

Immunotherapy in Asthma Management

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INTRODUCTION

Traditionally, asthma and other allergic diseases have been broadly defined and managed with nonspecific medications including bronchodilators and corticosteroids; however there has been an increasing appreciation of the heterogeneity of asthma, particularly- the allergic phenotype. This newfound appreciation has reignited an interest in molecularly targeted therapy. Although only three targeted therapies have been approved to date-omalizumab, mepolizumab and reslizumab, many more are currently in development and offering new promise in the previously stagnant field of asthma management.

PATHOGENESIS AND “THE ASTHMA SYNDROME”

An introduction to the pathogenesis and phenotypic diversity of asthma is necessary before one can understand the mechanism of action and potential impact of immunotherapy for the treatment of asthma. Although the recognition of distinct asthma ‘subgroups’ based on phenotype or endotype is a modern classification, the postulation of allergy as a main culprit of asthma is not.

In the early 1900's, Francis Rackemann subdivided asthma into extrinsic and intrinsic categories after recognizing that some asthmatics suffered from severe disease secondary to environmental factors [1]. Additionally, a large population study in 1980's revealed a strong correlation between age-adjusted blood IgE levels and asthma, thus suggesting an allergic component to asthma [2]. Analyses of sputum and bronchoalveolar lavage specimens collected from diagnosed asthmatics demonstrated significant eosinophilia. Despite the preponderance of evidence suggesting that asthma is indeed an allergic disease, not all asthmatic patients demonstrate eosinophils on sputum samples and, in fact, nearly 50% of diagnosed asthmatics on inhaled corticosteroid therapy do not demonstrate eosinophils in either sputum or bronchoalveolar lavage specimens [3]. Finally, studies have shown that asthmatic patients without eosinophils in respiratory specimens, termed non-eosinophilic asthma, often respond poorly to inhaled corticosteroid therapy [4,5].

The above evidence, suggests that asthma is not a single homogenous disease, but instead a multidimensional syndrome with varying clinical, physiologic, and pathologic domains. Multiple groups of researchers have attempted to define distinct phenotypes of asthma based on airflow obstruction, cellular inflammation and clinical characteristics- all of these classifications have at least an allergic phenotype [6,7]. Asthmatic patients with this particular phenotype tend to exhibit concomitant allergic rhinitis, eczema, or eosinophilic esophagitis [7]. Patients with allergic phenotype typically have positive skin prick test, high serum IgE, and high fractional excretion of nitric oxide (**FeNO**) [8].

Patients with allergic asthma primarily demonstrate a type 2 immune response (**TH2 cell**) driven by the production of IL-4, IL-5, and IL-13 [9]. To date, biologic therapies include those that target IgE, IL-5, IL-13, IL-4 receptor alpha (**IL-4R α**), and thymic stromal lymphopoeitin (**TSLP**). IL-4 and IL-13 are central to the type 2 immune response with both IL-4 and IL-13 promoting IgE isotype switching in B cells [10]. Additionally, IL-4 enhances T cell differentiation into mature TH2 cells [10,11]. IgE binds to high affinity IgE receptors on mast cells and basophils leading to degranulation with release of multiple inflammatory mediators, thus leading to the early asthmatic response. IL-5 is critical to eosinophil development and survival [10]. Less is known about TSLP, but it seems to enhance TH2 differentiation and maturation and is a major mediator involved in dendritic cell recruitment and mobilization [10,11].

IMMUNOTHERAPY IN ASTHMA

Despite the substantial evidence of relationship between allergy and asthma and role of type 2 inflammation in the pathogenesis of asthma, initial studies with immunotherapy in the 1990s were decidedly not promising.

An allergen-challenge, placebo controlled trial of an antibody to IL-5 failed to improve early/late asthmatic reactions or decrease airway hyperactivity [12]. A subsequent, larger study in patients with persistent asthma on inhaled corticosteroid therapy failed to show a significant decrease in exacerbations, spirometry, quality of life assays, or symptom scores despite a

significant decrease in blood and sputum eosinophils [13]. Furthermore, an antibody to the IL-4 receptor in moderate to severe asthma failed to show a significant reduction in all the relevant clinical outcomes [14].

