Supplement

New and Anticipated Therapies for Severe Asthma

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Learning objectives:

1. To recognize that asthma remains uncontrolled in a significant number of patients, due to uncertainty about the definition of control and severity, and multiple barriers to effective follow-up.

2. To utilize current evidence-based practice guidelines and strategies to improve asthma control in patients with severe asthma.

3. To integrate novel and emerging drugs into recommended and properly applied management strategies for asthma control in patients with severe asthma.

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Asthma is frequently undertreated, resulting in a relatively high prevalence of patients with uncontrolled disease, characterized by the presence of symptoms and risk of adverse outcomes. Patients with uncontrolled asthma have a higher risk of morbidity and mortality, underscoring the importance of identifying uncontrolled disease and modifying management plans to improve control. Several assessment tools exist to evaluate control with various cutoff points and measures, but these tools do not reliably correlate with physiological measures and should be considered a supplement to physiological tests. When attempting to improve control in patients, nonpharmacological interventions should always be attempted before changing or adding pharmacotherapies. Among patients with severe, uncontrolled asthma, individualized treatment based on asthma phenotype and eosinophil presence should be considered. The efficacy of the anti-IgE antibody omalizumab has been well established for patients with allergic asthma, and novel biologic agents targeting IL-5, IL-13, IL-4, and other allergic pathways have been investigated for patients with allergic or eosinophilic asthma. Fevipiprant (a CRT_H2 [chemokine receptor homologous molecule expressed on Th2 cells] antagonist) and imatinib (a tyrosine kinase inhibition) are examples of nonbiologic therapies that may be useful for

Abbreviations used
DDP-4- dipeptidyl peptidase 4
FENO- fraction of exhaled nitric oxide
GINA- Global Initiative for Asthma
ICS- inhaled corticosteroid
LABA- long-acting beta$_2$ agonist
SABA- short-acting beta$_2$ agonist
TSLP- thymic stromal lymphoprotein

patients with severe, uncontrolled asthma. Incorporation of new and emerging treatment into therapeutic strategies for patients with severe asthma may improve outcomes for this patient population. **(J Allergy Clin Immunol Pract 2017;5:S15-S24)**

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Asthma is a chronic respiratory disease characterized by inflammation and narrowing of the airways that leads to breathlessness and wheezing. According to the World Health Organization, asthma is one of the most common noncommunicable diseases worldwide, affecting approximately 235 million people. The Global Asthma Network, however, estimated in 2014 that the number of people affected by asthma worldwide may be as high as 334 million.[1] Asthma is also responsible for approximately 250,000 premature deaths each year, caused by various factors, most of which are preventable.[2]

Since 1995, the Global Initiative for Asthma (GINA) has published comprehensive reports intended to facilitate and guide treatment of this heterogeneous disorder. The GINA reports influence national and international clinical practice guidelines and have evolved in terms of recommendations and approaches to asthma treatment based on new information and research. Over the last 2 decades, our understanding of asthma has improved substantially. Consequently, the field has seen great advances in terms of medications as well as the genetic, environmental, and psychosocial factors that contribute to asthma and its control. In 2006, the GINA report was revised to emphasize the importance of asthma control, representing a major shift in asthma classification that distinguished asthma control from severity.[3] Although this was an important shift in thinking, only recently has the heterogeneity of asthma been well appreciated, and new medications and treatment paradigms have led to the possibility of individualized therapy in some patients with severe or uncontrolled asthma. This research led to the most recent large-scale revision of the GINA report in 2015, which provides practical clinical guidance toward asthma control worldwide.[4] Since then, GINA has released yearly updates to its asthma documents based on recent data.

Although asthma may be a highly treatable disorder with various resources and therapies available to physicians and most patients, many patients still suffer from ongoing symptoms and exacerbations, indicating suboptimal asthma control. In that regard, recent multinational surveys indicate that between 38% and 54% of patients with asthma have uncontrolled asthma.[5-8] In large part, the low rate of asthma control may be due to factors that are modifiable by nonpharmacological means—treatment adherence, inhaler technique, and allergen exposure.[9-11] For many patients with uncontrolled asthma, however, stepped up pharmacological interventions or new approaches may be in order.

Novel and emerging asthma treatments have recently become available for patients who have more severe disease and need more intense therapy. In some cases, even after providing treatment that would appear to be optimal, some patients continue to present with uncontrolled symptoms and exacerbations. When this occurs, patients are considered to have severe asthma. Patients in whom asthma remains uncontrolled may be at high risk for death.[12] Fortunately, several of the new and emerging asthma treatments, many of which are biologic agents, have shown efficacy in patients in this subgroup.

