood with initial eczema, followed by the subsequent sequential development of food allergy, allergic rhinitis, and asthma—the so-called “atopic march” (1). Allergic diseases are an example of a gene-environment interaction: Individuals with a particular genotype have IgE responses to environmental allergens such as pollens, dust mites, cats, or foods. Because allergic disease frequently runs in families, the search for genes that contribute to atopy (i.e., the ability to mount an IgE response), as well as to specific allergic diseases such as asthma, allergic rhinitis, or eczema, has received a great deal of attention. Many genes have been linked to atopic disease, but each identified gene contributes only a small amount to the observed phenotype (3). For example, >100 genes have been linked to asthma with no single gene contributing more than 5% to the observed phenotype (3).

Current therapies for allergic diseases include allergen avoidance where possible, medications (antihistamines, leukotriene inhibitors, topical and/or oral corticosteroids), and immunotherapy (subcutaneous allergen immunotherapy, anti-IgE) in selected patients. This review focuses on the development of novel immunomodulating therapeutic approaches that are currently investigational in the United States, and discusses results of human studies in terms of effectiveness and safety profiles. The approaches described here are sublingual immunotherapy (SLIT), cytosine phosphorothioate guanosine (CpG)-allergen conjugates, and anti-interleukin-5 (anti-IL-5).

ACHIEVING ALLERGEN-SPECIFIC TOLERANCE

The concept of vaccinating allergic individuals to prevent allergy was initially described in 1911 by Noon (4), an immunologist at St. Mary's Hospital in London. Noon demonstrated that he could immunize patients who had allergic rhinitis with subcutaneous injections of a grass pollen allergen to prevent symptoms during the grass pollen season. Since that time, the goal of allergen immunization in clinical practice has been to induce allergen-specific tolerance so that exposure to a particular allergen is not associated with symptoms (5, 6). The main limitation of this approach has been the potential to induce systemic allergic reactions. Because of this risk, allergen immunization must be conducted in a clinic, where a physician is immediately available to treat any reaction. In order to understand whether novel approaches to inducing allergen-specific tolerance are an advance over currently available therapies, we briefly review the evidence for the efficacy and safety of the standard therapy, subcutaneous immunotherapy (SCIT), in allergic diseases.

SUBCUTANEOUS IMMUNOTHERAPY TO INDUCE ALLERGEN-SPECIFIC TOLERANCE

The goal of SCIT is to induce allergen-specific clinical tolerance to the offending environmental allergen (5, 6). For example, patients with fall seasonal allergic rhinitis due to ragweed exposure are administered SCIT containing the major ragweed allergen Amb a 1 with the goal of inducing clinical tolerance to ragweed such that patients would not have characteristic symptoms of allergic rhinitis (i.e., sneezing, rhinorrhea, nasal congestion, postnasal drip) during the ragweed season. For SCIT to be effective, patients must have an appropriate history of allergic symptoms on exposure to the offending allergen, as well as evidence of IgE antibodies to the specific allergen [as demonstrated by immediate hypersensitivity skin test

or blood test, such as IgE radioallergosorbent test (RAST)]. Patients with allergic rhinitis are frequently sensitized to more than one environmental allergen. Thus, SCIT frequently utilizes multiple allergens administered in one or two injections, provided the history is consistent with symptoms upon exposure to each allergen, and IgE responses to each allergen are documented.

SCIT Clinical Efficacy

SCIT has been demonstrated to be clinically effective in significantly reducing symptoms in patients with allergic rhinitis, bee venom allergy, and asthma (5, 6). A Cochrane meta-analysis of SCIT in allergic rhinitis (51 double-blind placebo-controlled studies of 2871 subjects) demonstrated a mean reduction in symptoms of 73% and a mean reduction in medication use of 57% (7) (**Table 1**). Studies have demonstrated that after receiving SCIT for 3–5 years, patients experience long-term remission of allergic rhinitis symptoms for at least 3–5 years following discontinuation of SCIT (8). In addition, SCIT decreases the onset of new allergic sensitizations in children (9). In subjects with allergic rhinitis alone, SCIT reduces the likelihood of progression to asthma (10, 11).

