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7. Control of allergic airway inflammation through immunomodulation

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Among the asthma clinical trials published over the last several years, a unique subset has focused on novel means for inhibiting the airway inflammation that is believed to cause airway obstruction in many patients. Such interventions, broadly considered here as immune-modifying or immunomodulatory therapies, include several new drugs (omalizumab, suplatast tosilate, anti-cytokine antibodies, soluble receptors, and recombinant cytokines) and bacterial extracts. In this chapter we review the major findings with these clinical trials and indicate which have changed the management of asthma, which have not, and those that deserve further study. (J Allergy Clin Immunol 2006;117:S461-4.)

Key words: *Asthma, IgE, type I hypersensitivity, immunomodulation, T_H2 cell, eosinophil, mast cell, interleukin, airway hyperreactivity, immunostimulatory sequence*

Abbreviation used
sIL-4Rα: Soluble IL-4 receptor α

Allergic asthma is an increasingly common ailment, affecting at least 10% of adults in industrialized countries at some point in their lives. Consequently, research into the causes of asthma and attempts to improve therapies have increased substantially over the last decade. Increasingly, asthma clinical trials have focused on specific immune molecules and signaling pathways that regulate airway disease in asthma. Other interventions, although not directed at any specific inflammatory pathway, nonetheless inhibit allergic inflammation through novel means. Shared among these diverse studies is the recognition of the central role that inflammation, especially type I hypersensitivity mechanisms, play in asthma and the need to inhibit them (Fig 1). In this chapter we review results from recent studies that have used various immunomodulatory approaches to inhibit allergic inflammation in asthma. Many clinical trials are based on extensive analysis of particular agents in animal models, and where relevant, results from animal studies are briefly discussed. Although more established agents, such as glucocorticosteroids and leukotriene receptor antagonists, are also immunomodulatory, their use is considered separately in another chapter of this Primer. Many of the topics considered here were developed recently, and most of the available literature will be reviewed. However, other topics, such as abatement of sinusitis and allergen reduction, are very large, and only the most recent studies showing immunomodulatory-like effects in asthma will be considered.

RECENT CLINICAL TRIALS EXAMINING IMMUNOMODULATION IN ASTHMA

Manipulation of immunoglobulins

Omalizumab represents the first new class of anti-asthma therapeutics approved by the US Food and Drug Administration in more than 8 years, a humanized anti-IgE mAb. This novel drug binds to the Fc portion of IgE, preventing its association with immunoglobulin crystallizable fraction ε receptor 1 and therefore binding to mast cells. By thus ''disarming'' mast cells, omalizumab is intended to interrupt type I hypersensitivity reactions and lessen asthma attacks. Omalizumab reduces serum IgE levels by at least 95%,[1] reduces sputum eosinophilia by 90%, and, within the lung, significantly decreases the number of inflammatory cells expressing CD4, IL-4, immunoglobulin crystallizable fraction ε receptor 1, and CD20.[2] Early studies with omalizumab involved small numbers of patients and indicated that it suppressed early- and late-phase responses to inhaled allergen. Larger studies then showed that symptoms of adult patients were improved on the medication, and patients were able to

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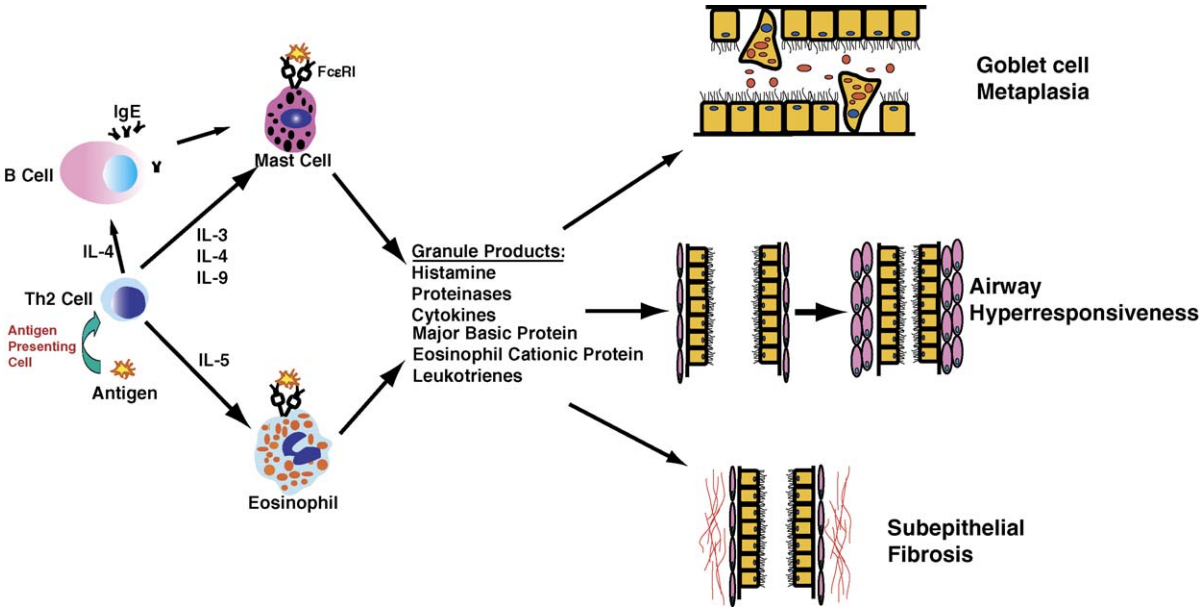