Large administrative databases and data analyses allow identification of patients with severe, persistent asthma, making targeted treatment interventions feasible. Identification of high blood eosinophil count frequently correlates with future risk of exacerbations and excessive short-acting beta$_2$ agonist (SABA) use.[13-15] Early identification of patients with high blood eosinophil counts and/or uncontrolled asthma may lead to substantial cost savings as well as a reduction in health care utilization.[16,17] Administrative data gleaned through information pharmacy technology can also allow clinicians to monitor factors related to asthma control in real time, allowing clinicians to flag patients with excessive asthma medication use and consequent persistent asthma symptoms.[18] If used properly, administrative databases may improve the overall state of asthma control monitoring, allowing clinicians to identify patients who might be at risk for future exacerbations.

Guidance for the effective use of new therapies in patients with severe, uncontrolled asthma is, however, limited. The 2017 GINA guidelines do not comprehensively describe the incorporation of biologics into treatment regimens, and direct comparisons between these agents are not available. In addition, the European Respiratory Society/American Thoracic Society clinical practice guidelines have not been updated since 2014.

The goal of this review was to highlight the importance of identifying patients who suffer from uncontrolled asthma, review possible nonpharmacological interventions, and discuss currently available approaches for treating patients with severe asthma.

UNCONTROLLED, SEVERE ASTHMA: UNDERRECOGNIZED AND UNDERTREATED

The degree of control is an important consideration when assessing a patient with asthma. As defined by GINA, asthma control consists of 2 separate domains, symptoms (impairments) and future risks, including exacerbations and adverse outcomes. Assessment of symptom control includes a consideration of the presence of daytime asthma symptoms, use of reliever medications (use more than twice per week is suboptimal), nighttime waking due to asthma, and activity limitation due to asthma. Risk factors for future exacerbations include the presence of uncontrolled symptoms, unavoidable environmental exposures, severe disease, and comorbidities such as nasal polyps and sinusitis.[19]

Because of the substantial impact of asthma exacerbations and continual symptoms on patients' lives, patients with uncontrolled asthma experience considerable morbidity. Uncontrolled asthma contributes to impaired work productivity and higher rates of absenteeism from both school and work.[20,21]

TABLE I. Characteristics of various asthma control assessment tools

						Parameters				
Tool	Age (y)	Recall window (wk)	No. of items	Scoring	Minimally important clinical difference	Symptom frequency (wheezing, shortness of breath)	Night waking	Rescue inhaler use	Activity limitations/ daily functioning	Other
ACT[26]	>12	<4	5	Sum of 5 answers: 5 (poor control) to 25 (complete control) Uncontrolled: ≤19 Very poorly controlled: ≤15	3	1-5	1-5	1-5	1-5	Self-perception of control (1-5)
ACQ-7[27]	>6	<1	7, including FEV_1	Mean of 7 answers: 0 (totally controlled) to 6 (severely uncontrolled) Controlled: Usually <1.0 Uncontrolled: Usually ≥1.5	0.5	0-6	0-6	0-6	0-6	FEV_1 predicted
GINA Symptom Control Tool	≥6	<4	4	Sum of 4 answers: 0 (well-controlled) to 4 (uncontrolled) Controlled: 0 Partly controlled: ≥1 Uncontrolled: ≥3	Not established	Yes (1) or No (0)	Yes (1) or No (0)	Yes (1) or No (0)	Yes (1) or No (0)	NA
ATAQ	≥18	<4	4	Sum of 4 answers: 0 (no control problems) to 4 (asthma control problems) Uncontrolled: ≥1 Very poorly controlled: ≥3	Not established	NA	Yes (1) or No (0)	0-11 puffs (0) or >12 puffs (1)	Yes (1) or No (0)	Self-perception of control (Yes [0] or No [1])

ACQ-7, Asthma Control Questionnaire 7; *ACT*, Asthma Control Test; *ATAQ*, Asthma Therapy Assessment Questionnaire; *NA*, not available/applicable.

