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The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes: Are we getting closer?

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Abstract

New therapeutic approaches are needed for severe asthmatics who are refractory to standard therapy with high doses of inhaled corticosteroids plus long-acting β_2 -agonists. Current treatment guidelines for severe asthmatics from the National Asthma Education and Prevention Program recommend the addition of oral corticosteroids, which are associated with significant morbidity, and for those with allergic asthma, anti-IgE. Genetic and translational studies, as well as clinical trials, suggest that in a sub-group of patients the pathobiology of severe asthma is mediated by immune pathways driven by Th2-type CD4⁺ T cells which produce a characteristic repertoire of interleukins, including IL-4, IL-5 and IL-13. Therefore, biological modifiers of Th2-type interleukins, such as monoclonal antibodies, soluble receptors and receptor antagonists, represent a rational strategy for developing new treatment approaches, but will need to be targeted to selected individuals in whom the appropriate Th2 immune pathway is “active.” The benefits of immune modifier therapies targeting Th2-type cytokines, however, will 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 will 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.

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Potential Conflicts of Interest: Dr. Levine is the holder of a patent entitled, “Regulators of type-1 tumor necrosis factor receptor and other cytokine receptor shedding,” U.S. Patent # 7,135,303. Dr. Levine also has a patent application pending entitled, “TNF-alpha converting enzyme inhibitory agents and stimulatory agents.”

Dr. Wenzel has received consulting fees from Centocor and was Chair of the Steering Committee for the Anti-TNF trial in severe asthma. She has received consulting fees from Genentech and Novartis in relation to treatment of severe asthma. She has consulted for GlaxoSmithKline, Wyeth, Amgen, and Altair. She serves on the Scientific Advisory Board for Altair. Dr. Wenzel has received grants from GlaxoSmithKline, Cepion, Medimmune and Aerovance.

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Case Presentation

A 27 year old female with rhinosinusitis, hypertension, diabetes, osteoporosis, and gastroesophageal reflux, and lifelong severe allergic asthma presents after poor response to a trial of anti-IgE therapy, which was started because of poor control despite high dose inhaled and oral corticosteroids, long-acting beta-agonists, and leukotriene modulators. She awakens with asthma nightly, uses an albuterol inhaler every 3–4 hours, and requires frequent corticosteroid bursts. On physical exam she is obese and cushingoid in appearance. She has occasional high-pitched expiratory wheezes and diminished breath sounds. Pulmonary function testing showed moderately severe airflow obstruction with reversible airflow obstruction. Chest computed tomography shows airway wall thickening. Her serum IgE is 356 IU/ml (normal range is 0 – 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 Th2 immune pathways.

Severe Asthma

What is Severe Asthma?

While early definitions of severe asthma utilized the degree of airway obstruction and symptoms present prior to treatment, more recent definitions have advocated that severity of disease cannot be determined until patients have received optimal and aggressive care of their disease, as well as have co-morbidities and environmental triggers identified and addressed. The American Thoracic Society definition of severe asthma is purely clinical and requires that patients have a diagnosis of asthma, have co-morbidities (including compliance/adherence) addressed, and then: 1) have been treated with high dose inhaled corticosteroids for the previous year or oral corticosteroids for 50% or more of the previous year and 2) have ongoing symptoms and exacerbations or recurrent symptoms/exacerbations when controller medications are tapered(1). Using this definition, both interventional studies and surveys suggest that at least 5–10% of the asthma population has “severe” asthma(2,3). Thus, severe asthma represents a significant public health problem as more than 22 million individuals in the United States have asthma(4).

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 co-morbidities, such as obesity, hypertension, sinusitis, and type 2 diabetes (2,5). This small subgroup of asthma drives the majority of the health care costs related to the disease(6,7). Although compliance/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 compliance rates in asthma differ very little from any other chronic diseases(8,9). Thus, while the current treatment guidelines from the Expert Panel 3 Report of the National Asthma Education and Prevention Program (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 either are associated with significant morbidity (oral corticosteroids) or modest efficacy (anti-IgE)(4). Add-on therapy with omalizumab has been shown to reduce the frequency of asthma exacerbations, improve-quality-of-life scores and allow a reduction in inhaled corticosteroid dosage, but can only be used in allergic asthmatics with documented atopy and serum IgE levels of 30 to 700 IU/ml, while remaining very expensive(10–14). Omalizumab requires parenteral administration (subcutaneous injection) by a health care provider, is associated with anaphylaxis in 0.1% – 0.2% of recipients, and may increase the risk of malignancy (0.5% of patients receiving omalizumab versus 0.2% of control patients) (11,15,16). Also, the Food and Drug Administration recently announced that an interim analysis of an ongoing safety study suggested an increased number of cardiovascular and

