



MOC-CME Review

New and emerging therapies for asthma



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At the conclusion of this activity, participants should be able to:

- Describe the biomarkers associated with type 2 or Th2 asthma
- Identify novel biologic agents for asthma and the molecules targeted by such agents and discuss the key outcomes of clinical trials with these agents

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Introduction

A 34-year-old woman with severe persistent asthma, atopic dermatitis, and allergic rhinitis presents for evaluation of asthma refractory to conventional therapy. The patient has a history of asthma commencing in early childhood, with progression to uncontrolled disease in the past 2 years. Allergen skin prick testing in childhood showed positive reactions to dust mites, cat and dog dander, and multiple pollens. Her principal triggers are inhaled allergens, especially animal dander, and irritants including tobacco smoke. Despite compliance with maximal dose inhaled corticosteroid and long-acting β -agonist, leukotriene receptor antagonist, nasal corticosteroid, and avoidance measures, she continues to experience nightly wheezing and chest tightness that requires daily β -agonist inhalations. Furthermore, in the past year she has been hospitalized twice for asthma exacerbations after viral infections and has received 5 courses of oral corticosteroids. Her Asthma Control Test score at initial consultation is 7.

Physical examination is notable for bilateral expiratory wheezes in the lower lung fields. Total IgE level is 650 IU/mL and previous allergen sensitivities are confirmed. Lung function testing shows a baseline forced expiratory volume in 1 second (FEV₁) of 50% of predicted by age, improving to 66% after bronchodilator administration (460-mL increase). Fraction of exhaled nitric oxide (FeNO) levels are 125 and her peripheral eosinophils are elevated at 1,350 cells/ μ L. In addition, the patient's inhaler technique is assessed and she demonstrates excellent technique with the controller and rescue devices.

Further questioning addresses any gaps in her asthma management. The patient has excellent medication compliance corroborated by her significant other, has installed dust mite covers, and denies first- or secondhand smoking or furry animal ownership or exposure. A recently performed pregnancy test showed negative results, and she denies a history of chronic sinus disease, including nasal polyposis, aspirin or nonsteroidal anti-inflammatory drug sensitivity, occupational exposures, or gastroesophageal reflux disease. There are no socioeconomic or psychological stressors identified as possible contributors to her uncontrolled asthma and no clinical evidence to support paradoxical vocal fold motion. Evaluations for eosinophilic granulomatosis with polyangiitis and allergic bronchopulmonary

aspergillosis are negative. What therapeutic strategies (present and future) can be used to optimize her severe uncontrolled asthma?

Background

Asthma afflicts more than 330 million people and aside from the significant morbidity for patients across many demographics, the financial burden of asthma is enormous. In the United States, asthma care was estimated to cost \$56 billion in 2007 and severe asthma has been associated with increased health care expenditures and usage.¹ An estimated 12% of patients with asthma in the Severe Asthma Research Program required intensive care unit management.² Despite implementation of the National Asthma Education and Prevention Program and Global Initiative for Asthma guidelines, 10% of asthma remains refractory to conventional therapy.

Advances in asthma phenotyping and “endotyping” based on molecular and cellular analyses of patient samples have greatly improved our understanding of asthma pathogenesis. Asthma has been conventionally considered a T-helper cell type 2 (T_H2)-mediated inflammatory disorder that is primarily treated with corticosteroids. However, despite the demonstrated efficacy of corticosteroids in most patients with asthma, there are subpopulations of patients in whom standard therapeutics fail. The use of cluster analyses such as those reported by the Severe Asthma Research Program and the incorporation of high-throughput genomics and proteomics have led to a paradigm shift in characterization of asthma subgroups that might differentially respond to novel therapies.^{2–5}

Asthma is increasingly recognized as a diverse spectrum of diseases with distinct clinical and molecular features encompassing putative disease endotypes. The role of clinical phenotypes and endotypes in driving asthma pathophysiology remains largely undefined, but the integration of clinical phenotypes with genomics and proteomics has the potential to revolutionize asthma care through personalized therapies.^{3–5} The development of biological therapeutics targeting specific molecular pathways is a result of improved understanding of the genetic and molecular mechanisms of asthma pathogenesis during the past few decades.³