TABLE II. Stepwise asthma treatment recommendations according to GINA report

Treatment types	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller choice	None	Low-dose ICS	Low-dose ICS, LABA	Medium- or high-dose ICS, LABA	Medium- or high-dose ICS, LABA plus add-on therapy
Other controller options	Consider low-dose ICS	LTRAs, low-dose theophylline	Medium- or high-dose ICS, add-on LTRA, add-on theophylline	Add-on tiotropium, add-on LTRA, add-on theophylline	Add-on tiotropium, add-on low-dose oral corticosteroids, or biologics
Reliever	As-needed SABA	As-needed SABA	As-needed SABA, low-dose ICS/formoterol	As-needed SABA, low-dose ICS/formoterol	As-needed SABA, low-dose ICS/formoterol

LTRA, Leukotriene receptor antagonist.

Furthermore, uncontrolled asthma correlates with both reduced mental and physical health-related quality-of-life scores.[20,21] At the systems level, patients with uncontrolled asthma have significantly higher resource use due to hospitalizations, medication costs, and indirect costs (eg, work absenteeism or disability).[22] In The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, the natural history of uncontrolled asthma was characterized. Patients with difficult-to-treat asthma had high health care utilization and a considerable asthma burden despite extensive use of reliever medications.[23]

Identification of uncontrolled asthma is an essential first step to ensure better outcomes for patients. With proper therapeutic regimens, asthma treatment is more likely to be effective in the vast majority of patients, and patients with well-controlled asthma do not have significantly different health-related quality-of-life scores compared with patients without asthma.[24]

Assessment of control

Asthma control should be assessed at each patient visit. Factors that reflect asthma control include daytime and nocturnal symptoms, need for rescue medication, results of pulmonary function tests, and exacerbations, and as such, are all important components in this assessment. Several validated tools are available to aid in assessing the impairment dimension of asthma control. These tools include the GINA Symptom Control Tool, the Asthma Control Test, the Asthma Therapy Assessment Questionnaire, the 30-Second Asthma Test, and the Asthma Control Questionnaire 7.

Most of these assessments are numerical tools that rank asthma control on a scale, which contains different cutoff points to evaluate levels of symptom control. Numerical tools are useful because they allow clinicians to monitor patients' progress over time. When selecting a tool to assess asthma control, clinicians should consider the validity, reliability, accuracy, and responsiveness of the test as well as practical matters (eg, time to administer and ease of administration).[25] The characteristics of the various assessment tools, as they have been established, are described in Table I.

Although the asthma assessment tools broadly correlate with each other, several differences have been noted in the literature. In a prospective study, the GINA tool, the Asthma Control Questionnaire, the Asthma Control Test, and the Asthma Therapy Assessment Questionnaire were compared in terms of the classification of patients. The tests were only moderately in agreement, indicating an inability to use them interchangeably.[28]

The Asthma Control Questionnaire 7 is the only asthma assessment tool that considers physiologic parameters even though lung function is an essential component of the GINA criteria for controlled asthma. Furthermore, when compared with results of physiologic measures of lung function and inflammatory markers (eg, FEV_1 and sputum eosinophils, respectively), asthma control assessments have discordant results, highlighting the different dimensions assessed by symptom control tools and lung function tests.[29] To appropriately assess lung function, spirometry, including FEV_1/forced vital capacity ratio and FEV_1% predicted, should be measured at the time of diagnosis, 3 to 6 months after treatment initiation, and, at a minimum, every 1 to 2 years thereafter. In patients with high future risk, lung function should be measured more frequently.

To assess asthma control in accordance with GINA guidelines, clinicians should also consider the future risk for poor asthma outcomes. Most asthma instruments do not accurately consider future risk of asthma exacerbations, loss of lung function over time, and long-term medical side effects.

Causes of uncontrolled and severe asthma

The high prevalence of uncontrolled asthma can occur through various causes, many of which are modifiable through nonpharmacologic means. Incorrect inhaler technique is frequently cited as a cause of uncontrolled asthma and should always be evaluated before modifying treatment regimens. Estimations of device use errors vary greatly between studies, but approximately 50% to 100% of patients incorrectly use their devices, and between 14% and 92% of patients make critical errors.[30] Risk factors for incorrect inhaler use include older age, lower levels of education, and a lack of instruction on inhaler technique by health care providers.[31] Guidelines recommend that all patients receive instructions on device use by a prescriber or educator, and technique should be evaluated at follow-up appointments or when a lack of control is observed. Adherence should also be assessed at this time, to ensure that patients are using their medications at the correct intervals and doses.