Meta-analysis of SCIT in asthma (75 randomized controlled studies of 3188 subjects) has demonstrated that SCIT also induces a significant reduction in asthma symptoms, medication use, and bronchial hyperreactivity (12). However, there are also individual studies that have shown no discernible benefit from SCIT in allergic children with perennial asthma who

ALLERGIC INFLAMMATION

Sites of allergic inflammation are characterized by the uptake of allergens by antigen-presenting cells (APCs). APCs digest allergens and present fragments of allergen to allergen-specific CD4⁺ T cells. CD4⁺ cells secrete Th2 cytokines, such as IL-4 (a switch factor for IgE synthesis) and IL-5 (an eosinophil growth factor). Upon re-exposure, allergens activate Th2 cells to express Th2 cytokines, as well as cross-link IgE affixed to mast cell high-affinity IgE receptors and induce mast cell degranulation.

were receiving appropriate medical treatment (13). One of the limitations of using SCIT in asthma is that, for safety reasons, its administration is limited to asthmatics whose FEV₁ (forced expiratory volume in one second) is >70% of predicted. Thus, many of the moderate to severe asthmatics who might most benefit from immunotherapy have a contraindication that precludes SCIT.

SCIT is not indicated for the treatment of food allergy or eczema because at present there is insufficient evidence of the efficacy and/or safety of SCIT for these conditions.

Immune Response Induced by SCIT

In inducing tolerance to inhaled allergens, SCIT has effects on T cell as well as B cell immune responses (5, 6). SCIT induces immune deviation from Th2 immune responses, characteristic of allergic inflammation (see sidebar “Allergic Inflammation”), to Th1 immune responses. SCIT also induces regulatory T cells (Tregs) (see sidebar “Regulatory T Cells”), which have the potential to downregulate Th2 immune responses (14). SCIT effects on B cells include a blunting of the seasonal increase in IgE levels as well as induction of IgG4 antibodies (5, 6). Associated with these effects on T cell and B cell immune responses, SCIT suppresses the number and activation of effector cells, including mast cells, basophils, and eosinophils, in target organs such as the nasal mucosa in allergic rhinitis (5, 6).

Table 1 Summary of meta-analysis studies of SCIT (7) and SLIT (23) in allergic rhinitis

	SCIT	SLIT
Double-blind studies (number)	51	22
Study subjects (number)	2871	979
Symptom reduction (%)	73	42
Medication reduction (%)	57	43

REGULATORY T CELLS

Whereas Th2 cells may play a role in promoting allergic inflammation, regulatory T cells (Tregs) have the ability to downregulate Th2 cell function and thus potentially reduce levels of allergy. There are two broad categories of Tregs: natural Tregs and inducible or adaptive Tregs. Adaptive Tregs have many features in common with natural Tregs but exhibit marked cytokine-dependent suppressive mechanisms *in vitro*. These are mediated through the secretion of IL-10 and TGF- β , which may suppress Th2 cells. Thus, immunotherapy strategies that induce Tregs may provide one mechanism of inducing tolerance to allergens.

SCIT Side Effects

To minimize the risk of allergic responses to the allergen(s) administered in SCIT, initial dosages are diluted 10,000- to 100,000-fold from the target effective dose, which for most allergens ranges from 6 to 20 μ g to induce tolerance (5, 6). To reach the target SCIT maintenance dose necessitates a slow up-dosing phase of weekly SCIT injections for 4–6 months in a clinic setting, where systemic allergic reactions can be immediately treated with epinephrine. Approximately 0.1% of subjects receiving SCIT develop significant systemic reactions that require epinephrine administration (7). Efforts to reduce the allergenicity of allergen immunotherapy have failed in the past because allergoids, which are denatured allergens with reduced allergenicity, also have reduced immunogenicity and reduced clinical effectiveness (5, 6). A variety of novel strategies are currently being investigated to improve the safety and effectiveness of immunotherapy. These include SLIT, CpG allergen conjugates, and allergen peptides.

SUBLINGUAL IMMUNOTHERAPY

SLIT is currently the focus of considerable investigation (15–19) because of the ease of oral administration compared to subcutaneous injection. In addition to the ease of administration, SLIT appears to have a good safety profile, with the main side effects being local (oral

itching) as opposed to systemic allergic reactions (20–22). In most studies, the reported oral itching is mild, self-resolving, and does not frequently cause patients to discontinue SLIT.