All these initial studies with immunotherapy were done in non phenotype populations. Although molecularly targeted therapy did not prove to be beneficial in all patients with asthma, it may still hold promise for patients with the allergic asthma phenotype who demonstrate the aforementioned type 2 immune response. This may especially true for this subset of patients with significant symptoms and frequent exacerbations despite optimization on maximal medical therapy. This subgroup has been defined by the American Thoracic Society and European Respiratory Society (**ATS/ERS**) as severe asthma.

TARGETING IGE

Atopy, or the genetic predisposition to develop specific IgE antibodies directed against environmental allergens has been established as one of the strongest identifiable risk factors for the development of asthma [15]. As such, interest in the development of a biologic agent blunting the systemic response to free IgEs not surprising and, in fact, has been pursued since the 1970s.

In contrast to early studies targeting IL-4 and IL-13, anti-IgE, omalizumab was validated in multiple placebo controlled randomized trials. In these trials, Omalizumab suppressed both the early and delayed hypersensitivity response to nebulized inhaled allergens in patients with mild asthma and atopy [16]. Additionally, it also blunted the decrease in FEV1 and asthma symptom scores in patients with documented cat dander allergies after cat chamber exposure [17].

Three major placebo controlled, randomized trials including patients with moderate to severe allergic asthma have been published and have consistently shown significant reductions in frequency of exacerbations, serum IgE, asthma symptom scores, oral or inhaled corticosteroid requirements, and use of rescue inhaler therapy after administration of subcutaneous anti-IgE therapy [18-20]. Additionally, adverse events were similar in both the anti-IgE and placebo groups. Thereafter, a retrospective analysis by Hanania divided patients into those with and without the type 2 immune response based on biomarkers (FeNO, serum periostin, or serum eosinophils) and revealed that omalizumab was more efficacious in those patients with increased markers of type 2 inflammation [21]. Finally, a 2014 systemic review of 25 randomized trials of patients with moderate to severe asthma receiving inhaled corticosteroids demonstrated a significant reduction in exacerbations, hospitalizations, and inhaled corticosteroid use when omalizumab was used as an add-on therapy [22].

Further studies have demonstrated efficacy in patients with allergic rhinitis, food allergy, and atopic dermatitis although this indication will not be discussed further [23-25].

Currently omalizumab is FDA approved for patients 6 years or older with moderate to severe asthma uncontrolled on inhaled corticosteroid (high dose inhaled corticosteroids in

Europe) therapy with total serum IgE levels between 30-700 international units/mL and allergic sensitization demonstrated by positive skin testing or other allergen-specific testing. Although not yet a specific indication for prescription, limited studies have demonstrated a benefit with omalizumab in patients with serum eosinophilia (serum eosinophil count > 300 cell/micro liter) [26].

TARGETING IL-4 AND IL-13

As discussed above, both IL-4 and IL-13 are instrumental to the type 2 immune response. Initial studies performed in the 1990s populations were non-efficacious [12-14]. However, these studies were done on asthma patients considering them a homogenous population as opposed to studying them based on phenotype. Excitement regarding biologic agents targeting IL-4 and IL-13 reignited after the appreciation of multiple asthma phenotypes, especially allergic asthma as defined by serum biomarkers or positive skin prick testing.

Lebrikizumab, a humanized IgG4 monoclonal antibody to IL-13 has since been shown to increase FEV1 and decrease exacerbations in patients with high type 2 biomarkers, most notable one being serum periostin [27]. Additionally, Hanania et al. pooled data from two previous studies on patients with moderate to severe asthma uncontrolled on inhaled corticosteroid therapy and demonstrated a 60% reduction in exacerbations and an increase in FEV1 in the subset of patients with high serum periostin, thus suggesting a benefit in patients demonstrating the allergic asthma phenotype [28]. Currently, lebrikizumab is undergoing further phase III clinical trials.

Dupilumab, a humanized monoclonal antibody to IL-4R α , has been more extensively studied. In patients with moderate to severe asthma uncontrolled on inhaled corticosteroid and long acting beta agonist therapy with sputum or blood eosinophilia (>3% or 300 cells/mL respectively), dupilumab has been shown to decrease exacerbations, rescue inhaler use, and increase FEV1. It also improved asthma symptom scores and quality of life scores [29]. Additional studies have further revealed benefit in patients with atopic dermatitis [30,31]. The US FDA granted dupilumab priority status review which is currently ongoing.

TARGETING IL-5

IL-5, another type 2 immune response cytokine, is the most potent eosinophilic cytokine known [10]. Its receptor IL-5R α is extensively found on eosinophils and basophils. Since peripheral eosinophilia is often pronounced in patients with allergic asthma, it's not surprising that IL-5 was identified as a potential target.