Comorbidities such as smoking and obesity are also associated with a lack of asthma control.[32] Despite the known detrimental effects of smoking on asthma outcomes, the prevalence of smoking among people with asthma is comparable with that in the general population, at 19% to 25%.[33] Health care providers

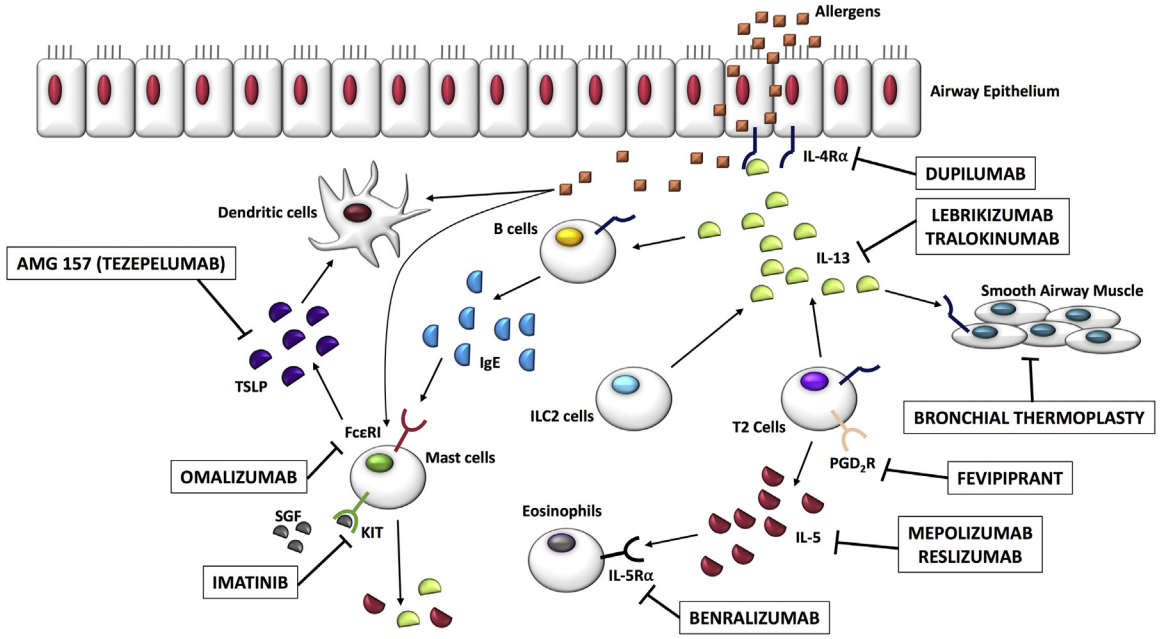

FIGURE 1. Mechanisms of action of new and emerging treatments for severe asthma. Therapeutic targets for selected biologics and other novel treatments for patients with severe, uncontrolled asthma. Adapted with permission from Fajt and Wenzel.[49] *FcεRI*, High-affinity IgE receptor; *ILC2*, innate lymphoid type 2; *PGD_2R*, prostaglandin D_2 receptor; *SCF*, stem cell factor.

TABLE III. Biologic agents with potential for treating patients with severe asthma

Target	Agent	Mechanism
IgE	Omalizumab*	Prevents IgE from binding to the high-affinity IgE receptor
IL-5	Mepolizumab*	Inhibits IL-5
IL-5	Reslizumab*	Inhibits IL-5
IL-5R	Benralizumab	Prevents IL-5 from binding to the IL-5 Ra receptor
IL-13	Lebrikizumab	Inhibits IL-13
IL-13	Tralokinumab	Inhibits IL-13
IL-4/IL-13	Dupilumab	Prevents IL-4 and IL-13 from binding to the IL-4 Ra receptor
TSLP	AMG 157, tezepelumab	Inhibits TSLP

*Approved for use in severe asthma by the Food and Drug Administration.

should encourage patients to quit smoking, regardless of patient "readiness," and provide quitting aids such as behavioral counseling, nicotine replacement therapy, or pharmacotherapy (ie, varenicline or bupropion).[33] Obesity in patients with asthma can lead to poor control and reduced quality of life. Fortunately, weight loss has been shown to improve asthma control and increase lung function, as have moderate amounts of exercise and healthy dieting, even without concomitant weight loss.[34-36] Other comorbidities associated with poor asthma control include anxiety, panic disorder, and depression.[37,38]