“Type 2” or “T_H2” asthma is associated with elevations in the cytokines interleukin (IL)-4, IL-5, and IL-13 that promote airway

Table 1
Emerging therapies for severe asthma

Target	Therapy	Mechanism of action	FDA status for asthma
IgE	omalizumab	blocks IgE from binding to high-affinity IgE receptor	FDA approved in June 2003 for moderate to severe asthma
Smooth muscle	bronchial thermoplasty	thermal energy applied to smooth muscle in the airway walls	FDA approved in April 2010 for severe asthma
IL-4 and/or IL-13	dupilumab	blocks IL-4 and/or IL-13 from binding to IL-4R α	not FDA approved
	lebrikizumab	blocks IL-13	not FDA approved
IL-13	tralokinumab	blocks IL-13	not FDA approved
IL-5	mepolizumab	blocks IL-5	applied November 2014 to FDA
IL-5	reslizumab	blocks IL-5	not FDA approved
IL-5R	benralizumab	blocks IL-5 from binding to IL-5R α	not FDA approved
TSLP	AMG 157	blocks TSLP	not FDA approved
Muscarinic receptor	tiotropium	muscarinic receptor antagonist	not FDA approved
IL-1R	anakinra	blocks IL-1 from binding to the IL-1 receptor	not FDA approved

Abbreviations: FDA, Food and Drug Administration; IL, interleukin; TSLP, thymic stromal lymphopoietin.

inflammation, including tissue eosinophilia and remodeling in murine and human asthma studies.^{3,6} Recent work aimed at improved phenotyping of asthma has led to the identification of type 2 biomarkers, including the IL-13–regulated protein periostin, sputum or blood eosinophilia, and FeNO. All these biomarkers show promise toward directing treatment with specific immunomodulators.^{4,7} Unfortunately, none of these proposed asthma biomarkers have the same utility as the diabetes mellitus biomarker hemoglobin A1c. Within the type 2 asthma group, there appears to be heterogeneity, including patients with late-onset eosinophilic disease that responds to anti-IL-5 therapy.⁴ Importantly, targeting at least 1 cytokine within a particular asthma endotype has the potential to improve clinical outcomes in patients with refractory disease. Current and emerging therapies for severe asthma are presented in [Table 1](#) and are briefly reviewed below.

Treatments Approved by the Food and Drug Administration

Omalizumab is a recombinant humanized anti-IgE monoclonal IgG antibody that binds to the Fc portion of IgE, resulting in downregulation of the high-affinity IgE receptor FcεR1 on mast cells and basophils.⁸ Currently, omalizumab is the only biologic approved by the Food and Drug Administration (FDA) for severe asthma. Early studies of omalizumab treatment in adults with severe asthma, atopy, and an IgE level of 30 to 700 IU/mL found a significant decrease in asthma exacerbations compared with placebo.⁹ A more recent report showed that the presence of high levels of type 2 biomarkers (periostin, eosinophilia, and FeNO) correlated with a substantial decrease in the exacerbation rate after omalizumab treatment.¹⁰

Bronchial thermoplasty is another FDA-approved treatment modality for severe asthma and uses thermal technology to decrease airway smooth muscle mass. The randomized, double-blinded Asthma Intervention Research 2 (AIR2) trial demonstrated marked decreases in emergency department visits, severe exacerbations, and lost time at work or school in patients with severe asthma undergoing bronchial thermoplasty compared with a sham procedure at trial completion and at the end of 5 years of follow-up.¹¹

Future Biological Therapies Targeting Molecular Pathways

Targeting IL-4 and IL-13

Interleukin-4 and IL-13 have distinct and overlapping roles in asthma pathophysiology. Both cytokines signal through the type 2 IL-4 receptor (IL-4Rα and IL-13Rα1 heterodimer) and are regulated by the master T_H2 transcription factor GATA3. IL-4 induces IgE class switching of B cells and is critical for T_H2 cell differentiation, whereas IL-13 promotes cellular influx, airway hyperresponsiveness, and remodeling features.^{3,5,6}

