Narrative Review: The Role of Th2 Immune Pathway Modulation in the Treatment of Severe Asthma and Its Phenotypes

Stewart J. Levine, MD, and Sally E. Wenzel, MD

New therapeutic approaches are needed for patients with severe asthma who are refractory to standard therapy comprising high doses of inhaled corticosteroids plus long-acting β2-agonists. Current treatment guidelines for patients with severe asthma from the National Asthma Education and Prevention Program recommend the addition of oral corticosteroids, which are associated with substantial morbidity, and, for those with allergic asthma, anti-IgE. Genetic and translational studies, as well as clinical trials, suggest that in a subgroup of patients, the pathobiology of severe asthma is mediated by immune pathways driven by T-helper 2 (Th2)-type CD4+ T cells, which produce a characteristic repertoire of interleukins (ILs), including IL-4, IL-5, and IL-13. Therefore, biological modifiers of Th2-type ILs, such as monoclonal antibodies, soluble receptors, and receptor antagonists, are a rational strategy for developing new treatment approaches but will need to be targeted to selected patients in whom the appropriate Th2 immune pathway is “active.” The benefits of immune-modifier therapies targeting Th2-type cytokines, however, need to be weighed against the toxicities associated with inhibition of key biological pathways, as well as the expense of future medications. Therefore, future clinical trials need to clearly establish the efficacy and safety of biological modifiers of Th2 immune pathways before these approaches can enter routine clinical practice for the treatment of severe asthma.


A 27-year-old woman with rhinosinusitis, hypertension, diabetes; osteoporosis; gastroesophageal reflux; and lifelong, severe allergic asthma presents after a poor response to a trial of anti-IgE therapy. This therapy was started because of poor control despite high doses of inhaled and oral corticosteroids, long-acting β-agonists, and leukotriene modulators. The patient awakens with an asthma exacerbation nightly, uses an albuterol inhaler every 3 to 4 hours, and requires frequent corticosteroid bursts. On physical examination, she is obese and cushingoid in appearance. She has occasional high-pitched expiratory wheezes and diminished breath sounds. Pulmonary function testing shows moderately severe airflow obstruction with reversible airflow obstruction. Chest computed tomography shows airway wall thickening. Her serum IgE level is 356 IU/mL (normal range, 0 to 160 IU/mL), and she has no peripheral blood eosinophilia. The early onset of allergic asthma suggests that she may be a candidate for biological modifier therapies of T-helper 2 (Th2) immune pathways.

Severe Asthma

What Is Severe Asthma?

Although early definitions of severe asthma used the degree of airway obstruction and symptoms present before treatment, more recent definitions have advocated that severity of disease cannot be determined until patients have received optimum and aggressive care and comorbid conditions and environmental triggers have been identified and addressed. The American Thoracic Society definition of severe asthma is purely clinical and requires that patients have a diagnosis of asthma, have comorbid conditions (including adherence) addressed, and receive ongoing treatment with high-dose inhaled corticosteroids, oral corticosteroids, or both for 50% or more of a year and have ongoing or recurrent symptoms or exacerbations when controller medications are tapered (1). If this definition is used, both interventional studies and surveys (2, 3) suggest that at least 5% to 10% of the asthma population has “severe” asthma. Thus, severe asthma represents a substan-
Asthma Education and Prevention Program (4) (lines from the Expert Panel Report 3 of the National Institute–sponsored Severe Asthma Research Program indicate that at least 5% to 10% of asthma is severe disease that is difficult to control despite optimum management of comorbid conditions and environmental triggers, optimum therapy, and good adherence to treatment regimens.

Experimental, genetic, and clinical studies support an important role for Th2 immune pathways in the pathogenesis of severe asthma.

Biological modifiers of Th2 immune pathways, such as neutralizing monoclonal antibodies, receptor antagonists, and soluble receptors, are a rational strategy for the development of new treatments of severe asthma.

Severe asthma is a heterogeneous disease comprising distinct clinical, immunologic, and genetic phenotypes. Therapies directed against Th2 immune mediators need to be targeted to persons with the appropriate underlying pathobiology.

Potential toxicities are associated with inhibition of Th2 immune pathways.