Multiple other nonmodifiable factors are associated with uncontrolled asthma. There is a well-documented relationship between aspirin sensitivity, nasal polyps, and severe asthma, believed to be caused by increased production of proinflammatory mediators upon aspirin, or related compound, ingestion.[39] In addition, uncontrolled asthma is associated with lower income and higher rates of unemployment.[40] Only 12.9% of adults with an annual income of more than $75,000 have uncontrolled asthma, compared with 41.6% of people who make less than $15,000 annually. Furthermore, adults who are white had a significantly lower proportion of very poorly controlled asthma compared with those of other race (22.7% vs 31.4%).[7] Education level, pollution, and reporting cost as barriers are also associated with uncontrolled asthma.[22,23,41]

APPROACHES TO SEVERE ASTHMA

Asthma management is responsive to changes in the patient's symptoms and lung function, using pharmacological and nonpharmacological adjustments in a continuous cycle of assessment, adjustment, and then reviewing the response. Initial assessment begins at the time of diagnosis but should continue after treatment has begun. Furthermore, when patients present with uncontrolled or partially controlled asthma, assessment of inhaler technique and adherence should be determined. If necessary, treatment should then be adjusted with new medications or nonpharmacological methods. Furthermore, any modifiable risk factors should be addressed during the treatment adjustment phase. After treatment regimens have been modified, the response should be reviewed to determine symptoms, exacerbations, side effects, patient satisfaction, and lung function.

Importantly, the current GINA guidelines and national associations are population-level recommendations. Every time that a treatment regimen is introduced or changed, several different medication options exist with varying safety and efficacy data. Although guidelines provide good options that work broadly in many different patients, clinicians should endeavor to make individualized medication decisions that consider patient- and disease-related factors.

Conventional therapeutic options

Asthma management uses a stepwise decision model (Table II). After initial treatment has been selected, clinicians and patients begin the cycle of assessment, adjustment, and review. Controller medication can be stepped up or down, depending on the response to the treatment, to find the minimum effective treatment level that controls symptoms and reduces future risk.

Once asthma has been diagnosed, almost all patients should be given SABAs, which are used as needed for acute relief of symptoms or in a preventive manner, primarily before exercise. If SABAs are only needed less than twice a week, asthma symptoms are considered controlled, and if patients have no risk factors for future exacerbations, then controller therapy with inhaled corticosteroids (ICSs) may not be needed or stepped down. However, research has shown that early initiation of daily controller therapy is ultimately beneficial, even in patients with mild asthma and apparently infrequent symptoms.[42-44] Because of this relationship to mild disease, low-dose ICSs should be at least considered for most patients. For those patients who need more intensive reliever medication (ie, step 3 in Table II), combination ICS/long-acting beta$_2$ agonist (LABA) can improve the control of asthma symptoms over low-dose ICS alone.

In patients with persistent symptoms despite low-dose ICS, other options that can be considered include leukotriene receptor antagonists, LABAs, antimuscarinics, and/or oral corticosteroids in severe cases. With each step up in therapy, the safety profile may become slightly more unfavorable, so the response should be evaluated after 2 to 3 months, and therapy should be adjusted, if possible.

Personalized therapeutic approaches

Conventional therapeutic options usually provide good asthma control in most patients with asthma, particularly those with mild disease. In patients who are uncontrolled with ICSs and other agents such as LABAs and/or tiotropium, the next step should be to establish whether asthma is eosinophilic or noneosinophilic. Typically, the presence of eosinophils indicates that T2 cells are responsible for the inflammation present. The critical cytokines involved in T_H2-type inflammation include IL-4, IL-5, and IL-13. Asthma has been categorized as T2-high or T2-low on the basis of blood eosinophil levels, but this assessment approach is limited in scope. Although expired nitric oxide, fraction of exhaled nitric oxide (FENO), correlates with eosinophilia, there are no currently recommended guidelines that make treatment decisions on the basis of FENO level alone.[45] Patients with blood eosinophilia values of greater than or equal to 150 cells/μL may be candidates for anti−eosinophil-directed therapy.