Given the myriad of roles of IL-4 in T_H2-mediated asthma, initial efforts focused on targeting IL-4. However, early studies with anti-IL-4 treatment failed to demonstrate clinical efficacy, possibly owing to redundancy with IL-13 and lack of subject phenotyping.³ Thus, a strategy to block both IL-4 and IL-13 signaling in patients with elevated biomarkers of type 2 inflammation was pursued.^{3,12} The humanized monoclonal antibody dupilumab binds to the IL-4Rα chain (shared receptor subunit for IL-4 and IL-13) and was evaluated in a prospective study of patients with moderate to severe asthma and a type 2 high phenotype (sputum $\geq 3\%$ or blood eosinophilia of 300 cells/ μ L). By trial end, the treatment group exhibited significant decreases in asthma exacerbations and improvements in other clinical outcomes, including quality of life and lung function (but not blood eosinophilia), highlighting the importance of targeting a specific asthma endotype with selective therapy.¹²

Further studies with anti-IL-13 treatment also showcased the impact of molecular phenotypes on treatment success. A double-blinded placebo-controlled trial of 219 adults with uncontrolled asthma investigated the efficacy of lebrikizumab in all subjects and in the type 2 high subgroup defined by elevated serum periostin levels.¹³ Although the total cohort demonstrated improved FEV₁ in subjects receiving lebrikizumab compared with placebo, there were no differences in other measured clinical outcomes. However, patients with high serum periostin levels before treatment had more significant improvements in FEV₁ and asthma exacerbations compared with placebo.

Targeting IL-5 and IL-5R

Interleukin-5 is a pro-eosinophilic type 2 cytokine that binds to the IL-5Rα expressed on eosinophils and basophils and promotes eosinophil recruitment, survival, and activation. Unfortunately, early studies evaluating the humanized anti-IL-5 monoclonal antibody mepolizumab in subjects with mild-intermittent to moderate-persistent asthma without additional phenotyping also lacked favorable clinical outcomes despite reduced eosinophil counts.³ The lack of early success of anti-IL-5 treatment might have been due to the enrollment of heterogeneous asthmatic populations and subsequent investigations were able to demonstrate the efficacy of anti-IL-5 treatment in patients with increased eosinophils. In patients with asthma and elevated blood eosinophil levels and marginal asthma control despite treatment with high-dose inhaled or oral glucocorticoids, asthma exacerbations were decreased in those receiving mepolizumab compared with placebo. The treatment group also had improved FEV₁, quality of life, and Asthma Control Questionnaire scores.¹⁴ Reslizumab is another humanized anti-IL-5 monoclonal antibody in phase 3 trials that has demonstrated significant decreases in asthma exacerbations in patients with inadequately controlled asthma and elevated blood eosinophil levels.¹⁵ Benralizumab, a humanized monoclonal antibody that targets IL-5Rα, has been shown in a phase 2b dose-ranging trial to decrease asthma exacerbations in severe eosinophilic asthma compared with placebo at higher doses.¹⁶ Importantly, 1 dose of benralizumab decreased asthma exacerbations in patients with severe asthma presenting to the emergency department by 49% and hospitalizations associated with these exacerbations by 60% compared with placebo in a 12-week period.¹⁷ In summary, targeting patients with high eosinophil levels appears to hold the most promise for the anti-IL-5 and IL-5R treatment strategy.

Targeting GATA3

A very recent proof-of-concept trial evaluated the GATA3-specific DNA enzyme SB010 on early- and late-phase allergen challenge responses in patients with mild allergic asthma.¹⁸ SB010 cleaves GATA3 mRNA transcripts that in turn decrease the downstream induction of GATA3-regulated genes, including IL-4, IL-5, and IL-13. The study showed that early- and late-phase responses were attenuated by 11% and 34%, respectively, after 28 days of inhaled SB010. Whether this strategy will have efficacy in severe asthma is currently unknown.

