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Special Article

Asthma Yardstick

Practical recommendations for a sustained step-up in asthma therapy for poorly controlled asthma

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ABSTRACT

Current asthma guidelines recommend a control-based approach to management that involves assessment of impairment and risk followed by implementation of treatment strategies individualized according to the patient's needs and preferences. The fact that many patients still experience severe symptoms that negatively affect quality of life suggests that asthma control remains an objective to be achieved. Tools are available to help patients (and families) manage the day-to-day and short-term variability in asthma symptoms; however, when and how to implement a sustained step-up in therapy is less clear. The Asthma Yardstick is a comprehensive update on how to conduct a sustained step-up in asthma therapy for the patient with not well-controlled or poorly controlled asthma. Patient profiles and step-up strategies are based on current guidelines, newer data, and the authors' combined clinical experience and are intended to provide a practical and clinically meaningful guide toward the goal of well-controlled asthma for every patient. The development of this tool comes in response to the continued need to proactively address the sustained loss of asthma control at all levels of severity.

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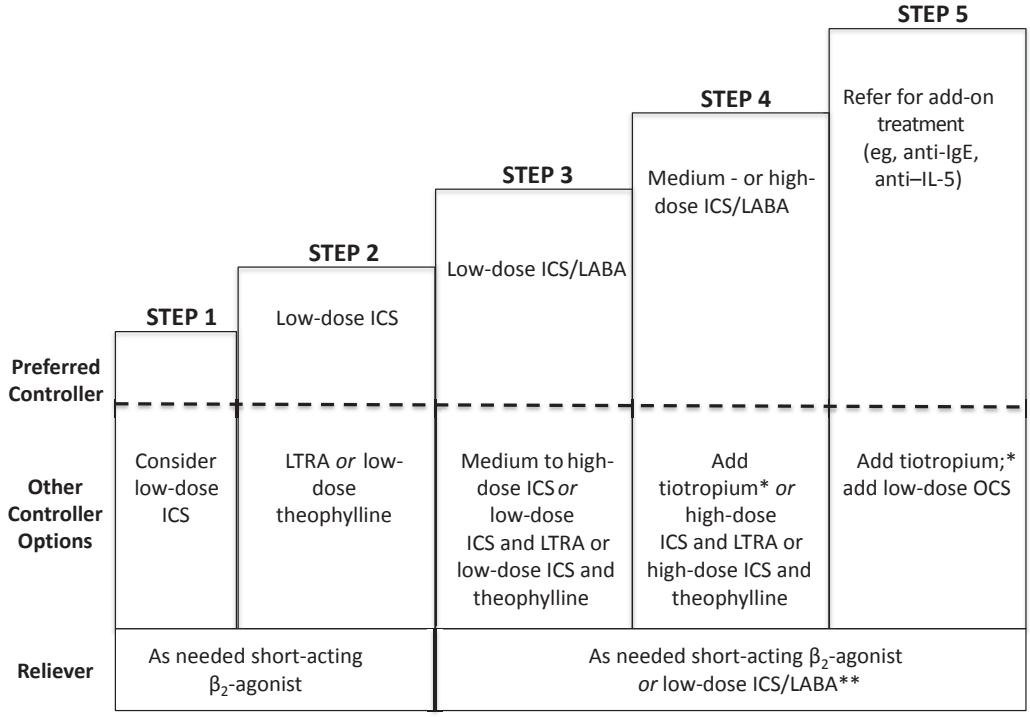

Figure 1. Step therapy for adult patients with asthma adapted from the 2015 Global Initiative for Asthma guidelines.[1] *Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children younger than 18 years old. **For patients prescribed beclomethasone/formoterol or budesonide/formoterol. IL indicates interleukin; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

Introduction

Asthma guidelines recommend a control- and risk-based model of disease management in which initial diagnosis is followed by treatment assigned by categorization of severity, then reassessment and adjustment of therapy based on disease control (eTable 1).[1,2] The model is evidence based in that positive outcomes are supported by high-quality data from randomized clinical trials and systematic reviews. However, implementation remains challenging because assessment and adjustment of asthma therapy are ongoing. A series of therapeutic steps based on disease severity and control classifications, incorporating a variety of treatment options and taking into account patient circumstances, values, and preferences is recommended (Fig 1); periodic reassessment is needed to ensure that control is maintained.[1,2]

Approximately 50% of patients with asthma continue to have not well-controlled or poorly controlled asthma despite using recommended step-care treatment.[3–6] Poorly controlled asthma contributes significantly to impairment of quality of life, and refractoriness to multiple medications should be regarded as a signal to review and modify treatment.[6] The question remains: how do we as clinicians help our patients successfully achieve and maintain control of their asthma? The answer has not been straightforward. Although the step concept has been a recognized pathway for treatment for several decades,[7–9] patient and health care system factors can be barriers to success (Table 1).[10] These barriers must be addressed before stepping up therapy. Once it is determined that increased symptoms and decreased lung function are attributable to asthma, 3 paradigms for adjusting therapy are suggested: day to day, short term, and sustained (Table 2).[1]

Managing day-to-day and short-term adjustments are well detailed in current guidelines, and tools are available to help the patient and family.[1,2] When and how to implement a sustained step-up is less clear. This article describes the Asthma Yardstick—a practical resource based on the therapeutic utility of recommended step-up strategies (ie, when and how to adjust controller therapy and/or use other treatment options) for patients who require a sustained step-up. The initial focus of the Asthma Yardstick is on adult patients (≥18 years of age) whose disease control is not optimal after multiple months of treatment (Fig 2). For decisions regarding pediatric patients, the reader is directed to current guidelines and reviews.[1,2,11–14]

The Asthma Yardstick (Fig 3) and accompanying text provide patient profiles followed by recommendations and commentary based on current guidelines[1,2] and contemporary data regarding treatment options and the authors' clinical experience. (See eMethods for a description of development.)