In 2009, a large placebo controlled, randomized trial enrolled patients with uncontrolled moderate to severe asthma on inhaled corticosteroid therapy with sputum eosinophilia-defined as $\geq 3\%$ eosinophils on at least one occasion in the last 2 years. Patients treated with mepolizumab for 1 year experienced a 48% reduction in exacerbations with improved asthma quality of life scores [32]. Another large multicenter, double blind, placebo controlled trial in 2012 demonstrated that

patients with uncontrolled eosinophilic asthma treated with mepolizumab exhibited a significant decrease in frequency of exacerbations [33]. Further studies also evaluated peripheral blood eosinophilia as a marker of allergic asthma and demonstrated similar findings [34]. Currently, mepolizumab is FDA approved in patients age 12 or older with severe asthma who demonstrate an eosinophilic phenotype, loosely defined as an absolute blood eosinophil count ≥ 150 cells/micro liter.

Another monoclonal anti-IL 5 antibody, reslizumab has been shown in multiple trials to decrease the frequency of exacerbations, improve FEV1, improve quality of life, and asthma symptom scores [35,36]. It is currently FDA approved for patients 18 years or older with severe asthma who demonstrate an eosinophilic phenotype. Although not defined, pivotal trials defined this as an absolute peripheral blood eosinophil count ≥ 400 cells/micro liter.

Benralizumab, a novel humanized monoclonal antibody targeting IL-5R α has been shown in a Phase II trial to reduce the frequency of exacerbations, improve FEV1 and improve quality of life scores in patients with asthma uncontrolled on inhaled corticosteroid therapy who demonstrate an eosinophilic phenotype based on peripheral blood eosinophils or FeNO [37]. Benralizumab is currently undergoing Phase III trials.

FUTURE THERAPIES

Other targets, including TSLP have most recently been evaluated in patients with uncontrolled moderate to severe allergic asthma. A randomized placebo controlled trial published in the NEJM in 2014 demonstrated an attenuation of both the early and delayed asthmatic hypersensitivity response in patients treated with an anti-TSLP humanized monoclonal antibody [38]. Other potential targets include an anti-IL-2R antibody and a GATA3-specific DNase; however these targeted therapies are still undergoing investigation.

CONCLUSION

Immunotherapy is a rapidly expanding field that offers an exciting promise and great potential as physicians move away from nonspecific management to an individually tailored therapy. This especially holds true in the management of asthma as we further comprehend and discover the diverse molecular pathophysiological mechanisms that underlie the distinct clinical phenotypes appreciated daily in clinic. To date, anti-IgE and anti-IL-5 targeted therapies have proven to be extremely effective in managing patients with allergic asthma who demonstrate significant symptoms despite maximal medical therapy.

Table 1: Comparison of both FDA approved and on-approved therapies for the management of severe allergic asthma.

FDA approved		Indications	Effects
	Anti-IgE (omalizumab)	>5 years old Moderate to severe asthma Serum IgE 30-700 IU/mL Positive skin prick testing	Decreased frequency of exacerbations Decreased frequency of hospitalizations Decreased corticosteroid use Improved quality of life
	Anti-IL-5 (mepolizumab)	>11 year old Severe asthma Eosinophilic phenotype	Decreased frequency of exacerbations Improved quality of life
	Anti-IL-5 (reslizumab)	>17 years old Severe asthma Eosinophilic phenotype	Decreased frequency of exacerbations Improved quality of life
Not-FDA approved			
	Anti-IL-13 (lebrikizumab)		Decreased frequency of exacerbations* Increased FEV1* *in the subset of patients with increased serum periostin levels
	IL-4R α (dupilumab)		Decreased frequency of exacerbations Decreased frequency of rescue inhaler use Increased FEV1 Increased quality of life
	IL-5R α (benralizumab)		Decreased frequency of exacerbations Increased FEV1 Increased quality of life
	Anti-TSLP		Attenuation of early and delayed asthmatic response

