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New and Emerging Therapies for Asthma

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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 last two years. Allergen skin prick testing in childhood was positive to dust mites, cat and dog dander, as well as multiple pollens. Her principle triggers are inhaled allergens, especially animal dander, as well as irritants including tobacco smoke. Despite compliance with maximal dose inhaled corticosteroid/long acting beta agonist (ICS/LABA), leukotriene receptor antagonist, nasal corticosteroid and avoidance measures, she continues to experience nightly wheezing and chest tightness that requires daily beta-agonist inhalations. Furthermore, in the last year she has been hospitalized twice for asthma exacerbations following viral infections and has received five courses of oral corticosteroids. Her Asthma Control Test (ACT) score at initial consultation is 7.

Physical exam 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 reveals a baseline FEV_1 of 50% of predicted by age, improving to 66% post-bronchodilator administration (460cc increase). Fraction of exhaled nitric oxide levels (FeNO) is 125 and her peripheral eosinophils are elevated at 1350 cells per microliter. Additionally, the patient's inhaler technique is assessed and she demonstrates excellent technique with both 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 second-hand smoking or furry animal ownership or exposure. A recently

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performed pregnancy test is negative, and she denies a history chronic sinus disease including nasal polyposis, aspirin/NSAID sensitivity, occupational exposures or gastroesophogeal 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 (EGPA) and Allergic Bronchopulmonary Aspergillosis (ABPA) are negative. What therapeutic strategies (present and future) can be utilized to optimize her severe uncontrolled asthma?

Body

Asthma afflicts over 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 dollars in 2007 and severe asthma has been associated with increased healthcare expenditures and utilization.[1] An estimated 12% of asthmatics in the Severe Asthma Research Program (SARP) required intensive care unit management.[2] Despite implementation of the National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) guidelines, 10% of asthma remains refractory to conventional therapy.

Advances in asthma phenotyping, as well as “endotyping” based on molecular and cellular analysis of patient samples, has greatly improved our understanding of asthma pathogenesis. Asthma has been conventionally considered a T_H2-mediated inflammatory disorder that is primarily treated with corticosteroids. However, despite the demonstrated efficacy of corticosteroids in the majority of asthmatics, there are subpopulations of patients in whom standard therapeutics fail. The utilization of cluster analyses such as those reported by SARP, as well as the incorporation of high-throughput genomics and proteomics, has led to a paradigm shift in characterization of asthma subgroups that may differentially respond to novel therapies.[2,3,4,5]

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.[3,4,5] The development of biological therapeutics targeting specific molecular pathways is a result of improved understanding of the genetic and molecular mechanisms of asthma pathogenesis over the past few decades.[3]

The “type-2 or T_H2” asthma is associated with elevations in cytokines IL-4, IL-5 and IL-13, that promote airway inflammation including tissue eosinophilia as well as remodeling in both murine and human asthma studies.[3,6] Recent work aimed at improved phenotyping of asthma has lead to identification of type-2 biomarkers including the IL-13-regulated protein periostin, sputum or blood eosinophilia, and FeNO. All of these biomarkers show promise towards directing treatment with specific immuno-modulators.[4,7] Unfortunately, none of these proposed asthma biomarkers has 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 respond to anti-IL-5 therapy.[4] Importantly, targeting one or more cytokines 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 outlined in Table 1 and are briefly reviewed below.

FDA-approved treatments

Omalizumab is a recombinant humanized anti-IgE monoclonal IgG antibody that binds to the Fc portion of IgE resulting in down regulation of the high-affinity IgE receptor FcεR1 on mast cells and basophils.[8] Currently, omalizumab is the only FDA-approved biologic for severe asthma. Early studies of omalizumab treatment in adults with severe asthma, atopy, and an IgE level between 30 to 700 IU/mL, demonstrated a significant reduction in asthma exacerbations compared to placebo.[9] A more recent report showed that the presence of high levels of type 2 biomarkers (periostin, eosinophilia, and FENO) was 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 utilizes thermal technology to reduce airway smooth muscle mass. The randomized double-blind Asthma Intervention Research 2 (AIR2) trial demonstrated marked reductions in emergency department visits, severe exacerbations and lost time at work or school in severe asthmatics undergoing bronchial thermoplasty compared to sham procedure at trial completion and also at the end of 5 years of follow-up.[11]

Future Biological Therapies Targeting Molecular Pathways

Targeting IL-4 and IL-13

IL-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 due to IL-4/IL-13 redundancy 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-4R α chain (shared receptor subunit for IL-4 and IL-13) and was evaluated in a prospective study of moderate to severe asthmatics with a type 2-high phenotype (sputum or blood eosinophilia >= 3% or 300 cells/uL, respectively). Importantly, the treatment group exhibited significant reductions in asthma exacerbations, as well as 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-blind placebo controlled trial of 219

uncontrolled adult asthmatics investigated the efficacy of lebrikizumab in all subjects as well as in the type 2-high subgroup defined by elevated serum periostin levels.[13] Although the total cohort demonstrated improved FEV_1 in subjects receiving lebrikizumab compared to placebo, there were no differences in other measured clinical outcomes. However, patients that possessed high serum periostin levels pretreatment had more significant improvements in FEV_1 as well as asthma exacerbations compared with placebo.