Table 1
Common Contributors to Loss of Asthma Control[1,10]

- Environmental exposures (eg, allergens, irritants, viruses)
- Conditions contributing to morbidity (eg, rhinosinusitis, obesity; respiratory infection, gastroesophageal reflux disease)
- Co-occurrence of another condition that may be interpreted as a loss of asthma control (eg, vocal cord dysfunction)
- Difficulty using inhalers; improper technique
- Poor adherence, which may reflect
  - Fear of medication adverse effects
  - Belief that the medication does not help (eg, in relation to patients reporting that they cannot feel an immediate effect)
  - Belief that the medication is not necessary (eg, in relation to patients reporting that they do not have symptoms and so do not need to take their medication)
  - Belief that even controller medication can be taken intermittently (eg, when symptoms become "noticeable")
  - Inconvenience, including using multiple medications or inhalers and having to take medications several times a day
  - Dislike of health care practitioner; distrust of medical establishments
- Cost, including lack of insurance or medication not covered by insurance
- Lack of access to health care

Table 2
Three Paradigms for Adjusting Asthma Therapy[1]

Type of medication adjustment	Description
Day to day	Small changes in dosing and/or reliever and control medications made by the patient (or caregiver) according to the patient's written asthma action plan
Occasional short-term (ie, 1–2 weeks) step up in controller medication	Adjustments made by the clinician or by the patient (or caregiver) according to their written asthma action plan in response to specific events or exposures (eg, during a viral infection or relevant allergy season)
A sustained step-up (for at least 2–3 months)	An adjustment made when the patient does not adequately respond to treatment and when the symptoms are confirmed to be attributable to asthma and the factors known to affect outcomes (Table 1) have been addressed and minimized. For most patients, a therapeutic trial with increased controller (and/or bronchodilator) medication is recommended and the response is reviewed (and treatment potentially modified) after 2–3 months. For some patients with severe asthma, other treatment options may be needed.

Step-up: Mild Persistent Asthma to Moderate Persistent Asthma (GINA Step 2 to Step 3)

Patient Profile

The patient who is symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument, such as the Asthma Control Test [ACT], the Asthma Control Questionnaire [ACQ], or the Asthma Therapy Assessment Questionnaire [ATAQ])[1,2] for at least 2 months or experiences 2 or more exacerbations requiring oral corticosteroids (OCSs) in the past year, despite preferred treatment (low-dose inhaled corticosteroid [ICS] monotherapy) for mild, persistent asthma.

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively impact response to therapy (Table 1), and to confirm that the increased level of symptoms is due to asthma.

Commentary

Three treatment strategies are suggested for the step-up according to the 2015 Global Initiative for Asthma (GINA) guidelines: (1) using a low-dose combination of an ICS (eg, beclomethasone dipropionate, budesonide, fluticasone propionate, fluticasone furoate, mometasone) with a long-acting β-agonist (LABA) (eg, formoterol, salmeterol, vilanterol); (2) increasing ICS monotherapy from low dose to medium dose; or (3) adding other medications (eg, leukotriene receptor antagonist [LTRA], sustained-release theophylline [SRT]) to low-dose ICSs. (Fluticasone furoate and mometasone are medium-dose ICS, but can be used in combination at step 3 if needed per formulary.) These are described below. Regardless of which strategy is chosen, 3 months of a therapeutic trial is recommended with reassessment of the patient's condition after 6 weeks of starting treatment.

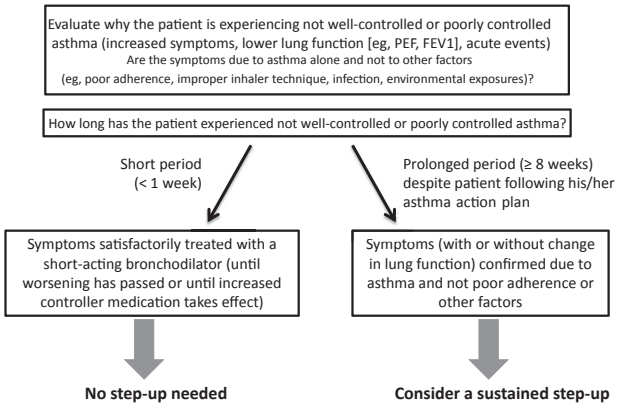

Figure 2. When should a sustained step-up in asthma therapy be considered?[1] FEV_1 indicates forced expiratory volume in 1 second; PEF, peak expiratory flow.

Low-dose ICS/LABA

A low-dose ICS/LABA strategy is preferred for most patients. Compared with ICS monotherapy, control can be maintained at a lower dose of ICS.[1] Comparisons with ICS monotherapy have suggested that using the combination of low-dose budesonide and the rapid-onset LABA formoterol in a single inhaler might reduce the number and severity of exacerbations.[16,17] The outcomes may not be limited to budesonide/formoterol. Although a 12-month, retrospective, matched-cohort study from the United States reported lower rates of exacerbation for budesonide/formoterol compared with fluticasone propionate/salmeterol,[18] a systematic review of 5 prospective randomized trials reported no significant differences between the 2 combinations for efficacy or exacerbation-related outcomes.[19] The prospective studies, all judged to be at low risk for selection and performance or detection bias, included 5,537 adults previously treated with ICSs who then received ICS/LABA for at least 12 weeks, most for 6 months. The outcomes are described in eCommentary 1. More data are needed to confirm the findings.

Whether regular treatment with a LABA may predispose patients to untoward outcomes, including asthma-related morbidity and mortality, even when combined with an ICS, remains controversial.[20] It has been suggested that the different properties of salmeterol and formoterol (eg, rapidity of onset, receptor activity) may differentiate their safety characteristics when taken on a regular basis. However, no significant between-treatment differences for nonfatal serious adverse events, either all cause or asthma related, were identified in 2 systematic reviews evaluating safety (described in eCommentary 1).[21,22]

More recently, 2 large multicenter, double-blind, 26-week studies reported no differences in the risk of asthma-related adverse events between fluticasone propionate/salmeterol and fluticasone propionate monotherapy in adults and children but fewer severe asthma exacerbations with the combination treatment.[23,24] Similar results were reported for a third study comparing budesonide/formoterol with budesonide monotherapy.[25] The outcomes of these large definitive clinical trials confirm the efficacy of the ICS and LABA combinations and lessen concerns about the risk of serious asthma-related adverse events.