SLIT Clinical Efficacy

A meta-analysis of SLIT in allergic rhinitis (22 double-blind placebo-controlled studies of 979 subjects) demonstrated a mean reduction in symptoms of 42%, and a mean reduction in medication use of 43% (23). Comparison of results of meta-analysis studies of SLIT and SCIT in allergic rhinitis suggests that SCIT is clinically more effective but SLIT is associated with fewer systemic adverse reactions (**Table 1**). However, no adequately powered double-blind studies have directly compared the safety and efficacy of SLIT versus SCIT. Although a double-blind, placebo-controlled study of SLIT versus SCIT in birch pollen allergic rhinitis demonstrated no significant difference in therapeutic efficacy, the study was not adequately powered to detect a difference if such a difference was present (24).

SLIT is usually administered as soluble tablets or drops to be kept under the tongue for 1–2 min and then swallowed (25). SLIT has been administered either prior to the spring or fall pollen allergy season, or continuously throughout the year to prevent symptoms from perennial allergens such as dust mites. Optimal dosing regimens and duration of therapy require further investigation.

At present, no double-blind studies have demonstrated that SLIT, like SCIT, can prevent the development of sensitization to new allergens, nor that it has long-lasting immunomodulating effects that result in sustained clinical remission after therapy is discontinued. Open-label studies with SLIT evaluating these end points (26) need to be validated in placebo-controlled double-blind studies.

SLIT Side Effects

Because safety is a key rationale for the use of SLIT instead of SCIT, the safety record

of SLIT in clinical trials has been examined in several reviews. Overall, the literature suggests that SLIT is generally safe; no fatal adverse events have been reported in the 20 years that SLIT has been administered, predominantly in Europe (21, 25). Based on a review of published studies of SLIT in 3984 patients, 14 SLIT-related serious adverse events (mainly asthma exacerbations) were reported (21, 25). There are three reported cases of anaphylaxis associated with SLIT administration (25, 27, 28). None of these reported adverse events with SLIT have been associated with hypotension or death (25). SLIT is not currently approved for use in the United States.

Immune Response Induced by SLIT

Studies have investigated whether SLIT, like SCIT, induces clinical tolerance by influencing B cell and T cell immune responses. In general, the B cell immune response to SLIT in terms of IgG4 response is more limited than that induced by SCIT (29, 30) and is dependent on the dose and duration of SLIT administration (31). Recent studies of T cell responses to SLIT in a small number of birch pollen-allergic subjects, who received SLIT for one year, demonstrated that SLIT induced Tregs within a month. After a year of therapy there was evidence that SLIT had induced immune deviation, i.e., inhibition of Th2 and induction of Th1 immune response (32).

TOLL-LIKE RECEPTOR-9 VACCINES

The use of bacterial-derived products for immunotherapy to prevent allergy gained momentum with the development of the “hygiene hypothesis,” which proposes that microbial exposure in early childhood protects against the development of allergy (1, 33). Subsequently, the discovery that several molecularly defined bacterial products are recognized by different toll-like receptors (TLRs) expressed by cells of the innate immune system provided an impetus to study whether these well defined bacterial

products could be used as immunomodulators in the therapy of allergy (33, 34).

CpG DNA, Toll-Like Receptor-9, and Innate Immune Response

Cytosine phosphorothioate guanosine (CpG) DNA is a noncoding six-base-pair sequence of DNA (Figure 1a) that is highly enriched in bacteria and binds with great specificity to its receptor, TLR-9, which is expressed by cells of the innate immune system such as dendritic cells (33, 34). Activation of TLR-9 in dendritic cells leads to activation of intracellular signaling pathways, including MAPK, NF- κ B, cytokine gene transcription (IFN- α , IFN- β ,