The T2-high phenotype may be more common in patients with severe asthma, but patients with T2-low phenotypes nonetheless are frequently also uncontrolled. In an analysis of patients with mild-to-moderate asthma, approximately half of all patients were persistently noneosinophilic.[46] Unfortunately, patients who have T2-low asthma are typically nonresponsive to controller therapy with ICSs and other anti-inflammatory drugs.[46,47] A stepwise increase in ICS dosing may be ineffective in this patient population and should be avoided because of the lack of clinical benefit and possible adverse effects. LABAs or antimuscarinics, which target bronchoconstriction through alternative pathways, are likely the preferred controller medications in this subgroup of patients, but few randomized controlled trials have evaluated therapies on the basis of an inflammation status. In a recent trial of tiotropium, however, lung function improved compared with placebo, regardless of allergic status (evaluated on the basis of clinician judgment, IgE, or blood eosinophilia).[48]

Patients with T2-high asthma have more options in terms of anti-inflammatory medications and biologics. If a patient with eosinophilic asthma is nonresponsive to ICSs, stepwise dose increases should be considered to help induce a response. T2-high asthma that remains uncontrolled with medium- or high-dose ICS in combination with long-acting bronchodilators can be treated with other anti-inflammatory therapies, including many of the newer biologic agents.

BIOLOGICS AND OTHER NOVEL AND EMERGING THERAPIES

A number of biologic targets appear to be important T2 inflammatory pathways (Figure 1). These include IgE, IL-5, IL-13, IL-4, and thymic stromal lymphoprotein (TSLP); mAbs have been created to block the activity of these cytokines (Table III).

Anti-IgE: Omalizumab

Omalizumab is an anti-IgE mAb approved for use in allergic asthma (Table III). By blocking free IgE, omalizumab disrupts the allergic signaling cascade by preventing interaction of IgE with immune cells essential to inflammation. Because omalizumab has been used for the longest period of time in asthma (approved in 2003), extensive clinical trial data and real-world data on the efficacy and safety of omalizumab have been compiled in various patient populations.

Multiple phase III studies have revealed that omalizumab significantly reduces the rate of asthma exacerbations, decreases ICS requirement, and improves lung function and quality of life compared with placebo or best standard care.[50-52] Furthermore, omalizumab has a good safety profile, with a comparable rate of adverse events compared with other treatments. Omalizumab has performed similarly well in observational real-world studies, reducing exacerbations and improving quality of life.[53,54]

Most research surrounding omalizumab focuses on patients with moderate-to-severe persistent asthma with an allergic phenotype, but proof-of-concept studies indicate that omalizumab may also have efficacy in patients with nonatopic asthma. In a randomized controlled study of patients with allergic and nonallergic asthma, omalizumab improved asthma symptoms and quality of life regardless of allergic status.[55] Similarly, in another study that specifically tested omalizumab in patients with severe uncontrolled nonatopic asthma, omalizumab significantly improved lung function compared with placebo but did not significantly decrease exacerbation rates.[56] Although the mechanisms of action of omalizumab in patients with nonatopic asthma are unclear, the high-affinity IgE receptor on basophils and dendritic cells can be downregulated in patients receiving omalizumab, a similar effect as has been seen in patients with allergic asthma. Overall, omalizumab is a good treatment solution for patients with severe allergic asthma and may be considered a safe and potentially efficacious treatment in patients with severe nonatopic asthma.

Anti−IL-5 therapies

Anti−IL-5 therapies target eosinophilic inflammation because IL-5 is critical for eosinophil maturation, activation, and survival. Both mepolizumab and reslizumab are anti−IL-5 mAbs

approved for use in severe asthma. Benralizumab is also an anti−IL-5 therapy but targets the IL-5 receptor.

Mepolizumab, which was studied in both intravenous and subcutaneous forms and ultimately approved as a subcutaneous therapy, reduces the frequency of asthma exacerbations, improves lung function, and increases control in patients with severe eosinophilic asthma.[57] Furthermore, mepolizumab was shown to reduce the need for oral corticosteroids without a loss of asthma control.[58]

Reslizumab, an intravenous anti−IL-5 therapy, has had efficacy in phase III clinical trials. In patients with severe eosinophilic asthma, primarily in settings with peripheral blood eosinophil levels of greater than or equal to 400 cells/μL, reslizumab reduced the frequency of asthma exacerbations. In another study, reslizumab improved lung function, increased asthma control, and also had a positive effect on quality of life.[59] Benralizumab, although not yet approved, also reduces asthma exacerbations and has a glucocorticoid-sparing effect in patients with elevated eosinophil levels. Benralizumab has the added benefit of inducing apoptosis in cells expressing the IL-5 receptor.[60,61] All the anti−IL-5 therapies have been shown to be well tolerated in patients with severe asthma.