Using the longer-acting LABA vilanterol in combination with the ICS fluticasone furoate allows once-daily dosing compared with twice-daily dosing for the other ICS and LABA combinations.[26] Although there may be advantages in terms of convenience with once-daily dosing,[27] a systematic review of 14 studies did not find any significant differences between once-daily fluticasone furoate/vilanterol and twice-daily fluticasone propionate/salmeterol in terms of efficacy or safety.[28]

Increasing the dose of ICS

Increasing the patient's ICS dose, usually a doubling of the dose or more, has been the traditional step-up recommended by previous editions of the guidelines.[7–9] This is now viewed as an alternative strategy to using an ICS/LABA, largely based on an increased risk of systemic adverse effects as the dose of ICS is increased.[1] In addition, although increasing the dose of ICS monotherapy has been associated with improved asthma outcomes, the data are

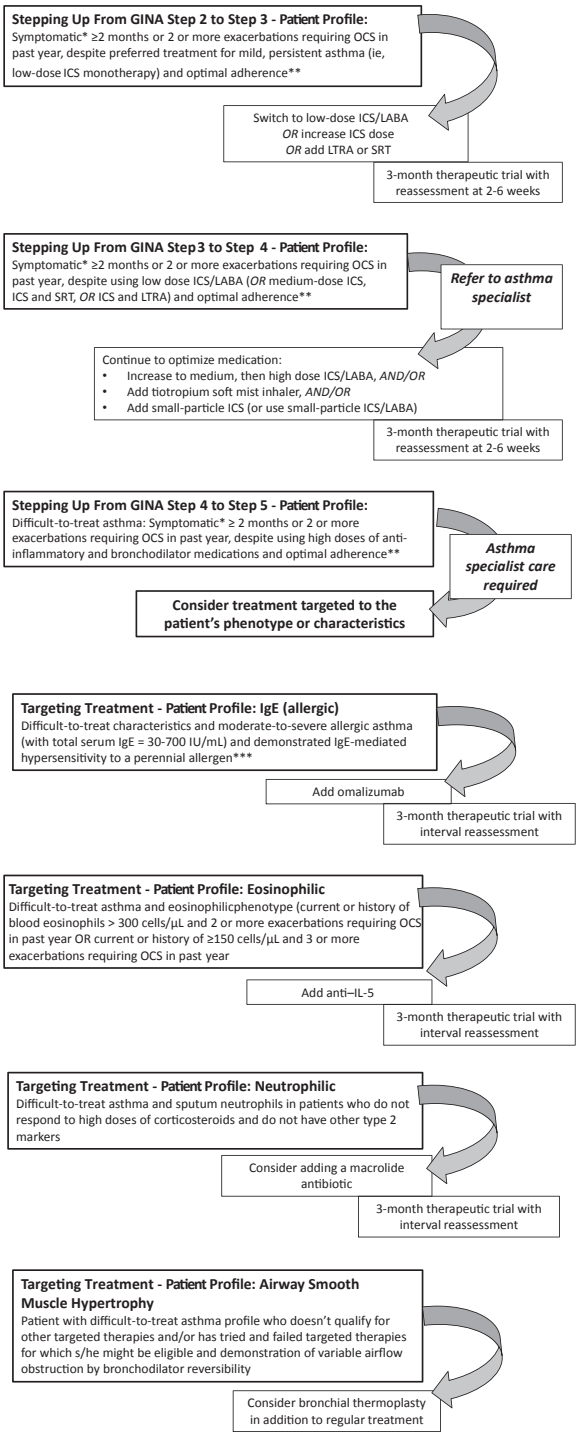

Figure 3. The Asthma Yardstick flowchart. The patient profiles and recommendations for treatment are based on current guidelines and newer data and the authors' clinical experience as described in the text. *Symptomatic indicates poorly or not well-controlled asthma according to a validated instrument, such as the Asthma Control Test, the Asthma Control Questionnaire or the Asthma Therapy Assessment Questionnaire. **Before stepping up therapy, assess the patient for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy (Table 1) and to confirm that the increased level of symptoms is attributable to asthma. ***Persistent eosinophilic inflammation and recurrent exacerbations may be indicators of poor adherence with therapy in patients with difficult-to-treat asthma. Consideration should be given to observing high-dose inhaled corticosteroid (ICS) therapy with monitoring of fractional exhaled nitric oxide before initiating therapy with biologics in patients in whom this might be a consideration.[15] GINA indicates Global Initiative for Asthma; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SRT, sustained-release theophylline.

controversial. When used as a comparator for clinical trials of ICS/LABA, doubling the ICS monotherapy dose generally had minimal positive benefit.[29] Quadrupling the dose, however, has similar or greater efficacy to the combination treatment. More recently, matched retrospective cohort analyses of large primary care databases have suggested that stepping up asthma therapy by increasing the ICS dose may be as effective as switching to an ICS/LABA in terms of improving asthma control for a year in adults and children.[13,30] The risk of potential systemic effects from higher doses of ICS must be carefully considered.

Whether doubling the dose of ICS in the early stages of an asthma exacerbation can help reduce the severity of the exacerbation or prevent the need for OCSs, an acute care visit, or hospital care also has been questioned.[31] Treatment for acute exacerbations is beyond the scope of the Asthma Yardstick: the reader is directed to the current GINA guidelines (2015)[1] and the review article by Kew et al.[31]

Adding a LTRA or SRT to an ICS

The available data indicate better outcomes with the ICS and LABA combination than adding a LTRA or SRT to an ICS.[1,32] However, the addition of an LTRA may be an option for patients who are at increased risk for untoward effects from LABAs (eg, tachyarrhythmias).

Step-up: Moderate Persistent Asthma to Severe Persistent Asthma (GINA Step 3 to Step 4)

Patient Profile

The patient who remains symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument [eg, ACT, ACQ, ATAQ]) for at least 2 months or experiences 2 or more exacerbations requiring OCSs in the past year despite using a low-dose ICS/LABA or medium-dose ICS monotherapy or a low-dose ICS plus SRT or an LTRA.

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively impact response to therapy (Table 1), and to confirm that the increased level of symptoms is due to asthma.

Commentary

The first approach—that of continued medication adjustment, addressing comorbidities, and attention to adherence—may benefit many patients and should be pursued before introducing targeted treatments. Referral to an asthma specialist is recommended in all cases.

The strategies for fine-tuning the patient's medications follow the same principles as described for the step-up from mild persistent asthma to moderate asthma (Fig 1). Thus, patients can be stepped up to a therapeutic trial of a medium- and then, if required, a high-dose ICS/LABA, and higher-strength ICS and LABA combinations may be preferred (eg, potentially switching to mometasone/formoterol or fluticasone furoate/vilanterol). Increasing the dose of ICS monotherapy or the combination of ICS and LTRA can also be tried but are less likely to produce positive outcomes compared with a high-dose ICS/LABA.[1] Some patients may benefit from daily or alternate day low-dose maintenance therapy with OCSs, but the risks of systemic adverse effects must be considered and the patient monitored regularly.[1] If these strategies do not bring the patient's asthma under control or if the patient is sensitive to increasing the ICS dose, 2 other medication options may be considered: (1) the addition of the long-acting muscarinic agent (LAMA) tiotropium bromide by soft-mist inhaler[1,33] and (2) use of a small-particle ICS.[30,34–36]

The length of the therapeutic trial should reflect the outcomes sought: for a reduction in symptoms, 1 to 2 months may

suffice, whereas for a reduction in exacerbations, 6 months or more may be needed. Interval reassessment based on impairment is recommended.