FIG 1. Type I hypersensitivity and asthma. This figure depicts one of the major mechanisms by which T_H2 cells, B cells and IgE, mast cells, and eosinophils contribute to major features of asthma through the type I hypersensitivity response.

decrease their use of other asthma medications, such as glucocorticosteroids.[1,3] In a similar manner children also benefited from omalizumab, showing less reliance on other medications and fewer disease exacerbations.[4] There is further evidence that omalizumab sustains these benefits over periods of up to a year of continuous treatment and that it improves subjective assessments of quality of life.[5,6] However, although a statistically significant improvement is detectable, omalizumab probably does not provide clinically meaningful improvement in airflow obstruction, as assessed by means of measurement of airflow and airway hyperreactivity.[2,3] Furthermore, as yet, no clinical studies comparing the relative efficacy and safety of omalizumab and glucocorticosteroids have been published. Thus although omalizumab appears in many ways to be an effective anti-inflammatory intervention, especially in patients with severe asthma, its precise role in the management of allergic asthma remains to be fully defined.

T-cell suppression

Suplatast tosilate is a dimethylsulphonium compound that inhibits the release of cytokines that are the products of T_H2 cells, such as IL-4 and IL-5 (Fig 1). This orally administered agent is effective in modestly improving peak expiratory flows (from 360 L/min before to 405 L/min after therapy, $P < .01$)[7] and airway hyperresponsiveness (36% improvement in PC_{35} values over placebo).[8] Suplatast tosilate reduces sputum and blood eosinophils (26% and 15%, respectively; $P < .05$ each) and reduces blood IgE levels 2- to 3-fold below those seen in control asthmatic patients,[9] suggesting that these anti-inflammatory features might be responsible for the beneficial effects on airway function. This promising investigational agent is currently only available in Japan.

Cytokine neutralization

Soluble IL-4 receptor α chain. IL-4 is a cytokine that is required for B-cell IgE responses and is therefore critical to type I hypersensitivity responses (Fig 1). Not surprisingly, IL-4 was therefore one of the first cytokines to be targeted in asthma clinical trials by using a soluble form of the IL-4 receptor α chain (sIL-4Rα), which binds to and inactivates IL-4. In the largest study reported, partial efficacy of IL-4 inhibition was noted in that airway function, as assessed by means of determination of airflow, deteriorated in placebo-treated patients but did not decrease in the group treated with sIL-4Rα; nonetheless, airflow limitation failed to improve with treatment.[10] Similarly, asthma symptom scores did not worsen in treated patients compared with those seen in patients receiving placebo but neither did they improve. Other measures of efficacy, including many inflammatory parameters (serum vascular cell adhesion molecule, intercellular adhesion molecule 1, eosinophil cationic protein, CD23, total IgE, and specific IgE levels and total blood eosinophil counts) were not different between the 2 groups. Although administration of sIL-4Rα was shown to be safe, further clinical studies with this agent are unlikely.[11] IL-13 is another cytokine that has many of the same effects as IL-4 but is not inhibited by sIL-4Rα. Future studies might therefore attempt to inhibit both IL-4 and IL-13 simultaneously.

Anti-IL-5 antibodies. Many investigators believe that eosinophils contribute importantly to asthma through their release of potentially toxic products that contribute to airway obstruction *in vivo*. Patients with mild or severe

asthma treated with 2 closely related neutralizing anti-IL-5 antibodies showed no clinical improvement, despite marked suppression of blood eosinophilia (>90% decrease from placebo at the highest dose) for at least 2 months, remarkably with only a single dose of antibody.[12,13] These findings were initially interpreted as indicating that the eosinophil is not pathogenic in human asthma.[14] However, subsequent studies have shown that anti-IL-5 antibody treatment during established disease does not ablate tissue eosinophils[15] nor does it diminish sputum eosinophils,[12] thereby reinvigorating the concept that at least lung eosinophils might be pathogenic. In future clinical studies, anti-IL-5 antibodies can be combined with other agents to inhibit multiple inflammatory pathways.