Targeting IL-5/IL-5R

IL-5 is a pro-eosinophilic type 2 cytokine that binds to the IL-5 receptor α 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 non-phenotyped mild intermittent and moderate persistent asthma subjects also lacked favorable clinical outcomes despite reduced eosinophil counts.[3] The lack of early success of anti-IL-5 treatment may have been due to the enrollment of heterogeneous populations of asthmatics and subsequent investigations were able to demonstrate the efficacy of anti-IL-5 treatment in patients with increased eosinophils. In asthmatics with elevated blood eosinophil levels and marginal asthma control despite treatment with high-dose inhaled or oral glucocorticoids, asthma exacerbations were reduced in those receiving mepolizumab compared with placebo. The treatment group also had improved FEV_1, quality of life, and ACQ scores.[14] Reslizumab is another humanized anti IL-5 monoclonal antibody in Phase 3 trials that has demonstrated significant reductions in asthma exacerbations in patients with inadequately controlled asthma and elevated blood eosinophil levels.[15] Benralizumab, a humanized monoclonal antibody that targets IL-5 receptor α, has been shown in a phase 2b dose-ranging trial to decrease asthma exacerbations in severe eosinophilic asthma compared to placebo at higher doses.[16] Importantly, one dose of benralizumab has been shown to reduce asthma exacerbations in severe asthmatics presenting to the ED by 49% and hospitalizations associated with these exacerbations by 60% compared to placebo in a 12 week follow-up period.[17] In summary, targeting eosinophil-high patients appears to hold the most promise for the anti-IL-5/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 mild allergic asthmatics.[18] SB010 cleaves GATA3 mRNA transcripts that in turn reduces 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 TSLP

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that induces activation of innate and adaptive type 2 responses in human asthmatic airways that have been shown to have higher levels of TSLP compared to healthy controls.[3] A recent double-blind 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 groups showed a decrease in early and late phase FEV1 reduction as well as blood and sputum eosinophil counts and FENO.[19] Though this study was a small proof of concept trial, targeting cytokines upstream of several effector cells in type 2 immunity may hold promise as a future therapeutic strategy.

Muscarinic receptor antagonism

The long-acting muscarinic receptor antagonist tiotropium is not currently FDA approved for asthma, although recent clinical data is promising. A systematic review of tiotropium revealed a reduction in exacerbations as well as lung function improvements in severe asthmatics not optimally controlled on ICS/LABA.[20]

Non-T_H2 biologics

Type 2-low asthmatics 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 TNF-α receptor inhibitor etanercept demonstrated some improvement in AHR, lung function and symptoms in a small number of severe corticosteroid dependent asthmatics.[3] The monoclonal antibody to TNF-α, infliximab, reduced asthma exacerbations in moderate asthmatics but a subsequent double blind placebo controlled study using another humanized antibody to TNF-α, golimumab, did not demonstrate any improvement in FEV_1 or reduction 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 ICS use and lower FEV_1. CXCR2 is the receptor for IL-8 that mediates neutrophil migration to sites of inflammation. A CXCR2 receptor 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 LPS, and may be a future therapeutic strategy in those with neutrophilic asthma.[21] Lastly, brodalumab is an anti-IL-17 receptor antibody targeting the T_H17 pathway that has roles in host defense and tissue neutrophilia.[3] Unfortunately, brodalumab treatment in severe asthmatics did not show an improvement in clinical benefit compared to placebo even when multiple subset analysis was performed with respect to ACQ 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 impact asthma. Further, available add-on therapeutic options were discussed. 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 utilization 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. Though the long-term safety and efficacy of novel therapies need to be assessed, there is reason to be optimistic that improved personalized treatment for refractory asthmatics will be available in the future.

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Abbreviations

ICS	Inhaled corticosteroid
LABA	Long-acting beta agonist
ACT	Asthma control test
FEV_1	Forced expiratory volume in 1 second
FENO	Fraction of exhaled nitric oxide
SARP	Severe Asthma Research Program
NAEPP	National Asthma Education and Prevention Program
GINA	Global Initiative for Asthma
T_H2	Type 2 helper T cell
T_H17	Type 17 helper T cell
FDA	Federal Drug and Food Administration
ACQ	Asthma control questionnaire
TSLP	Thymic stromal lymphopoietin
TNF-α	Tumor necrosis factor α
IL	Interleukin

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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/IL-13	Dupilumab	Blocks IL-4 and/or IL-13 from binding to IL-4Rα	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-5Rα	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