Adding tiotropium bromide

The data indicate noninferiority of tiotropium vs a LABA as an addition to ICS monotherapy.[37–40] Thus, tiotropium and an ICS may be considered in place of an ICS/LABA for patients with moderate or severe asthma who are very sensitive to the adverse effects (eg, palpitations, tremulousness) of LABAs. In addition, for patients who need a step-up from medium dose ICS/LABA, adding the LAMA may provide clinical benefit without increasing the ICS dose.[33,37,41]

Inhaled anticholinergics have been primarily used in the treatment of chronic obstructive pulmonary disease (COPD), but in 2015 the US Food and Drug Administration (FDA) approved use of tiotropium at a dose of 2.5 μg for the long-term, once-daily maintenance treatment of asthma in patients 12 years or older. Five pivotal trials were included in the US development program in which tiotropium was added to the background treatment of symptomatic individuals: 3 studies in individuals taking low- to medium-dose ICSs with bronchodilator reversibility of approximately 500 mL and 2 studies in patients with severe uncontrolled asthma using ICS/LABA.[42] The primary and secondary efficacy variables for the studies were forced expiratory volume in 1 second (FEV_1) and prednisone-requiring exacerbations, respectively. Efficacy was demonstrated for both outcomes, with a differential response between the 2.5-μg and 5-μg doses favoring the former. This finding led to the approval of the 2.5-μg dose for asthma as opposed to the 5-μg dose approved for COPD. The GINA 2015 guidelines suggest using tiotropium at the non–FDA-approved 5-μg dose in patients with severe asthma.[1]

Adding a small-particle ICS

A small particle or extrafine ICS (defined as having a mass median aerodynamic diameter [MMAD] of 1–2 μm) may be added to the treatment of patients with severe asthma (ie, in addition to standard ICA/LABA or ICS/LAMA therapy) with the goal of targeting the small airways with the increased anti-inflammatory dose. The rationale is based on several proof-of-concept studies conducted in selected populations of patients with asthma, such as those with small airways disease as shown by physiologic testing or the presence of air trapping.[43,44] Although no randomized controlled studies have been conducted to assess whether such effects occur in larger populations, epidemiologic real-life studies have suggested there may be an advantage to the use of small-particle formulations of ICSs. Small-particle hydrofluoroalkane beclomethasone (MMAD, 1.1 μm) is superior to larger-particle formulations of beclomethasone (MMAD, 2.9 μm)[36] and fluticasone (MMAD, 2.8 μm)[34] as both initial and step-up therapy in terms of asthma control. For the step-up population, patients in both the large- and small-particle ICS groups had improved asthma control but at lower doses for the small-particle formulation hydrofluoroalkane-beclomethasone; these patients had a significantly greater odds of achieving asthma control without requiring additional therapy or a change in therapy.[34,36] Better odds for achieving overall asthma control (ie, no asthma-related hospitalizations, bronchial infections, or short-term OCS use; albuterol ≤200 μg/d) was also observed in patients who switched to extrafine-particle beclomethasone/formoterol (not available in the United States) from fluticasone propionate/salmeterol.

Step-up: Severe Persistent Asthma to Severe Difficult-to-Treat Asthma (GINA Step 4 to Step 5)

It is estimated that between 5% and 30% of patients with severe asthma do not achieve complete asthma control with anti-inflammatory and bronchodilator medications, despite optimal adherence.[5,6,45,46] For these patients, targeting treatment to the asthma phenotype or specific characteristics of the patient's condition may aid in improving asthma control. Referral to a tertiary center with the necessary tools (eg, sputum analysis, bronchoscopy) to define the asthma phenotype and rule out other conditions is important.

Asthma represents a heterogeneous group of phenotypic conditions reflecting the underlying mechanisms of the disease. This is particularly true for patients with difficult-to-treat asthma.[45,47,48] Targeted therapy focuses on specific mechanisms that drive asthma symptoms (eg, increased mucous production, airway cellular and structural abnormalities).[49] For some patients, high serum IgE levels and/or high eosinophil counts and high fractional exhaled nitric oxide (FeNO) levels are associated with increased symptoms and acute exacerbations; for others, thickening of airway smooth muscle (ASM) may be the major contributor.[47,49–52] All may be targets for treatment.

Targeting IgE

Patient Profile

Patients with moderate-to-severe allergic asthma who have a total serum IgE level between 30 and 700 IU/mL *and* demonstrated IgE-mediated hypersensitivity via cutaneous or in vitro testing to a perennial allergen (eg, house dust mite, animal dander, cockroach, mold) *and* who are still symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument, such as the ACT, ACQ, or ATAQ) or experiencing exacerbations while taking high doses of anti-inflammatory and reliever medications or who may be sensitive to the adverse effects of higher doses of ICS are candidates for omalizumab.

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively impact response to therapy (Table 1) and to confirm that the increased level of symptoms is attributable to asthma. Persistent eosinophilic inflammation and recurrent exacerbations may be indicators of poor adherence with therapy in patients with difficult-to-treat asthma. Consideration should be given to observing high-dose ICS therapy with monitoring of FeNO before initiating anti-IgE therapy in patients where this might be a consideration.[15]

Commentary

Omalizumab is an IgG1k humanized monoclonal antibody with high affinity to IgE.[53] Administered by subcutaneous injection, it binds to IgE, thereby blocking the interaction of IgE with receptors on mast cells, basophils, and other cells responsible for the T2 inflammatory cascade in asthmatic airways (eCommentary 2).[54] A therapeutic trial with omalizumab is recommended for patients with moderate-to-severe allergic asthma for whom other add-on therapies (eg, LABA, tiotropium) provide inconsistent or incomplete control.[1,55] There is no evidence to support the use of omalizumab in nonatopic asthma or in patients who do not fulfill the label criteria stipulated above.

A systematic review of 25 randomized studies in patients with moderate-to-severe uncontrolled allergic asthma found that omalizumab reduced the risks of exacerbations (odds ratio [OR], 0.55; 3,261 patients: representing a reduction from 26% in the placebo group to 15% in the omalizumab group during 16–60 weeks of treatment) and asthma-related hospitalizations (OR, 0.16; 1,824 patients: representing a reduction from 3% in the placebo group to 0.5% in the omalizumab group during 28–60 weeks).[56] Patients treated with omalizumab were more likely to withdraw from ICS treatment compared with placebo (40% vs 21%) but not from chronic OCS treatment.