Targeting Thymic Stromal Lymphopoietin

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that induces activation of innate and adaptive type 2 responses and is elevated in human asthmatic airways.³ A recent double-blinded placebo-controlled study investigated the effect of AMG 157, a fully human anti-TSLP monoclonal antibody, on early and late asthmatic responses after allergen challenge.¹⁹ The treatment group showed a decrease in early- and late-phase FEV₁ as well as decreased blood and sputum eosinophil counts and FeNO.¹⁹

Although this study was a small proof-of-concept trial, targeting cytokines upstream of several effector cells in type 2 immunity could hold promise as a future therapeutic strategy.

Muscarinic Receptor Antagonism

The long-acting muscarinic receptor antagonist tiotropium is not currently approved by the FDA for asthma, although recent clinical data are promising. A systematic review of tiotropium showed a decrease in exacerbations and lung function improvements in patients with severe asthma not optimally controlled on inhaled corticosteroid or long-acting β -agonist.²⁰

Non- T_H2 Biologics

Patients with type 2 low asthma do not have unifying biomarkers but typically have later-onset disease associated with neutrophilia, smoking, obesity, and infection.³ Unfortunately, recent strategies to target neutrophilic asthma have not yielded the same success as the novel therapies for T_H2 high asthma.

The tumor necrosis factor- α (TNF- α) receptor inhibitor etanercept demonstrated some improvement in airway hyper-responsiveness, lung function, and symptoms in a small number of patients with severe corticosteroid-dependent asthma.³ The monoclonal antibody to TNF- α , infliximab, decreased asthma exacerbations in patients with moderate asthma but a subsequent double-blinded placebo-controlled study using another humanized antibody to TNF- α , golimumab, did not demonstrate any improvement in FEV₁ or decrease in asthma exacerbations. Importantly, an increase in systemic infections and malignancies led to early termination of the trial.³

Neutrophilic asthma has been linked to higher inhaled corticosteroid use and lower FEV₁. CXC receptor 2 is the receptor for IL-8 that mediates neutrophil migration to sites of inflammation. A CXC receptor 2 antagonist was developed to target neutrophilic asthma, but human studies did not demonstrate clinical benefit.³ More recently, anakinra, an IL-1 receptor antagonist, was shown to decrease airway neutrophilia in a proof-of-concept study of healthy subjects challenged with inhaled lipopolysaccharide and might be a future therapeutic strategy in those with neutrophilic asthma.²¹ Brodalumab is an anti-IL-17 receptor antibody targeting the T-helper cell type 17 pathway that has roles in host defense and tissue neutrophilia.³ Unfortunately, brodalumab treatment in patients with severe asthma did not show an improvement in clinical benefit compared with placebo even when multiple-subset analysis was performed with respect to Asthma Control Questionnaire score, FEV₁, and symptoms.³

Conclusion

In the patient presented, medication adherence and correct device technique were confirmed and allergen avoidance strategies were implemented. Moreover, comorbidities were ruled out that are known to negatively affect asthma. Available add-on therapeutic options were discussed, and while waiting for omalizumab approval, a trial with inhaled tiotropium was started. Depending on the patient's response, bronchial thermoplasty could be pursued in the future. For similar patients, several biologics hold promise for the future treatment of asthma and are undergoing FDA evaluation. There are currently many unknowns in the use of biologics

targeting IL-4, IL-5, and IL-13 in "real-life" asthma care. Knowledge gaps include lack of information about optimal treatment durations, optimal dosing, prototypical phenotyping, isolation of phenotype-specific biomarkers, and identification of specific parameters that determine long-term outcomes. Clearly, the development of novel and reliable biomarkers to guide future treatment is prudent. Although the long-term safety and efficacy of novel therapies need to be assessed, there is reason to be optimistic that improved personalized treatment for patients with refractory asthma will be available in the future.

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