TLR: toll-like receptor

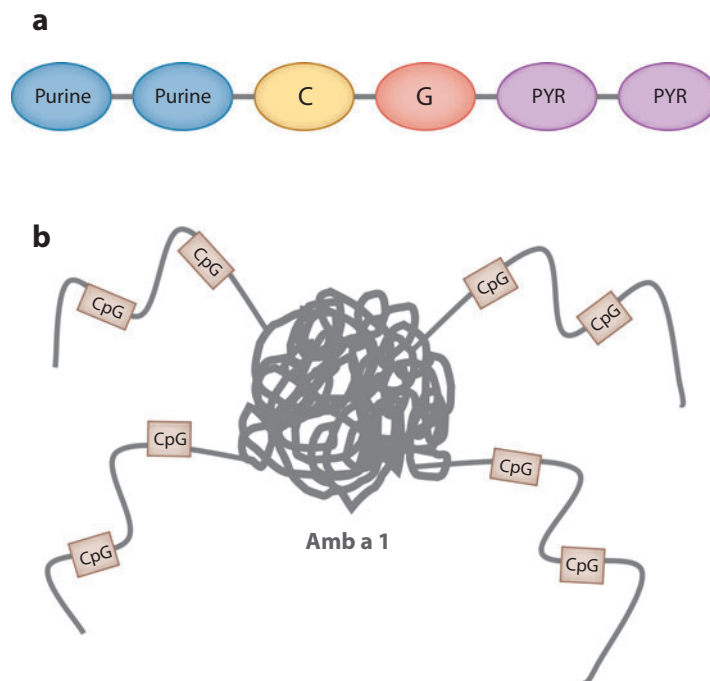


Figure 1

(a) CpG DNA is a six-base-pair sequence of noncoding DNA that comprises a central cytosine (C) linked to a guanosine (G) through a phosphorothioate linkage (p). To have immunodulating properties, the CpG sequence must be flanked on the 5' end by two purines, and on the 3' end by two pyrimidine base pairs. (b) A ragweed-based TLR-9 vaccine was constructed by chemically linking the major ragweed protein allergen, Amb a 1, to four strands of DNA. Each of the four strands contains two CpG sequences. The CpG sequences bind to TLR-9 receptors expressed intracellularly by cells of the innate immune system, such as dendritic cells, which take up injected allergens.

AIC: Amb a 1 immunostimulatory DNA conjugate

IL-10, IL-12), and expression of costimulatory molecules (e.g., CD40, B7). These pathways can influence the adaptive immune response to allergens away from a proallergic response characterized by high levels of Th2 cytokines including IL-4 and IL-5 (33, 34). Studies in mouse models of allergy and asthma have demonstrated that administration of the TLR-9 ligand CpG DNA inhibits Th2 cytokine responses, eosinophilic airway inflammation, mucus expression, airway remodeling, and airway hyperreactivity (35, 36). Additional studies have demonstrated that conjugating the allergen to CpG DNA (as compared to administering the allergen and the CpG DNA separately) enhances the immune response to the allergen by approximately a hundredfold (37). The enhancement of immunogenicity is presumed to be due to the allergen and the CpG DNA localizing to the same antigen-presenting cell when administered as a conjugate, and localizing to different antigen-presenting cells when administered separately (38).

TLR-9 Vaccines and Allergy

Studies in human subjects with ragweed-induced allergic rhinitis have investigated whether the major ragweed protein allergen Amb a 1 conjugated to CpG DNA—a conjugate referred to as Amb a 1 immunostimulatory DNA conjugate (AIC) (**Figure 1b**)—would inhibit Th2 cytokine responses as well as reduce allergic rhinitis symptoms during the ragweed season. Initial studies demonstrated that the AIC vaccine inhibited Th2 responses in peripheral blood (39, 40, 41) as well as Th2 cytokine responses and eosinophilic inflammation in the nasal mucosa of ragweed-allergic subjects challenged with ragweed intranasally out of the ragweed season (42). In a subsequent double-blind placebo-controlled study, subjects with allergic rhinitis who received the AIC vaccine prior to the ragweed season had significantly reduced allergic rhinitis symptoms and used less allergy-relief medication during the ragweed season compared to placebo-treated subjects (43). Interestingly, although subjects only re-

ceived the AIC vaccine before the first ragweed season, the protective effect lasted through the second ragweed season. In contrast to the slow six-month buildup phase required with administration of SCIT to safely reach the target dose of 6–12 μg of Amb a 1, the AIC vaccine was administered in only six weekly injections to reach a target dose of 12 μg of Amb a 1 without evidence of inducing any systemic allergic responses. A potential reason for the reduced allergenicity of the TLR-9 vaccine is suggested from the structure of the AIC vaccine, which contains a central allergen protein, Amb a 1, conjugated to four CpG-containing DNA consequences radiating peripherally (**Figure 1b**). When Amb a 1 alone is injected subcutaneously, it can cross-link IgE bound to mast cells and induce an allergic response. In contrast, when the AIC vaccine is injected subcutaneously, the four radiating sequences of CpG DNA reduce the ability of the central Amb a 1 allergen protein to bind and cross-link IgE bound to mast cells. In vitro studies in which basophils were incubated with either Amb a 1 or a conjugate of the same concentration of Amb a 1 with CpG DNA have demonstrated that whereas the Amb a 1 allergen alone readily binds to IgE affixed to basophils and induces basophil degranulation, the conjugate induces significantly less basophil histamine release (44).