A minimum of 12 weeks of treatment is needed to determine whether omalizumab is effective in reducing asthma symptoms for a given patient,[57] although in more equivocal cases and for reducing exacerbations and/or lowering OCS use, up to 6 months or more may be preferable.[58]

The optimal duration of omalizumab therapy in patients with clinical improvement in their asthma has not been determined. Uncontrolled studies suggest that there may be persistent improvement for variable periods after omalizumab treatment has been stopped, and it is unclear whether duration of treatment has an effect on this continuing benefit. There is no indication that asthma symptoms rebound after cessation of treatment.[59] Reducing the omalizumab dose below the standard dose is likely to result in a loss of efficacy.[60] There are no data to support an increase in dosing interval beyond every 2 or 4 weeks.

A small number of clinical trials have found that omalizumab may be efficacious in the treatment of allergic rhinitis[61] and chronic rhinosinusitis with nasal polyposis,[62] both of which occur frequently in patients with asthma, may contribute to asthma severity, and significantly affect quality of life.

The most common adverse effect of omalizumab is mild-moderate injection site reaction.[53] Although this was reported in 44% of patients in the pivotal clinical trials, it does not match the clinical experience of the authors. Systemic hypersensitivity reactions to omalizumab are rare (0.1%–0.2% of patients); most occurred after 1 of the first 3 doses, within 2 hours of administration. Other concerns that have been raised with the long-term use of omalizuamb, including cancer and thromboembolic events, have not been conclusively demonstrated (eCommentary 3).[53,63,64] Recommended precautions before using omalizumab include having the patient sign an informed consent form, prescription of an epinephrine auto-injector to be carried in association with receiving injections of omalizumab, and observation of the patient for 2 hours after each of the first 3 injections and for 30 minutes after each injection thereafter.

Targeting Eosinophils: Anti–IL-5

Patient Profile

Patients who are still symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument, such as the ACT, ACQ, or ATAQ) despite treatment with high-dose ICS/LABA and/or other anti-inflammatory and reliever medications and who have persistent eosinophilic inflammation (documented by a blood eosinophil count ≥300 cells/μL and 2 or more exacerbations requiring OCSs in the past year or ≥150 cells/μL and 3 or more exacerbations requiring OCSs in past year).

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively impact response to therapy before stepping up therapy (Table 1) and to confirm that the increased level of symptoms is attributable to asthma. Persistent eosinophilic inflammation and recurrent exacerbations may be indicators of poor adherence with therapy in patients with difficult-to-treat asthma. Consideration should be given to observing high-dose ICS therapy with monitoring of FeNO before initiating anti–IL-5 therapy in patients in whom this might be a consideration.[15] Parasitic diseases are an alternative diagnosis for high eosinophil levels and if necessary should be ruled out with appropriate testing.

Commentary

Treating the eosinophilic asthma phenotype has targeted molecules involved in the activation and recruitment of eosinophils, such as the cytokine interleukin- (IL-) 5. To date, 2 IL-5 antagonist monoclonal antibodies have been FDA approved as add-on maintenance treatment for patients with severe asthma: mepolizumab (for patient ≥12 years old) and reslizumab (for patients ≥18 years old).[65–67] Mepolizumab is administered via subcutaneous injection at a standard dose of 100 mg every 4 weeks.[66] Reslizumab is administered by weight-based intravenous dosing.[67] Both reduce sputum and blood eosinophil counts, usually within 1 month, although clinical improvement usually takes longer.[65,68–70]

Clinically, treatment effectiveness with anti–IL-5 monoclonal antibodies is strongly associated with the exacerbation history of the patient. Currently available data support the use of anti–IL-5 monoclonal antibodies in patients with recurrent exacerbations and evidence (current and probably historical) of type 2 inflammation (eCommentary 2) as indicated primarily by blood eosinophil counts; a small number of patients may have high sputum eosinophils or FeNO without blood eosinophilia.[65,70]

The data suggest that patients with a history of eosinophil counts greater than 300 cells/μL and 2 or more exacerbations per year are likely to experience a reduction in exacerbations. Patients with a greater exacerbation rate (eg, ≥3 per year) may respond at levels as low as 150 cells/μL. Reduced exacerbations and health care use are indicators of successful treatment in most cases; however, some patients with a baseline bronchodilator response may have some improvement in FEV_1 and symptoms.[70] Because there are no studies directly comparing the 2 agents in the same population, it is not possible to definitively state that there are significant differences between them. Interval reassessment is recommended; improvements in exacerbations may take 6 months or longer.

The most common adverse effect with mepolizumab is injection site reactions, although hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticaria, rash) and herpes zoster infections have been reported.[66] There are no formal recommendations regarding administration of zoster vaccines before initiating anti–IL-5 therapy. Anaphylaxis has been reported after reslizumab infusion.[67] After treatment with either agent, the patient should be observed for potential hypersensitivity reactions. For patients with an inadequate response to one of the anti–IL-5 agents, a trial with the other may be attempted provided that the patient meets the criteria for treatment. For obese patients in particular, weight-based dosing with reslizumab might be considered for those who failed a trial of mepolizumab, although no studies have been conducted to provide evidence in this regard.

Targeting Neutrophils: Macrolides

Patient Profile

Patients with difficult-to-treat asthma with neutrophils in their sputum who are not responding to high doses of corticosteroids and do not have other type 2 inflammatory markers (eCommentary 2).

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities and other factors that might negatively impact response to therapy prior to stepping up therapy (Table 1) and to confirm that the increased level of symptoms is attributable to asthma.

Commentary

A subset of patients with severe asthma are corticosteroid insensitive and do not respond well to traditional anti-inflammatory treatments. Some patients in this group have increased levels of eosinophils, whereas others have sputum neutrophilia. For the latter, macrolides may, in some cases, be an effective treatment option. The underlying mechanisms are not clear.[71–74]

Macrolides, the most widely used group of antibiotics, treat a wide spectrum of respiratory diseases, including chronic conditions

(eg, cystic fibrosis, COPD).[75] Their potential value in asthma lies in the common characteristics of chronic airway inflammation and bronchial hyperresponsiveness and the fact that some patients experience acute exacerbations and/or deterioration of their asthma triggered largely by respiratory infections. Macrolides have demonstrated efficacy against a broad range of respiratory bacteria, including those implicated in chronic asthma and asthma exacerbations (eg, *Chlamydophila pneumoniae*, *Mycoplasma pneumonia*).[76] Neutrophilic asthma, a phenotype characterized by high levels of neutrophils in the airways with or without concomitant eosinophils, has been associated with increased bacterial load (eg, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*) and IL-8.[77] Immunomodulatory effects independent of antibacterial activity have been demonstrated in several models, including stimulated human neutrophils and sputum, and affecting various pathways, including type 1 and type 2 immune mechanisms. Comprehensive discussion is beyond the scope of this article; the reader is directed to the 2014 review by Wong and colleagues.[74]