Anti−IL-5 therapies are useful for patients with severe, uncontrolled asthma who are receiving medium-to-high doses of ICS and are T2-high. When reslizumab was evaluated in patients with low blood eosinophils, no clinically meaningful effects on lung function or symptom control were observed, indicating that reslizumab—and likely other anti−IL-5 therapies—should be limited to patients with eosinophilic asthma.[62] In a post hoc analysis, researchers established that mepolizumab had an effect regardless of prior omalizumab use, indicating that mepolizumab and other anti−IL-5 therapies may be useful for patients who continued to have exacerbations or declining lung function when receiving omalizumab.[63] These observations are still preliminary.

Anti−IL-13 and anti−IL-4 therapies

IL-13 is a critical component of eosinophil-mediated inflammation because it induces eosinophil recruitment to the lung tissues. Two anti−IL-13 therapies are currently under investigation for their utility in asthma: tralokinumab and lebrikizumab. Although phase II and III trials of tralokinumab and lebrikizumab have not consistently shown reductions in exacerbations, the drugs do improve lung function.[64,65] In the phase II trial of tralokinumab, patients were required to have only severe uncontrolled asthma, but a phase III trial will stratify patients by biomarker, using dipeptidyl peptidase 4 (DPP-4) and periostin as indicators of IL-13 activation. In the phase III trials of lebrikizumab, however, patients were stratified by serum periostin concentration, and no reduction in asthma exacerbation was observed in biomarker-high patients. Lebrikizumab did interfere with the IL-13 pathway, and clinically meaningful changes might have occurred. The future of anti−IL-13 therapies in asthma is currently under reevaluation. More clinical trials involving lebrikizumab in different asthma subgroups are ongoing.

Dupilumab is an mAb that targets the IL-4/IL-13 alpha subunit of their receptor and leads to inhibition of both IL-4 and IL-13 signaling. In a phase II trial, patients with uncontrolled asthma despite medium- to high-dose ICS had improved lung function and fewer severe exacerbations when receiving dupilumab. Furthermore, this effect was observed regardless of eosinophil count, indicating potential for use in noneosinophilic uncontrolled asthma.[66] Dupilumab was also well tolerated, with the most common adverse events including injection-site reactions and upper respiratory tract infections.

Anti-TSLP therapies

TSLP is an epithelial-derived cytokine that acts upstream to promote allergic inflammation.[67] It is released in response to various stimuli and acts on a number of innate immune cells to increase the number of T_H2 cells and IL-5 and IL-13 production, and subsequently blood and airway eosinophils.[68,69] A proof-of-concept study demonstrated that an anti-TSLP, AMG 157 (tezepelumab), inhibited both the early and late allergic response to a whole long allergen challenge and also resulted in a decrease in blood and sputum eosinophils and FENO during the nonallergen challenge phase of study.[70] A phase II dose-ranging study using this drug in patients with severe asthma has just been completed.

CRT_H2 antagonism: Fevipiprant

Fevipiprant is a CRT_H2 antagonist that inhibits prostaglandin D_2 receptor 2, a driver of inflammation in eosinophilic asthma. In recent clinical trials, fevipiprant has been shown to be safe and efficacious. Among patients with uncontrolled moderate-to-severe eosinophilic asthma, fevipiprant reduced airway inflammation compared with placebo.[71] Fevipiprant is now entering phase III clinical trials, and the outlook is optimistic for this therapy. Unlike mAbs currently preferred in uncontrolled severe asthma, fevipiprant is a twice-daily oral pill, which will likely be an attractive option for many patients with asthma.

Tyrosine kinase inhibition: Imatinib

Mast cells are often present in the tissue of patients with severe asthma and are regulated by stem cell factor−bound KIT proto-oncogene receptor tyrosine kinase (KIT). In those patients with severe asthma, serum stem cell factor is often elevated. Imatinib, a KIT inhibitor, was recently tested in patients with uncontrolled severe asthma in a phase II proof-of-concept study.[72] Compared with placebo, imatinib decreased airway hyperresponsiveness (measured by concentration of methacholine required to decrease FEV_1 by 20%) and reduced markers of mast cell activation. Importantly, this study revealed that eosinophil counts were inversely correlated with reduced airway hyperresponsiveness, indicating that imatinib may be more effective in those patients with a nonallergic phenotype. Further research will be critical in determining the utility of imatinib in patients with uncontrolled, severe asthma.