Although these initial early phase II studies of CpG DNA conjugated to Amb a 1 are encouraging in terms of demonstrating the potential for TLR-9 vaccines in allergic rhinitis, further studies with larger numbers of subjects are needed to confirm these observations. In addition, because TLR-9 vaccines induce Th1 immune responses, subjects need to be carefully monitored for the development of autoimmune disease. As yet, there are no reports of induction of auto-antibodies or autoimmune disease in subjects who have received the TLR-9 vaccine.

Studies have also examined whether administration of CpG DNA alone, not conjugated to allergen, can reduce allergen-induced responses in human asthmatics. CpG DNA has previously been shown to be effective in reducing airway inflammation, remodeling, and

airway responsiveness in mouse (35) and primate (45) models of allergen-induced asthma. In studies of mild asymptomatic asthmatics with normal pulmonary function, administration of nebulized CpG DNA did not reduce the number of eosinophils in sputum during the late-phase response to allergen challenge, nor did it reduce airway hyperreactivity to methacholine and the late-phase reduction in FEV₁ (see sidebar “Late-Phase Response to Allergen Challenge”) (46). Further studies are needed to determine whether CpG DNA would be effective in reducing asthma symptoms in patients with persistent symptoms as opposed to studies using allergen challenge in asymptomatic asthmatics.

ANTI-IL-5

The presence of tissue eosinophils is a prominent feature of several allergic diseases, including allergic rhinitis, asthma, eosinophilic esophagitis, and the idiopathic hypereosinophilic syndrome. Although the eosinophil has the capacity to generate a variety of proinflammatory mediators that could theoretically contribute to the pathogenesis of diseases associated with tissue eosinophilia, without therapeutic interventions that narrowly target eosinophils it has not previously been possible to determine the role of the eosinophil in the pathogenesis of individual diseases. The recognition that IL-5 is a lineage-specific growth factor for eosinophils (47) has provided a novel therapeutic target to specifically reduce eosinophilic inflammation in particular diseases. Evidence of a role for IL-5 in eosinophilic inflammation is derived from studies of mutant mice deficient in IL-5, which have significantly reduced levels of eosinophils (48). Increased levels of IL-5 and eosinophils are noted in the airway of asthmatics, and administration of IL-5 by the inhalation route induces sputum eosinophilia in asthmatics. Studies administering anti-IL-5 to human subjects have demonstrated that a single dose can reduce blood and sputum levels of eosinophils by >90% for approximately three months (48, 49).

LATE-PHASE RESPONSE TO ALLERGEN CHALLENGE

Under experimental conditions, a patient with mild asthma can be exposed to a defined dose of an inhaled allergen to which he is sensitized and his lung function monitored to determine whether he develops an immediate response (fall in FEV₁ of $\geq 15\%$ within 10–30 min of allergen challenge), as well as a late-phase response (fall in FEV₁ of $\geq 15\%$ 4–6 h after initial allergen challenge). The early-phase fall in FEV₁ reflects mast cell activation, whereas the late-phase fall in FEV₁ is considered to reflect recruitment of inflammatory cells from the circulation. Study subjects pretreated with investigational therapies can be assessed as to whether the therapy blocks the early- or late-phase response to allergen challenge.

Anti-IL-5 and Asthma

Building on these encouraging findings, further studies with anti-IL-5 were performed in asymptomatic asthma patients undergoing allergen challenge (49), as well as in subjects with moderate asthma who had persistent symptoms (50). Although anti-IL-5 did reduce blood and sputum levels of eosinophils by >90% in mild asymptomatic asthmatics, anti-IL-5 did not reduce the late-phase response to inhalation allergen challenge, nor airway responsiveness (49). Subsequent studies of anti-IL-5 in patients with moderate persistent asthma also did not demonstrate improvements in asthma symptoms or pulmonary function when anti-IL-5 was added to inhaled corticosteroid therapy (50).

Anti-IL-5 and Airway Remodeling in Asthma

In contrast to these anti-IL-5 studies, which did not demonstrate a benefit in asthma, other studies have demonstrated that anti-IL-5 can reduce selected features of airway remodeling in asthma (51). Airway remodeling in asthma is characterized by the development of subepithelial fibrosis, deposition of extracellular matrix proteins beneath the epithelium, smooth

HES:
hypereosinophilic
syndrome

muscle hypertrophy/hyperplasia, mucus metaplasia, and angiogenesis. These structural changes, which occur in a subset of asthmatic subjects, may be due to persistent airway inflammation and/or impaired tissue repair mechanisms.