Clinical trials are needed to establish the benefits and harms of Th2 immune modulator therapies before these expensive treatments can be recommended for severe asthma.

**Key Summary Points**

- At least 5% to 10% of asthma is severe disease that is difficult to control despite optimum management of co-morbid conditions and environmental triggers, optimum therapy, and good adherence to treatment regimens.
- Experimental, genetic, and clinical studies support an important role for Th2 immune pathways in the pathogenesis of severe asthma.
- Biological modifiers of Th2 immune pathways, such as neutralizing monoclonal antibodies, receptor antagonists, and soluble receptors, are a rational strategy for the development of new treatments of severe asthma.
- Severe asthma is a heterogeneous disease comprising distinct clinical, immunologic, and genetic phenotypes. Therapies directed against Th2 immune mediators need to be targeted to persons with the appropriate underlying pathobiology.
- Potential toxicities are associated with inhibition of Th2 immune pathways.
- Clinical trials are needed to establish the benefits and harms of Th2 immune modulator therapies before these expensive treatments can be recommended for severe asthma.

Th2 Immune Pathway Modulation in Severe Asthma

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### Steps as recommended by the Expert Panel Report 3 of the National Asthma Education and Prevention Program (4).

- **Step 1**
  - **Alternative:** cromolyn, LTRA, nedocromil, or theophylline
- **Step 2**
  - **Alternative:** low-dose ICS + LTRA, theophylline, or zileuton
- **Step 3**
  - **Alternative:** medium-dose ICS + LTRA, theophylline, or zileuton
- **Step 4**
  - **Alternative:** high-dose ICS + LABA and consider omalizumab if allergies are present
- **Step 5**
  - **Alternative:** high-dose ICS + LABA + oral corticosteroids and consider omalizumab if allergies are present

Steps as recommended by the Expert Panel Report 3 of the National Asthma Education and Prevention Program (4). Therapy should be increased to the next step if symptoms are not well controlled or are very poorly controlled, as indicated by the use of short-acting β2-agonists or by the presence of asthma symptoms more than 2 days per week, nighttime awakenings due to asthma symptoms at least once per week, some interference with normal activities, or a reduction in FEV1 or peak flow below 80% of predicted or personal best. Allergen immunotherapy may be considered for patients at steps 2 to 4, especially those with single allergies to house dust mites, animal danders, or pollens. Health care providers should be ready to identify and treat anaphylaxis that can be associated with immunotherapy and omalizumab. All patients should receive education, environmental control, and management of co-morbid conditions. If asthma is well controlled for at least 3 months, then therapy should be decreased downward to the next step. ICS = inhaled corticosteroids; LABA = long-acting β2-agonists; LTRA = leukotriene-receptor antagonists; PRN = as needed; SABA = short-acting β2-agonists.

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At least 5% to 10% of asthma is severe disease that is difficult to control despite optimum management of co-morbid conditions and environmental triggers, optimum therapy, and good adherence to treatment regimens.

Studies from the National Heart, Lung, and Blood Institute–sponsored Severe Asthma Research Program identified both frequent and severe exacerbations of asthma as hallmarks of severe disease. In addition, severe asthma is associated with comorbid conditions, such as obesity, hypertension, sinusitis, and type 2 diabetes (2, 5). This small subgroup of asthma drives most of the health care costs associated with comorbid conditions, such as obesity, hypertension, sinusitis, and type 2 diabetes (2, 5). This small subgroup of asthma drives most of the health care costs related to the disease (6, 7). Although adherence certainly must be addressed in all patients with severe asthma, some studies suggest that patients with more severe disease are more likely to take their medications and that adherence rates in asthma differ very little from any other chronic disease (8, 9). Thus, although the current treatment guidelines from the Expert Panel Report 3 of the National Asthma Education and Prevention Program (4) (Figure 1) recommend the addition of oral corticosteroids and, perhaps in appropriate patients, anti-IgE (omalizumab) for step 6 treatment of severe asthma, these approaches are associated with either substantial morbidity (oral corticosteroids) or modest efficacy (anti-IgE). Add-on therapy with omalizumab has been shown to reduce the frequency of asthma exacerbations, improve quality-of-life scores, and allow reduced doses of inhaled corticosteroids; however, it can only be used in allergic patients with asthma who have documented atopy and serum IgE levels of 30 to 700 IU/mL, and it also remains very expensive (10–14). Omalizumab requires parenteral administration (subcutaneous injection) by a health care provider, is associated with anaphylaxis in 0.1% to 0.2% of recipients, and may increase the risk for cancer (0.5% of patients receiving omalizumab vs. 0.2% of control participants) (11, 15, 16). Also, the U.S. Food and Drug Administration announced that an interim analysis of an ongoing safety study suggested an increase in cardiovascular and cerebrovascular adverse events in patients treated with omalizumab (17). Thus, new approaches to therapy in this difficult-to-treat group are desperately needed, as exemplified by the patient discussed previously. Because the costs and comorbid conditions are so high in this population, some degree of side effects with new treatments is probably acceptable.