Although using macrolides to treat patients with ICS-resistant asthma may be tempting based on the drugs' anti-inflammatory and antimicrobial properties, mixed results were observed in clinical trials evaluating asthma related to chronic atypical respiratory infection.[73,75–77] Later studies using a phenotyping approach found that macrolide-responsive patients have high airway neutrophilia and/or non–type 2 inflammation (eCommentary 2).[78,79] For example, azithromycin therapy significantly reduced the rate of exacerbations in a subgroup of patients with severe neutrophilic asthma but not in a broader group of patients with asthma.[79] There are grounds, albeit limited, for optimism for the use of macrolides in asthma. Currently, these drugs are not FDA approved for treating asthma, and most studies of macrolide use for asthma have been conducted broadly and not limited to patients with neutrophilia. These drugs will need to be further studied in a smaller subset of asthma patients defined by a non–type 2 physiology.

If initiated, macrolide therapy should extend for 3 months, at which time discontinuation should be strongly considered unless there have been objective changes in exacerbations, asthma control scores, or measurements of airway function.[80] The parameters necessary to achieve adequate outcomes must be carefully weighed with regard to adverse effects and promoting antibiotic resistance.[74] The most common adverse effects are those typically associated with long-term use of antibiotics: nausea and diarrhea. Serious cardiac and hepatic effects are rare but of concern for certain patients.[74] The emergence of macrolide resistant species is a greater concern.

Targeting ASM: Bronchial Thermoplasty

Patient Profile

Patients with difficult-to-treat asthma who have uncontrolled symptoms despite optimal treatment with high-dose anti-inflammatory and bronchodilator medications for 2 to 3 months, who do not qualify for other targeted therapies or have tried and failed other targeted therapies for which they are eligible, and who have variable airflow obstruction as demonstrated by bronchodilator reversibility are candidates for treatment. Another prognostic factor based on the authors' clinical experience is quick deterioration after LABA withdrawal.

Prior to stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy (Table 1) and to confirm that the increased level of symptoms is attributable to asthma.

Commentary

Increase in ASM mass is a well-documented finding in chronic asthma, and patients with severe asthma have thicker airway walls than patients with mild or moderate disease.[52,81,82] Wall thickness is inversely related to lung function and bronchial hyperresponsiveness[47,81] and likely reflects underlying processes related to remodeling and inflammation over time (eg, epithelial thickening, subepithelial fibrosis, smooth muscle hypertrophy or hyperplasia, inflammatory cell infiltration, goblet cell hyperplasia).[50–52,82,83]

Bronchial thermoplasty is an FDA-approved endoscopic treatment option to reduce ASM thickness by delivering radiofrequency (thermal energy) to the airway wall through a catheter and bronchoscope. It is indicated for the treatment of severe asthma with uncontrolled symptoms despite optimal treatment with high-dose ICS/LABA. Three treatments are usually given approximately 3 weeks apart. Evidence suggests that the thermal energy denudes the airway epithelium and diminishes ASM mass. The epithelium repopulates, but the ASM remains attenuated.[49,84–88]

In clinical trials, patients treated with bronchial thermoplasty had an increased number of symptom-free days, fewer exacerbations, fewer hospitalizations, better asthma control, improved quality of life, and less use of rescue medication compared with the control group, excluding exacerbations that occurred during the period of treatment.[85,89,90] The decreases in exacerbations and associated health care use were observed for up to 5 years of follow-up in the intervention group without comparison to controls.[90–92] The patients entered into these trials had to have variable airflow obstruction as demonstrated by bronchodilator reversibility, airway reactivity as demonstrated by methacholine challenge, and/or quick deterioration after LABA withdrawal—characteristics expected to be associated with increased airway wall thickness. Patients with FEV_1 less than 50% predicted or more than 3 exacerbations per year were excluded. The data also revealed reductions in chemokine and cytokine levels in bronchoalveolar lavage.[85]

Patients undergoing bronchial thermoplasty have better outcomes if at baseline there is greater ASM mass.[87] There is no airway fibrosis after bronchial thermoplasty, and the procedure is safe, although a transient increase in adverse events (including severe exacerbations) were observed immediately after the procedure compared with controls who underwent sham bronchoscopy.[90,93] A small study of 42 patients undergoing bronchial thermoplasty suggested that a shorter duration of asthma and increased exacerbation rate might be predictors of bronchial thermoplasty response.[94] Other factors that might be predictive included higher baseline OCS dose, lower quality-of-life scores, and older age. More research is needed to better identify patient characteristics or a specific phenotype that is more likely to benefit; most asthma guidelines recommend additional clinical trials.

Discussion

The Asthma Yardstick is the most comprehensive update on how to conduct a sustained step-up in asthma therapy for the patient with not well-controlled or poorly controlled asthma to date. Patient profiles, based on current guidelines and authors' combined clinical experience, provide a practical and clinically meaningful guide to aid physicians in managing their patients to achieve the goal of well-controlled asthma. The development of this tool comes in response to the continued need to proactively address loss of asthma control at all levels of severity.

The implementation of asthma guidelines, past and present, remains a challenge. A cohort study using administrative claims to evaluate asthma step care reported that only 28% of patients with uncontrolled asthma at all levels of severity were stepped up as recommended by guidelines.[95] Patients with the greatest disease severity were least likely to have a sustained step change in medications and were more likely to have been prescribed OCSs. Most of

these patients did not see an asthma specialist, and of those prescribed an OCS, only 12% were using appropriate controller medications (ie, ICS, ICS/LABA, omalizumab). A separate claims analysis reported that up to one-third of patients with asthma had poor control as evidenced by the need for hospital or emergency department admission and/or use of reliever medications (short-acting bronchodilators, OCSs), despite being adherent with ICS/LABA controller therapy.[46]

Both patients and clinicians may need to become more adept at identifying poorly controlled asthma and recognizing the need for a sustained step-up in controller therapy. The ratio of controller medication to total asthma medications, the Asthma Medication Ratio, may be helpful to assess asthma control and has been endorsed by the National Quality Forum as a useful measure of the quality of asthma care for health care systems.[96,97] Higher ratios ($\geq$0.50) are associated with improved asthma outcomes, including fewer asthma-related hospitalizations, emergency department visits, and use of OCS.[96] Higher ratios also have been associated with increased use of asthma specialist care.