The importance of IL-5 and eosinophils to airway remodeling is suggested by studies in mouse models (48). Chronic allergen challenge in mice induces features of airway remodeling that are characteristic of asthma; these features are significantly reduced in IL-5-deficient mice, which are deficient in eosinophils. As eosinophils are a significant source of the profibrotic growth factor TGF- β 1, reduction of eosinophilic inflammation and the number of TGF- β 1⁺ eosinophils may explain the reduced airway remodeling in IL-5-deficient mice (48). Studies in human asthmatics have also suggested an important role for IL-5 in airway remodeling. In a double-blind placebo-controlled study of human asthmatics treated with anti-IL-5, airway biopsies were performed and bronchoalveolar lavage fluid was obtained at baseline prior to anti-IL-5 therapy and repeated three months after the anti-IL-5 therapeutic intervention (51). Anti-IL-5 significantly reduced airway biopsy eosinophils, by ~60%, as well as levels of the extracellular matrix proteins tenascin and lumican, which are deposited in increased amounts beneath the airway epithelium in remodeled airways. As in mice deficient in IL-5, anti-IL-5 therapy decreased the number of eosinophils expressing TGF- β and the total levels of TGF- β 1 (51). The contribution of TGF- β 1 to allergen-induced airway remodeling is implied by the significant reductions in airway remodeling noted in wild-type mice treated with an anti-TGF- β 1 antibody (52), as well as in smad 2/3-deficient mice (which do not respond to TGF- β 1) (53). Further studies are needed to investigate whether anti-IL-5 reduces other features of airway remodeling, in addition to deposition of extracellular matrix components beneath the airway epithelium.

It should be noted that anti-IL-5 is much more effective in reducing blood and sputum

eosinophils (reduction >90%) than in reducing airway eosinophils (reductions of 50%–60%) (54). The lower effectiveness of anti-IL-5 in reducing airway eosinophils may be due to other eosinophil growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), being present in the airway and maintaining the viability of eosinophils when IL-5 is neutralized.

In summary, current studies do not support a role for anti-IL-5 in the therapy of asthma because anti-IL-5 does not reduce the late-phase response to allergen challenge, nor does it reduce asthma symptoms (49, 50). Preliminary studies do suggest that anti-IL-5 reduces selected features of airway remodeling (51). Further studies with anti-IL-5, and/or other novel therapies that more completely deplete airway eosinophils (e.g., chemokine antagonists that block eosinophil migration), are needed to finally determine the role of eosinophils in allergic asthma.

Anti-IL-5 and the Idiopathic Hypereosinophilic Syndrome

In addition to studies investigating the use of anti-IL-5 in asthma, other studies have examined the role of anti-IL-5 in treating idiopathic hypereosinophilic syndrome (HES) (55–57). The HESs are a group of diseases characterized by persistent blood eosinophilia (>1500 eosinophils/ μ l) and evidence of end organ damage with no identifiable cause (such as parasitic infection or other known causes of hypereosinophilia) (58, 59). Imatinib mesylate, a tyrosine kinase inhibitor, is first-line therapy for the myeloproliferative variant of HES, which is associated with the fusion gene *FIP1L1-PDGFR α* (Fip1-like 1 platelet-derived growth factor receptor α) (60). Systemic corticosteroids, hydroxyurea, and IFN- α have been the mainstays of therapy in HES but are associated with considerable adverse effects and are not always effective (57).

Because eosinophil proliferation is induced by IL-5, studies have investigated whether patients with HES who do not have the

FIP1L1-PDGFR α gene benefit from anti-IL-5 therapy. In a double-blind placebo-controlled study, subjects with HES were stabilized in terms of symptoms and eosinophil count ($<1000/\mu\text{l}$) on monotherapy with prednisone and then randomized to receive either anti-IL-5 or placebo on a monthly basis for eight months (57). The primary end point was the ability of HES patients to reduce the dose of prednisone to ≤ 10 mg/day for at least two months. Starting at week one of anti-IL-5 therapy, the prednisone dose was tapered using a predetermined algorithm based on eosinophil counts and symptoms. Significantly more HES patients receiving anti-IL-5 (84%) compared to placebo (43%) were able to taper their dose of prednisone to ≤ 10 mg/day for at least two months (Table 2). Prior to receiving anti-IL-5 or placebo, the mean prednisone dose of HES subjects was ~ 30 mg/day, whereas after therapy, the mean daily dose of prednisone was 6 mg in the anti-IL-5 group and 22 mg in the placebo group. Among the HES subjects treated with anti-IL-5, 47% were able to taper off of prednisone completely, in contrast to only 5% of the placebo group. Over the nine-month treatment period, the rates of adverse events other than those due to HES were similar in the anti-IL-5 and placebo groups.