**Phenotypes of Severe Asthma and Implications for Therapy**

One of the reasons for the poor response to medication in severe asthma may be the heterogeneity of the disease. Interest is increasing in understanding these “pheno-
Th2 Immune Pathway Modulation in Severe Asthma

An early step in the initiation of allergic airway inflammation is the activation and maturation of antigen-presenting dendritic cells in response to TSLP, an IL-7–like cytokine that is produced by airway epithelial cells, fibroblasts, and mast cells. Mature dendritic cells induce the differentiation of naive CD4+ T cells into Th2 cells, which produce a characteristic repertoire of cytokines, such as IL-4, IL-5, IL-9, IL-13, as well as TNF. Th2 cytokines mediate airway eosinophil and mast-cell recruitment, B-cell IgE isotype class switching, and mucus secretion. Dendritic cells also secrete IL-6, which plays an important role in the differentiation of both Th2 and Th17 cells. Interleukin-17, which is produced by Th17 cells, mediates airway neutrophilia by inducing the production of CXC chemokines, which are chemoattractant factors, and G-CSF, a survival and proliferation factor, by bronchial epithelial cells. Interleukin-17 also induces mucin gene expression. Tregs negatively regulate immune responses via the production of IL-10 and TGF-β. G-CSF = granulocyte colony-stimulating factor; TGF = transforming growth factor; TNF = tumor necrosis factor; Treg = regulatory T cell; TSLP = thymic stromal lymphopoietin.

Figure 2. Modulating Th2 immune pathways for the treatment of asthma.

Although data in humans have been less definitive (primarily because of the low levels of these cytokines found in human airways), inflammatory pathways downstream of IL-4 and IL-13, including eotaxin-1 and -3 (CCL11 and CCL26), which are chemoattractant factors for eosinophils (an important effector inflammatory cell in allergic asthma); 15-lipoxygenase, an enzyme that generates proinflammatory lipid mediators from arachidonic acid; and inducible nitric oxide synthase, the enzyme responsible for producing exhaled nitric oxide (FeNO), are all statistically significantly increased in bronchial epithelial cells obtained from humans with severe asthma (29, 30). Of note, FeNO is strongly linked to eosinophilic (and particularly allergic) inflammation. Although FeNO can decrease with inhaled and oral corticosteroid therapy in patients with severe asthma, it stays elevated compared with healthy control participants (2). The association of FeNO with Th2 immune processes was also confirmed after its reduction in response to antagonism of the IL-4 pathway (31).

Genetic studies of the Th2 pathway also support the importance of these pathways in severe asthma in humans. Polymorphisms in IL-4, the IL-4 receptor α-chain (IL-4Rα), and IL-13 are the most consistently observed and replicated genes associated with human asthma (32). Polymorphisms in both IL-4 and IL-4Rα have been associated with the Th2 inflammatory phenotype, support the idea that this approach will lead to better clinical outcomes and will better contribute to the understanding of the pathobiology of the underlying phenotypes.