The patient with difficult-to-treat asthma should be evaluated by an asthma specialist experienced in the management of severe asthma and use of adjunctive treatments. These patients, for whom asthma specialist care is underused,[46,95,96] represent a small proportion of all patients with asthma but are significant contributors to costs related to treatment and morbidity.[5,6,98] Evaluating patient phenotypes within this population and applying targeted treatment can reduce costs by limiting therapies to those more likely to respond and by decreasing acute events requiring unscheduled office visits, emergency department visits, and hospitalizations. Although acquisition costs for this type of care can be substantial, identifying and treating these patients aggressively might improve clinical outcomes and, subsequently, reduce the economic burden.[98] The challenge, yet to be overcome, is the initial cost to the patient, which may not be covered by the insurer.

It is also important to demonstrate that the loss of asthma control is attributable to asthma. As emphasized throughout the Asthma Yardstick, before considering a step-up in treatment, attention should be given to factors that might negatively affect asthma control. Is the patient adherent with his/her medication plan? Are there comorbid conditions that might exacerbate symptoms? Are other factors at play? Inconvenience of dosing, high cost, difficulty using an inhaler, and negative perceptions of treatment are all barriers to successful therapy. For some patients, managing these issues may lead to better asthma control. Within most medication classes (eg, ICS, ICS and LABA combination), differences in efficacy and safety are minimal and nonlimiting.[27,34] However, other features, such as once-daily dosing, flexibility of dose timing, and easy use of the device, may be advantageous to some patients. If patients have medication and/or device-specific preferences, they should be incorporated into management planning.

Dialogue is critical to ensure that patients, families, and clinicians agree on what is meant by good asthma control and how to achieve it. This should emphasize the regular and not intermittent use of controller medications and recognition of not well-controlled or poorly controlled disease. All patients should be aggressively managed if they develop signs of poor control, and patients should know those signs and have asthma action plans to implement. The Asthma Yardstick provides a practical resource, based on current evidence and clinical experience, for managing patients not responsive to standardized step care.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2016.12.010.

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eMethods

The authors worked in teams to review the current evidence for various US Food and Drug Administration–approved treatment options identified by the most recent guidelines according to the type of step-up (mild persistent asthma to moderate persistent asthma [Global Initiative for Asthma (GINA) Step 2 to Step 3]; moderate persistent asthma to severe persistent asthma [GINA Step 3 to 4], and severe persistent asthma to severe difficult-to-treat asthma [GINA Step 4 to 5]).[e1,e2] Newer data and potential treatment options not yet described in the guidelines were also evaluated, but the evidence was not graded. Patient profiles were created as practical points of reference for the reader, and the associated flow diagram (Fig 3 in the text) provides the authors' concept for a "best practice summary" of the available strategies for increasing and/or modifying therapy according to the patient's severity and control of asthma. All authors reviewed and provided appropriate revisions to the manuscript in development, and all gave written approval to the final document. It is anticipated that like the guidelines, the Asthma Yardstick will be updated on a regular basis according to new research findings.

eCommentary 1. ICS/LABA Comparison

It is important for asthma care practitioners to be aware of whether there is high-quality evidence demonstrating that one fixed dose combination is superior in terms of efficacy or safety for management of moderate persistent asthma. In a systematic review that analyzed this question in terms, randomized trials with a parallel design, comparing fixed-dose fluticasone/salmeterol and budesonide/formoterol of 12 weeks or longer were included.[e3] Five studies with a total of 5,537 adults who had previously been treated with inhaled corticosteroid (ICS) monotherapy fulfilled the inclusion criteria. Most of the studies were of 6 months' duration and were judged to be at low risk for selection and performance or detection bias. The odds ratio (OR) for exacerbations requiring oral corticosteroids (OCSs) was lower with fluticasone/salmeterol but did not reach statistical significance (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.74–1.07; 4 studies, N = 4,949). With an assumed risk with budesonide/formoterol of 106 per 1,000 participants requiring OCSs, this estimate implies that treatment with fluticasone/salmeterol would lead to between 25 fewer and 7 more patients per 1,000 requiring a course of OCS. The odds for hospitalization were higher with fluticasone/salmeterol but again did not reach statistical significance (OR, 1.29; 95% CI, 0.68–2.47; 4 studies, 4,879 participants). With an assumed risk with budesonide/formoterol of 7 per 1,000, between 2 fewer and 10 more people per 1,000 would be hospitalized in association with fluticasone/salmeterol treatment. The odds of a serious adverse event related to asthma was higher with fluticasone/salmeterol but did not differ significantly between treatments (OR, 1.47; 95% CI, 0.75–2.86; 3 studies, 4,054 participants). With an assumed risk with budesonide/formoterol of 7 per 1,000, between 2 fewer and 13 more people per 1,000 would experience a serious adverse event taking fluticasone/salmeterol. Overall, the quality of evidence based on GRADE for the above 3 coprimary outcomes was moderate, implying that further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.

Lung function, symptoms, rescue medication, composite of exacerbations leading to emergency department visits or hospitalization, withdrawals, and adverse events did not differ significantly between fluticasone/salmeterol and budesonide/formoterol.[e3] Assessment of quality of life was limited to 2 studies: the differences were not statistically significant.

The findings from this systematic review do not provide evidence to support the contention that either agent is superior to the other.

The safety of the 2 long-acting β_2-agonists (LABAs) in these fixed-dose combinations also was evaluated in 2 more recent systematic reviews.[e4,e5] One assessed the risk of mortality and nonfatal serious adverse events in randomized trials of at least 12 weeks' duration, associated with formoterol vis-a-vis salmeterol, with each LABA taken in combination with an ICS as part of the randomized treatment protocol.[e4] The search identified 8 studies that fulfilled the eligibility criteria, in which 6,163 adults and adolescents were enrolled, with 7 studies (N = 5,935) comparing budesonide/formoterol to fluticasone/salmeterol. In every study except one, ICSs and LABAs were taken as a combined inhaler. There were 2 deaths overall, 1 with each combination, but neither was related to asthma. There was no significant difference between treatment groups for nonfatal serious adverse events, either all-cause (Peto OR, 1.14; 95% CI, 0.82–1.59; I_2 = 26%) or asthma-related (Peto OR, 0.69; 95% CI, 0.37–1.26; I_2 = 33%). In 23 weeks, the rates for all-cause serious adverse events were 2.6% with budesonide/formoterol and 2.3% for fluticasone/salmeterol; the rates for asthma-related serious adverse events were 0.6% and 0.8%, respectively.[e4]