cerebrovascular adverse events in patients treated with omalizumab(17). Thus, new approaches to therapy of this difficult group are desperately needed, as exemplified by the patient in the case presentation. As the costs and co-morbidities are so high in this population, some degree of side effects for new treatments are likely to be 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. Recently there is increasing interest in understanding these “phenotypes” better, as targeted therapy is more likely to work in those with similar underlying pathobiologic features. Interestingly, both biased and unbiased population studies in humans suggest clinically meaningful differences in severe asthma which begins in childhood versus that which begins in adulthood(2,18,19). In simple terms, childhood onset asthma represents the “classic allergic” asthma whereas, asthma which begins in adulthood represents a more heterogeneous group which often has little to no association with allergy, but instead may be related to aspirin sensitivity, hormonal influences, occupational exposures or a post-infectious history. While it is likely that some overlap exists with allergic asthma, the pathobiology of these phenotypes remains less well defined than that of allergic asthma. Other phenotypes include those defined by molecular and cellular inflammation, asthma triggers, and physiologic parameters (19–21). This heterogeneity strongly supports the investigation of targeted therapies only in the patients with the appropriate underlying pathobiology. Recently published studies on anti-interleukin-5, which targeted an “eosinophilic” inflammatory phenotype, support the concept that this approach will lead to better clinical outcomes as well as better contribute to the understanding of the pathobiology of the underlying phenotypes (see below).

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 interleukins, 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). IL-4 and IL-13 are canonical Th2-type cytokines that play a key role in human allergic asthmatic responses. IL-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 , have been thought 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 suggest that Th1 responses may actually enhance allergy and airway hyperreactivity in asthma(26,27). Th17 cells, which produce IL-17 with resultant neutrophilic inflammation, are another important type of T helper cell that has been shown to mediate steroid-resistance in a murine model of asthma(28).

While data in humans have been less definitive, primarily due to the low levels of these cytokines found in human airways, inflammatory pathways downstream of IL-4/-13, including eotaxins-1, 3 (CCL11 and 26), which are chemoattractant factors for eosinophils (an important effector inflammatory cell in allergic asthma), 15-lipoxygenase, an enzyme that generates pro-inflammatory lipid mediators from arachidonic acid, and inducible nitric oxide synthase (iNOS), the enzyme responsible for producing exhaled nitric oxide (FeNO), have all been found to be significantly increased in bronchial epithelial cells obtained from severe human asthmatics(29,30). Interestingly, FeNO is strongly linked to eosinophilic (and particularly allergic) inflammation. While FeNO can decrease with inhaled and oral corticosteroid therapy in severe asthmatic patients, it remains elevated compared to normal controls (2). The

association of FeNO with Th2 immune processes was also confirmed following 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 to human severe asthma. Polymorphisms in IL-4, the IL-4 receptor α -chain (IL-4R α), and IL-13, are the most consistently observed and replicated genes associated with human asthma (32). Polymorphisms in both IL-4 and IL4R α have been associated with a severe exacerbating phenotype of severe asthma (33,34). These single nucleotide polymorphisms in IL-4R α 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 suggests that a “Th2 gene signature” is present in only about 50% of asthmatic patients(21). This group was characterized by more airway responsiveness, eosinophils and remodeling. Interestingly, this group responded well to inhaled corticosteroids, while the non-Th2 group did not. This is further evidence that biologic modifiers of Th2 pathways will need to be targeted to individuals 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 this pathway is specifically blocked in studies of human asthmatics. The development of specific biological modifiers that modulate the Th2 immune system will both determine the role of this pathway in severe asthma, as well as the efficacy and safety of these approaches for the treatment of severe asthma. Since Th2 immune pathways also modulate other essential biological functions besides asthma, the benefits of biological modifier therapies will need to be weighed against the risks of untoward effects before these approaches can enter clinical practice. Furthermore, the cost of biological modifier therapies of the Th2 immune pathway may represent a limiting factor.

Interleukin-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 are effective at reducing eosinophils in blood, it only partially depletes airway eosinophils and has not been associated with clinical benefit in mild or moderate asthmatics(37–40). Two recent randomized, double-blind, parallel-group, placebo-controlled, phase 2 clinical trials, however, have targeted anti-IL-5 antibody therapy to a subset of severe, corticosteroid-dependent asthmatics with an eosinophilic inflammatory phenotype defined by > 3% sputum eosinophilia(40–42). Anti-IL-5 therapy significantly improved asthma exacerbations, but did not consistently improve other clinical or physiological 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 severe asthmatics 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 severe asthmatics with an eosinophilic inflammatory phenotype is required before anti-IL-5 therapies can enter clinical practice as a strategy to prevent disease exacerbations in this sub-group.