Bronchial thermoplasty

Bronchial thermoplasty is unique among the other recently approved therapies for severe, uncontrolled asthma in that it is not a pharmaceutical product but instead a procedure. Radiofrequency-generated heat is delivered to the bronchial tree of the lungs with a flexible bronchoscope. The applied heat is believed to reduce the volume of airway smooth muscle, which decreases the ability of the smooth muscle to bronchoconstrict, improving asthma control; however, there is limited direct evidence that bronchial thermoplasty reduces airway smooth muscle volume.

In randomized clinical trials, bronchial thermoplasty has been shown to improve asthma symptoms, reduce mild exacerbations, and improve quality of life.[73,74] Furthermore, bronchial

thermoplasty can provide long-term control of asthma in conjunction with ICSs and other controller medications. Up to 5 years after bronchial thermoplasty, treated patients had reduced ICS use and lower rates of exacerbations and emergency room visits compared with pretreatment rates.[75] Unlike the mAb treatments, which are typically well tolerated in most patients, bronchial thermoplasty is associated with short-term adverse events related to the procedure itself. Patients receiving treatment were more likely to be hospitalized for acute asthma during the treatment period and had a greater incidence of mild/moderate respiratory adverse events.

Although bronchial thermoplasty does not directly address the cause of inflammation as other targeted treatments do, this may be an advantage, because the procedure may be an option for patients with non-T2 uncontrolled asthma. Furthermore, other patients may be interested in the durable effects of the treatment, particularly those who have been nonresponsive to other options.

Applying new therapies in practice

When a patient presents with uncontrolled severe asthma, various considerations go into the selection of therapy. Once nonpharmacological reasons for a lack of control are ruled out, new therapy should be considered, because long-term outcomes are unfavorable for patients with asthma that remains uncontrolled. Selection of step-up therapy for severe asthma must be individualized to the patient on the basis of patient- and disease-related factors. Patient factors will include the phenotype of the patients, as well as preference for route of administration and cost. Most options currently available or on the horizon target eosinophilic asthma specifically.

CASE STUDIES AND THOUGHT EXERCISE

Sample case scenario

A 40-year-old woman with adult-onset asthma, diagnosed at age 30 years, presents to you with daily symptoms, nocturnal awakenings at least twice a week, and an FEV_1 of 85% predicted with an FEV_1/forced vital capacity ratio of 69%. She is receiving high-dose ICS, LABA, and tiotropium. She has had 4 asthma exacerbations requiring oral corticosteroids in the past year. You are confident of the diagnosis of asthma in this patient. She is adherent with her medications, uses her inhalers correctly, and has had her only comorbidity, gastroesophageal reflux, addressed with a proton-pump inhibitor. She is not obese. Laboratory studies include a total IgE level of 40, a skin test positive response to house dust mite, total blood eosinophils of 200/μL, and a FENO of 40.

You are considering a biologic agent for her next treatment option. What class of agent would you suggest, while acknowledging that agents in all these classes have not been approved for use by the Food and Drug Administration?

A. An anti-IgE
B. An anti—IL-5
C. An anti—IL-13 or anti—IL-4/IL-13
D. An anti-TSLP

Answer: The current state of our knowledge does not allow us to make an informed choice at this point in time. Concerning the alternatives offered:

A. Because it has been on the market for a long period of time, omalizumab, an anti-IgE, has likely been tried in this patient. She meets the indications for this drug on the basis of her IgE level, perennial allergen sensitization, and her weight. Although her total IgE level is not high, omalizumab has been shown to be equally effective in patients with "high" and "low" IgE levels.
B. Patients with elevated blood eosinophils often respond to an anti—IL-5. However, her blood level of 200 cells/μL is barely above the lowest level (150 cells/μL) used as a cutoff for treating some patients with mepolizumab. In general, patients with higher blood eosinophils are more likely to respond to this class of agents than those with lower blood levels.
C. The patient's FENO level, particularly for a patient on high-dose ICS, is higher than normal, although not markedly so. Because it appears that elevated FENO levels are associated with inflammation driven by the IL-4/IL-13 pathway, one of the IL-13 agents, or perhaps the IL-4/IL-13 agent (dupilumab), might be a reasonable choice here.
D. We are not sure of the clinical benefits that might be offered by an anti-TSLP, although such data will be soon available. The fact that it appears to be an "upstream" cytokine generally involved in allergic inflammation in general could hold significant promise for use in patients such as the one presented.

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