References

1. Rackemann FM. A clinical study of one hundred and fifty cases of bronchial asthma. Archives of Internal Medicine. 1918; 22: 517-552.
2. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. New England Journal of Medicine. 1989; 320: 271-277.
3. Wenzel SE. Eosinophils in asthma-closing the loop or opening the door?. New England Journal of Medicine. 2009; 360: 1026-1028.
4. Haldar P, Pavord ID. Noneosinophilic asthma: a distinct clinical and pathologic phenotype. Journal of Allergy and Clinical Immunology. 2007; 119: 1043-1052.
5. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. The Lancet. 1999; 353: 2213-2214.
6. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, et al. Cluster analysis and clinical asthma phenotypes. American journal of respiratory and critical care medicine. 2008; 178: 218-224.
7. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. American journal of respiratory and critical care medicine. 2010; 181: 315-323.
8. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. Journal of Allergy and Clinical Immunology. 2011; 127: 355-360.
9. Robinson DS, Hamid Q, Ying S, Tsicopoulos A, Barkans J, et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. New England Journal of Medicine. 1992; 326: 298-304.
10. Locksley RM. Asthma and allergic inflammation. Cell. 2010; 140: 777-783.
11. Stoller J. Murray & Nadel's text book of respiratory medicine. Annals of the American Thoracic Society. 2015; 12: 1257-1258.

12. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *The Lancet*. 2000; 356: 2144-2148.
13. Flood-Page P, Swenson C, Faierman I, Matthews J, Williams M, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *American journal of respiratory and critical care medicine*. 2007; 176: 1062-1071.
14. Corren J, Busse W, Meltzer EO, Mansfield L, Bensch G, et al. A randomized, controlled, phase 2 study of AMG 317, an IL-4R α antagonist, in patients with asthma. *American journal of respiratory and critical care medicine*. 2010; 181: 788-796.
15. National Asthma Education, Prevention Program (National Heart, Lung, & Blood Institute). Second Expert Panel on the Management of Asthma Expert panel report 2: guidelines for the diagnosis and management of asthma. DIANE Publishing. 1997.
16. Ong YE, Menzies-Gow A, Barkans J, Benyahia F, Ou TT, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *Journal of allergy and clinical immunology*. 2005; 116: 558-564.
17. Corren J, Wood RA, Patel D, Zhu J, Yegin A, et al. Effects of omalizumab on changes in pulmonary function induced by controlled cat room challenge. *Journal of Allergy and Clinical Immunology*. 2011; 127: 398-405.
18. Soler M, Matz J, Townley R, Buhl R, O'brien J, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *European Respiratory Journal*. 2001; 18: 254-261.
19. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005; 60: 309-316.
20. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Annals of internal medicine*. 2011; 154: 573-582.
21. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *American journal of respiratory and critical care medicine*. 2013; 187: 804-811.
22. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *The Cochrane Library*. 2014.
23. Tsabouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *The Journal of Allergy and Clinical Immunology: In Practice*. 2014; 2: 332-340.
24. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, et al. A phase II, randomized, double blind, parallel group, placebo controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *Journal of Allergy and Clinical Immunology*. 2011; 127: 1309-1310.
25. Iyengar SR, Hoyte EG, Loza A, Bonaccorso S, Chiang D, et al. Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *International archives of allergy and immunology*. 2013; 162: 89-93.
26. Busse W, Spector S, Rosén K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *Journal of Allergy and Clinical Immunology*. 2013; 132: 485-486.
27. Corren J, Lemanske Jr RF, Hanania NA, Korenblat PE, Parsey MV, et al. Lebrikizumab treatment in adults with asthma. *New England Journal of Medicine*. 2011; 365: 1088-1098.
28. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax, thoraxjnl-2014*. 2015.
29. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *New England Journal of Medicine*. 2013; 368: 2455-2466.
30. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *New England Journal of Medicine*. 2014; 371: 130-139.
31. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *The Lancet*. 2016; 387: 40-52.
32. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *New England Journal of Medicine*. 2009; 360: 973-984.
33. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *The Lancet*. 2012; 380: 651-659.
34. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *New England Journal of Medicine*. 2014; 371: 1189-1197.

35. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *American journal of respiratory and critical care medicine*. 2011; 184: 1125-1132.
36. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet Respiratory Medicine*. 2015; 3: 355-366.
37. Castro M, Wenzel S, Kolbeck R, Khatry D, Christine W, et al. Late-breaking abstract: A phase 2 study of benralizumab on exacerbations, lung function, and asthma control in adults with uncontrolled eosinophilic asthma. *European Respiratory Journal*. 2014; 44: 2909.
38. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *New England Journal of Medicine*. 2014; 370: 2102-2110.