Interleukin-4 (IL-4) and Interleukin-13 (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 interleukin-4 (pitakinra) that binds the IL-4R α and thereby blocks the effects of both IL-4 and IL-13(31). A small

randomized, double-blind, placebo-controlled, parallel group phase II trial in mild-to-moderate asthmatics showed that inhaled pitrakinra reduced the late phase decline in lung function in response to inhalational allergen challenge as compared to placebo(31). No serious adverse events related to pitrakinra were reported. Additional studies are required to demonstrate 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 (TNF)—Tumor necrosis factor (TNF) has also been identified as a potential therapeutic target in severe asthma. TNF is a pro-inflammatory cytokine, expressed by mast cells, eosinophils, CD4+ T lymphocytes and alveolar macrophages, which promotes airway inflammation and hyperreactivity, as well as mucin hyperproduction. A randomized, double-blind, dose-ranging, multi-center phase II clinical trial recently assessed the efficacy and safety of golimumab, an anti-TNF monoclonal antibody, in 309 patients with symptomatic severe asthma for 76 weeks(43). Golimumab treatment did not improve either of the co-primary end-points of change in pre-bronchodilator FEV₁ or number of severe exacerbations. Furthermore, the study was discontinued early due to an unfavorable risk-to-benefit profile as serious adverse events, which included serious infections (tuberculosis, pneumonia and death due to septic shock) and malignancy (breast cancer, lymphoma, melanoma, as well as colon, renal, cervical and basal carcinomas), were significantly increased in the golimumab group. This demonstrates that anti-TNF approaches are not suitable for a general population of severe asthmatics. Furthermore, the authors concluded that the unacceptable risk-to-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 and/or sinusitis were less likely to experience serious asthma exacerbations when treated with golimumab, which suggests that a sub-type with physiologically defined severe asthma might be identified as a target population if further clinical trials of anti-TNF are considered. However, any potential benefit in severe asthma would need to out-weigh the risks of this approach. Additional serious toxicities associated with anti-TNF for treatment of inflammatory arthritides have included opportunistic infections, hepatitis B reactivation, demyelinating disorders, aplastic anemia, and pancytopenias(44).

Conclusion

Th2 immune pathways play an important role in the pathogenesis of sub-groups of severe asthmatics, such as those with IL-5-mediated eosinophilic airway inflammation. Therefore, biological modifiers of Th2 immune pathways represent a rational approach for developing new treatments of severe asthma that could be added on when standard therapies, such as inhaled corticosteroids plus long-acting β_2 -agonists or oral corticosteroids, do not provide adequate control. Since asthma has a complex and heterogeneous pathogenesis, the efficacious use of immune modulator therapies will require the identification of subsets of severe asthmatics with the appropriate pathobiology, whose treatment could be targeted in a personalized fashion, 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, as well as expense of the medications, before these approaches can be recommended for the treatment of severe asthma.

Summary Table of Take-home Points

- Five to ten percent of asthma is severe disease that is difficult to control despite optimal management of co-morbidities and environmental triggers, optimal 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, represent a rational strategy for the development of new treatments for severe asthma.
- Severe asthma is a heterogeneous disease comprised of distinct clinical, immunologic, and genetic phenotypes. Therapies directed against Th2 immune mediators need to be targeted to individuals with the appropriate underlying pathobiology.
- There are potential toxicities associated with inhibition of Th2 immune pathways.
- Clinical trials are needed to establish the benefits and harms of Th2 immune modulator therapies before recommending these expensive treatment approaches for severe asthma.

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Figure 1. Stepwise approach for managing asthma in youths greater than 12 years of age and adults as recommended by the Expert Panel 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 poorly controlled, as indicated by the use of short-acting β_2 -agonists or 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 2–4, especially those with single allergies to house-dust mites, animal danders or pollens. Health care providers should be prepared to identify and treat anaphylaxis that can be associated with immunotherapy and omalizumab. All patients should receive education, environmental control and management of co-morbidities. If asthma is well controlled for at least 3 months, then therapy should be decreased downward to the next step. Abbreviations are as follows: ICS (inhaled corticosteroids), LABA (long-acting β_2 -agonists), LTRA (leukotriene receptor antagonists), and SABA (short-acting β_2 -agonists).

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

An early step in the initiation of allergic airway inflammation is the activation and maturation of antigen-presenting dendritic cells in response to thymic stromal lymphopoietin (TSLP), an interleukin-7-like cytokine that is produced by airway epithelial cells, fibroblasts and mast cells. Mature dendritic cells induce the differentiation of naïve 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 tumor necrosis factor (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. IL-17, which is produced by Th17 cells, mediates airway neutrophilia by inducing the production of CXC chemokines, which are chemoattractant factors, and granulocyte-colony stimulating factor (G-CSF), a survival and proliferation factor, by bronchial epithelial cells. IL-17 also induces mucin gene expression. Regulatory T cells (Tregs) negatively regulate immune responses via the production of IL-10 and transforming growth factor- β (TGF- β).