These studies suggest that anti-IL-5 therapy may be of benefit as a corticosteroid-sparing agent in patients with HES who lack the *FIP1L1-PDGFR α* fusion gene. No studies

Table 2 Hypereosinophilic syndrome: anti-IL-5 facilitates corticosteroid tapering (57)

	Anti-IL-5	Placebo
Study subjects (number)	43	42
Prednisone dose at baseline	30 mg	30 mg
Prednisone dose at 9 months	6 mg	22 mg
Tapered prednisone to ≤ 10 mg/day (% of subjects)	84%	43%
Tapered off of prednisone (% of subjects)	47%	5%

have yet determined whether anti-IL-5 is effective in patients with acute presentations of HES, patients with HES that is unresponsive to corticosteroids, or HES patients with the *FIP1L1-PDGFR α* fusion gene (61).

Anti-IL-5 and Eosinophilic Esophagitis

The potential utility of anti-IL-5 as a therapy for eosinophilic esophagitis, a disorder associated with esophageal remodeling and strictures (62), has been explored in a small open-label phase I/II study in four adult patients with eosinophilic esophagitis and longstanding dysphagia and esophageal strictures (63). Esophageal eosinophilia decreased significantly with anti-IL-5, and patients reported a better clinical outcome and improved quality of life. Further double-blind placebo-controlled studies are needed to validate these observations and to determine whether anti-IL-5 is a promising therapeutic intervention for eosinophilic esophagitis.

SUMMARY POINTS

1. Administration of SCIT to induce clinical tolerance to allergens in patients with allergic rhinitis, asthma, and bee venom allergy is the current “gold standard” against which novel immunomodulator therapies need to be compared in terms of efficacy and safety.
2. Meta-analysis studies demonstrate that SLIT reduces symptoms of allergic rhinitis and medication usage. SLIT appears to be associated with fewer systemic allergic reactions than SCIT but appears less effective in reducing symptoms.
3. Preliminary phase II studies with CpG DNA, a TLR-9 adjuvant, conjugated to the major ragweed allergen, demonstrated that a reduced number of injections could be used to induce tolerance to ragweed allergen in subjects with allergic rhinitis.

4. Anti-IL-5 demonstrated effectiveness as a corticosteroid-sparing agent in patients with HES and no *FIP1L1-PDGFR*A fusion gene (57). In contrast, anti-IL-5 did not reduce asthma symptoms or improve lung function in mild asthmatics subjected to allergen challenge, nor in moderate asthmatics. Pilot studies demonstrate that anti-IL-5 reduces features of airway remodeling in asthma.

FUTURE ISSUES

1. SLIT: Studies directly comparing SLIT versus SCIT are needed to determine their relative effectiveness and safety. In addition, double-blind placebo-controlled studies are needed to determine whether SLIT, like SCIT, has long-lasting immunomodulating properties once SLIT is discontinued. The optimal dose and duration of SLIT, as well as the use of multiple allergens in SLIT, also need to be investigated.
2. CpG DNA: Large-scale studies are needed to validate the results of small-scale phase II studies of CpG DNA conjugated to Amb a 1 in allergic rhinitis. Long-term observation in large numbers of treated subjects is also needed to demonstrate that inducing a Th1 immune response is not associated with the subsequent development of autoimmunity.
3. Anti-IL-5: Studies are needed to determine the role of anti-IL-5 in the acute presentation of HES and in other eosinophil-associated diseases, such as eosinophilic esophagitis, airway remodeling in asthma, Churg-Strauss syndrome, and eosinophilic pneumonia.
4. The successful development of a safe and easily administered immunomodulator agent holds significant potential for early intervention among high-risk populations to prevent the development of allergy in early childhood.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENT

Dr. Broide is supported by NIH grants AI038425, AI072115, and AI070535.

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