The Th2 Inflammatory Phenotype

Childhood-onset “allergic asthma” has been considered a Th2 disease for nearly 20 years, although proof in humans has been limited. The initial focus on this pathway began with identification of an adaptive immune response in a murine model characterized by the release of a distinct set of ILs, including IL-4, IL-5, IL-9, and IL-13, from Th2-type (T-helper) CD4+ cells, which mediate the pathogenesis of allergic asthma (Figure 2) (22, 23). Interleukin-4 and IL-13 are canonical Th2-type cytokines that play a key role in human allergic asthmatic responses. Interleukin-4 promotes the differentiation and proliferation of Th2-type T cells and switching of B cells from IgG to IgE production, whereas IL-13 is an effector cytokine that mediates airway hyperreactivity and mucus hyperproduction (23, 24). Th1 cells, which characteristically produce interferon-γ, were believed to primarily play a role in clearance of intracellular infections and autoimmunity (25). Th1 cells were also considered to have a protective effect in allergic asthma by inhibiting Th2 responses; however, recent data from murine and human studies (26, 27) suggest that Th1 responses may actually enhance allergy and airway hyperreactivity in asthma. Th17 cells, which produce IL-17 with resultant neutrophilic inflammation, are another important type of T-helper cell that is shown to mediate steroid resistance in a murine model of asthma (28).

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with a severe exacerbating phenotype of severe asthma (33, 34). These single-nucleotide polymorphisms in IL-4Rα were also associated with an inflammatory pattern identified by increased airway mast cells and IgE(+) cells (35).

Although asthma was initially hypothesized to uniformly be a “Th2 disease,” recent gene-expression data in milder asthma suggest that a “Th2 gene signature” is present in only about 50% of patients with asthma (21). This group was characterized by more airway responsiveness, eosinophils, and remodeling. Of note, this group responded well to inhaled corticosteroids, whereas the non-Th2 group did not. This is further evidence that biological modifiers of Th2 pathways will need to be targeted to persons in whom the pathway is “active.”

**Will Specific Modulation of the Th2 Immune System Improve Outcomes in Severe Asthma?**

The most important confirmation of this pathway’s activation, however, is achieved only when the pathway is specifically blocked in studies of human patients with asthma. The development of specific biological modifiers that modulate the Th2 immune system will determine both the role of this pathway in severe asthma and the efficacy and safety of these approaches for the treatment of severe asthma. Because Th2 immune pathways modulate other essential biological functions besides asthma, the benefits of biological modifier therapies will need to be weighed against the risk for untoward effects before these approaches can be adopted in clinical practice. Furthermore, the cost of biological modifier therapies of the Th2 immune pathway may be a limiting factor.

**IL-5**

IL-5 is a key Th2-type cytokine that plays an important role in the differentiation, maturation, and survival of eosinophils (36). Although neutralizing anti–IL-5 monoclonal antibodies effectively reduce eosinophils in blood, it only partially depletes airway eosinophils and has not been shown to be clinically beneficial in patients with mild or moderate asthma (37–40). Two recent randomized, double-blind, parallel-group, placebo-controlled, phase 2 clinical trials (41, 42), however, have targeted anti–IL-5 antibody to a subset of patients with severe, corticosteroid-dependent asthma with an eosinophilic inflammatory phenotype defined by greater than 3% sputum eosinophila. Anti–IL-5 therapy statistically significantly improved asthma exacerbations but did not consistently improve other clinical or physiologic asthma outcomes. Serious adverse events in patients receiving anti–IL-5 included heart failure due to ischemic cardiomyopathy, fatigue and aches during prednisone dose reduction, maculopapular rash, and exacerbations of severe asthma. These studies show that eosinophils play an important role in mediating disease exacerbations in patients with severe asthma with an eosinophilic inflammatory phenotype, as defined by induced sputum analysis. Validation of the efficacy and safety of anti–IL-5 approaches in future clinical trials of patients with severe asthma and an eosinophilic inflammatory phenotype is required before anti–IL-5 therapies can enter clinical practice as a strategy to prevent disease exacerbations in this subgroup.