The other systematic review assessed the risk of mortality and nonfatal severe adverse events in 4 randomized trials with parallel design, with or without blinding, and in which patients with asthma were randomly assigned to regular treatment with formoterol or salmeterol.[e5] A total of 1,116 adults (and 156 children) were included. The studies were open-label, recruited patients who were taking ICSs, and compared 12 μg of formoterol with 50 μg of salmeterol twice daily administered by Foradil Aerolizer and Serevent Diskus, respectively. One death in an adult was unrelated to asthma. There were no significant differences in nonfatal serious adverse events comparing formoterol and salmeterol in adults (Peto OR, 0.77; 95% CI, 0.46–1.28). During a 6-month period, in the adult studies, serious adverse events were 5.1% for formoterol and 6.4% for salmeterol.[e5]

On the basis of the small number of participants in these studies, no definite conclusions can be made about differences in the relative safety of formoterol vs salmeterol or the relative safety of budesonide/formoterol compared with fluticasone/salmeterol; larger surveillance studies are required. There were no reported asthma-related fatalities, and asthma-related serious adverse events were rare.

eCommentary 2. Type 2 Endotypes

Asthma is a heterogeneous disorder and, historically, has been classified according to the patient's triggers (allergens, exercise, infections), clinical presentation, and/or inflammatory markers (eosinophils, neutrophils).[e6–e8] With greater understanding of the genetics of asthma, classification has shifted to endotyping based on the degree of type 2 inflammation (eFig 1)—either high or low corresponding to the level of T_H type 2 cells (type 2–high or type 2–low).[e7–e9]

Type 2 inflammation is mediated by interleukin- (IL-) 4, IL-5, and IL-13 released from lymphocytes, basophils, and mast cells, which have provided targets for drug development. Type 2–high disease is associated with increased numbers of eosinophils in the sputum and airways of patients, and most patients with type 2–high asthma have corticosteroid responsiveness characterized by fewer symptoms, improved lung function, and lower levels of eosinophils.[e7–e10] For the patient with type 2–high asthma who has a poor response to corticosteroids, antieosinophilic therapies (eg, anti-IgE, anti–IL-5 as described in the text) may be considered.

Different cytokines and mediators are thought to contribute to neutrophilic inflammation of type 2–low asthma: IL-1, tumor necrosis factor, IL-8, IL-23, IL-17, and IL-23.[e7,e8] Patients with type 2–low inflammation have normal levels of eosinophils and

increased or normal (paucigranulocytic) levels of neutrophils in the sputum and airways and tend not to respond to corticosteroids. Research for therapeutic options is ongoing.

eCommentary 3. Omalizumab and Malignancy and Cardiovascular Events

The package insert for omalizumab (Xolair) includes a warning for the potential risk of malignancy.[e11] This is based on an analysis of pooled data from controlled clinical trials of omalizumab in patients with asthma and other allergic disorders that reported cases of malignancy in 20 (0.5%) of 4,127 omalizumab-treated patients and 5 (0.2%) of 2,236 controls. However, a causal relationship between the occurrence of the malignant neoplasms and omalizumab treatment was unclear. Most of the studies were short term, approximately 60% of the patients developed malignant tumors within 6 months of omalizumab exposure, and heterogeneous tumor cell types were observed.

More recently, a postmarket surveillance study with a median follow-up time of approximately 5 years reported similar rates of malignancy in 5,007 patients with asthma who received omalizumab and 2,829 patients who did not (12.3 and 13.0 per 1,000 patient-years, respectively).[e12] The outcomes of the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) suggested that omalizumab treatment was not associated with any increased risk of malignant tumors. Data from the same study were used to evaluate the rate of cardiovascular and cerebrovascular events in the omalizumab-treated patients compared with the controls.[e13] A higher incidence of cardiovascular and cerebrovascular events was determined for those treated with omalizumab: 13.4 per 1,000 person-years compared with 8.1 per 1,000 person-years for non–omalizumab-treated participants. However, careful interpretation of the results is needed. Baseline differences in cardiovascular risk factors for the treated and control participants, increased severity of asthma in the treated participants, and a high rate of study discontinuation (44%) may have influenced the findings. Accounting for the confounding variables, the difference between the cohorts was substantially reduced.

A subsequent analysis of 25 randomized controlled trials of omalizumab involving 3,342 treated patients with asthma and 2,895 nontreated patients reported no difference in the rate of cardiovascular events.[e11] However, these observations were based on a low number of events in fewer studies with a younger cohort and a shorter duration of follow-up. Thus, the findings can neither confirm nor reject those of the earlier study.

Given the observational nature of this type of data, it is difficult to determine the clinical significance of these findings. Efforts to further understand possible risks for malignant tumors and for cardiovascular sequelae are continuing during postmarketing surveillance of omalizumab.

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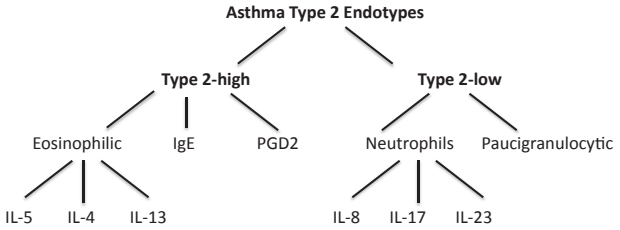

eFigure 1. Type 2 inflammation endotypes in asthma (adapted from Stokes and Casale[e7]). IL indicates interleukin; PGD2, prostaglandin D_2.

eTable 1
Classification of Asthma Control by Impairment and Risk (Adapted From National Asthma Education and Prevention Program, 2008)[e1]

Control component	Classification of asthma control		
	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days per week	>2 days per week	Throughout the day
Nighttime awakenings	≤2 times per month	1–3 times per week	≥4 times per week
Interference with normal activities	None	Some limitation	Extremely limited
Using SABA for symptoms (not prevention of EIB)	≤2 days per week	>2 days per week	Several times per day
FEV_1 or PEF	>80% predicted/personal best	60%–80% predicted/personal best	<60% predicted/personal best
Validated questionnaires			
ACT	≥20	16–19	≤15
ACQ	≤0.75	≥1.5	NA
ATAQ	0	1–2	3–4
Risk			
Exacerbations requiring OCS	≤1 per year	≥2 per year	
Progressive loss of lung function	Long-term follow-up required	Long-term follow-up required	Long-term follow-up required
Treatment-related adverse effects	May vary from none to troublesome/or worrisome. Intensity does not correlate with level of control but should be considered in overall assessment of risk.		

Abbreviations: ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ATAQ, Asthma Therapy Assessment Questionnaire; NA, not applicable; OCS, oral corticosteroid; SABA, short-acting β_2-agonist.