Immune deviation

Administration of IL-12. Administration of substances that inhibit T_H2 cells together with allergen was thought to offer greater efficacy than inhibitor alone. Perhaps the best studied of several candidate T_H2 inhibitors is IL-12, a cytokine that powerfully inhibits T_H2 responses.[16] When given to sensitized mice, IL-12 was very effective at inhibiting allergic lung disease.[17] However, IL-12 administered to asthmatic patients had no effect on airway obstruction, despite causing a significant reduction in sputum eosinophils ($P = .024$ relative to that seen in control patients), and was associated with marked toxicity, including cardiac arrhythmias and liver dysfunction.[18] A safer approach might be to administer agents that induce secretion of endogenous IL-12, as in the following approaches.

Administration of extracts of mycobacteria. A second approach to counteracting an allergic response in asthma is to administer extracts of mycobacteria, which generally promote T_H1 immunity by promoting the release of cytokines, such as IL-12. An additional rationale for this approach derives from the negative association between exposure to tuberculin (a protein derivative of *Mycobacterium tuberculosis*) and atopic disorders (ie, conditions associated with the production of IgE).[19,20] Mice given mycobacterial extracts showed reduced allergic inflammation and attenuation of airway obstruction.[21,22] Again, however, such promising experimental results could not be consistently replicated in human studies, with most showing no effect on airway physiology or inflammatory markers, such as serum IgE levels, blood eosinophil counts, and T cell–proliferative and cytokine responses.[23-25] Future studies are likely to focus on the effect of specific bacterial products conjugated to allergens, such as unmethylated DNA that contains cytosine-guanine dimers (CpG-containing immunostimulatory sequences). These short nucleic acids activate the innate immune receptor Toll-like receptor 9, a pattern recognition receptor present on many leukocytes and other cells that inhibits T_H2 cells.[26] In several mouse models concurrent immunization with CpG DNA during allergen immunization was protective against allergic lung disease.[27,28] Nonetheless, this seemingly promising approach has yet to be addressed in phase III clinical trials, but these are anticipated in the next few years.

SUMMARY

Novel means for treating asthma through immunomodulation have been attempted only in the last few years. As perhaps expected, many such attempts have proved to be less than entirely successful, yet the early successes appear to justify these innovative approaches. Omalizumab is now an established therapeutic alternative for patients with moderate-to-severe disease, although clinicians will struggle to find the best use of this expensive treatment pending future clinical studies that compare this mAb with more established therapies. If larger clinical trials continue to show promise, suplatast tosilate appears likely to win approval from the US Food and Drug Administration for use in asthma.

Other pharmaceuticals, such as anti-cytokine antibodies and receptors and bacteria-derived products, have proved to be either more hazardous, less effective, or both compared with established therapies, and additional studies with these drugs as single agents are unlikely. It is possible, however, that significant efficacy in asthma can be wrought by combining multiple relatively ineffective agents that target different aspects of the type I hypersensitivity response. Many additional novel immunomodulatory approaches to the treatment of asthma are on the horizon, portending a bright future for such therapies.

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8. Drug allergy

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Drug reactions can be considered as being either predictable or unpredictable. A predictable reaction would be the result of the pharmacologic action of the medication. An unpredictable reaction might be idiosyncratic, might be drug intolerance, or might have or imply an immunologic basis, such as being IgE mediated. Immediate reactions that are not IgE mediated can be considered as pseudoallergic (non–IgE-mediated mast cell activation). This review will discuss allergic and immunologic reactions to immunomodulators, penicillins and cephalosporins, sulfonamides, aspirin, and nonselective nonsteroidal anti-inflammatory drugs and consider the serious drug-related conditions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The field of drug "allergy" has expanded to include adverse reactions associated with immunosuppressive medications, anticytokine therapies, and mAbs. The cytokine release reaction that occurs with anti-CD20 antibody infusions in patients with leukemia and white blood cell counts of greater than 50×10^9/L is associated with high concentrations of TNF, IL-6, and IL-8. Because of the findings of fever, dyspnea, rigors, and hypotension, this reaction resembles the Jarisch-Herxheimer reaction that occurs 60 to 90 minutes after penicillin administration in patients with secondary syphilis. Furthermore, the care of the patient with penicillin allergy has been made more difficult in the absence of the major determinant, penicilloyl-polylysine, in that from 34% to 84% of patients who have positive skin test reactions to penicillin have exclusively positive reactions to the major determinant. SJS and TEN typically are caused by medications within 1 to 8 weeks of initiation of therapy. Evidence for death of the keratinocytes through (1) drug-specific cytotoxicity with the perforin-granzyme B-mediated killing and (2) activation of Fas on keratinocytes have provided explanations for the sloughing of skin. Unfortunately, intravenous immunoglobulin therapy for SJS and TEN has been disappointing. (J Allergy Clin Immunol 2006;117:S464-70.)

Key words: *Drug, allergy, immunosuppressive, keratinocytes, Stevens-Johnson syndrome, toxic epidermal necrolysis, penicillin*

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DRUG REACTIONS: GENERAL ASPECTS

One approach to assessing adverse drug reactions is to categorize them as either predictable or unpredictable.[1,2] Predictable adverse drug reactions include (1)