**IL-4 and IL-13**

Previous approaches that selectively inhibited IL-4 for the treatment of asthma have not been effective, which suggests that targeting IL-13 is in fact critical (23). Therefore, new therapeutic approaches that target IL-13, alone or in combination with IL-4, are being developed, such as a mutated IL-4 (pitrakinra) that binds the IL-4Rα and thereby blocks the effects of both IL-4 and IL-13 (31). A small randomized, double-blind, placebo-controlled, parallel-group, phase 2 trial (31) in patients with mild-to-moderate asthma showed that inhaled pitrakinra reduced the late-phase decline in lung function in response to inhalational allergen challenge compared with placebo (31). No serious adverse events related to pitrakinra were reported. Additional studies are required to show the efficacy of this approach in severe asthma, as well as to determine its safety profile. Neutralizing monoclonal antibodies targeting IL-4 or IL-13, as well as soluble IL-13 receptor fusion proteins that bind IL-13, are also being developed (23).

**Tumor Necrosis Factor**

Tumor necrosis factor (TNF) is a potential therapeutic target in severe asthma. It is a proinflammatory cytokine, expressed by mast cells, eosinophils, CD4+ T lymphocytes, and alveolar macrophages. It promotes airway inflammation and hyperreactivity, as well as mucin hyperproduction. A randomized, double-blind, dose-ranging, multicenter phase 2 clinical trial (43) assessed the efficacy and safety of golimumab, an anti-TNF monoclonal antibody, in 309 patients with symptomatic severe asthma for 76 weeks. Golimumab treatment did not improve either of the co-primary end points—change in prebronchodilator FEV₁ or number of severe exacerbations. Furthermore, the study was terminated early because of an unfavorable risk–benefit profile: Serious adverse events, including infections (tuberculosis, pneumonia, and death due to septic shock) and cancer (breast cancer, lymphoma, melanoma, as well as colon, renal, cervical, and basal carcinomas), occurred more frequently in the golimumab group. This shows that anti-TNF approaches are not suitable for a general population of patients with severe asthma. Furthermore, the authors concluded that the unacceptable risk–benefit ratio of golimumab therapy should preclude the initiation of additional large studies of anti-TNF therapy in this population. A post hoc subgroup analysis showed that patients with bronchodilator reversibility or sinusitis were less likely to have serious asthma exacerbations when treated with golimumab, which suggests that a subtype with physiologically defined severe asthma might be a target population if
Th2 immune pathways play an important role in the pathogenesis of subgroups of patients with severe asthma, such as those with IL-5–mediated eosinophilic airway inflammation. Therefore, biological modifiers of Th2 immune pathways are a rational approach for developing new treatments for severe asthma that could be added when standard therapies, such as inhaled corticosteroids plus long-acting β₂-agonists or oral corticosteroids, do not provide adequate control. Because asthma has a complex and heterogeneous pathogenesis, the efficacious use of immune modulator therapies will require identification of subsets of patients who have severe asthma and the appropriate pathobiology and whose treatment could be targeted in a personalized manner, perhaps guided by genetic or biological markers. Clinical trials will need to clearly establish that the benefits of Th2 immune modulator therapies outweigh the toxicities associated with inhibition of key biological pathways and the expense of the medications before these approaches can be recommended for the treatment of severe asthma.

CONCLUSION

Th2 immune pathways play an important role in the pathogenesis of subgroups of patients with severe asthma. Therefore, biological modifiers of Th2 immune pathways are a rational approach for developing new treatments for severe asthma that could be added when standard therapies, such as inhaled corticosteroids plus long-acting β₂-agonists or oral corticosteroids, do not provide adequate control. Because asthma has a complex and heterogeneous pathogenesis, the efficacious use of immune modulator therapies will require identification of subsets of patients who have severe asthma and the appropriate pathobiology and whose treatment could be targeted in a personalized manner, perhaps guided by genetic or biological markers. Clinical trials will need to clearly establish that the benefits of Th2 immune modulator therapies outweigh the toxicities associated with inhibition of key biological pathways and the expense of the medications before these approaches can be recommended for the treatment of severe asthma.

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Note: This manuscript is based on a National Institutes of Health Clinical Center Grand Rounds that was presented on 3 September 2008.

Acknowledgment: The authors thank Dr. James Shelhamer for his thoughtful comments and review of the manuscript.

Grant Support: By the Intramural Research Program of the National Heart, Lung, and Blood Institute, National Institutes of Health; the National Immunologic, Allergic and Infectious Disease Institute (AI 40600); and the University of Pittsburgh.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M09-1583.

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