

Novel Therapies in Asthma: Leukotriene Antagonists, Biologic Agents, and Beyond

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Asthma is one of the most common conditions seen in clinical practice and carries both a significant disease burden in terms of patient morbidity and a high economic burden in both direct and indirect costs. Despite this, it remains a comparatively poorly understood disease, with only modest advances in treatment over the past decade. Corticosteroids remain the cornerstone of therapy. Both patient compliance with medications and physician adherence to evidence-based guidelines are often poor, and a high percentage of patients continue to have inadequately controlled disease even with optimal therapy. Following a contextual overview of the current treatment guidelines, this review focuses on novel asthma therapies, beginning with the introduction of the leukotriene receptor antagonist zafirlukast in the 1990s, continuing through advanced endoscopic therapy and into cytokine-directed biologic agents currently in development. Along with clinically relevant biochemistry and pharmacology, the evidence supporting the place of these therapies in current guidelines will be highlighted along with data comparing these agents with more conventional treatment. A brief discussion of other drugs, such as those developed for unrelated conditions and subsequently examined as potential asthma therapies, is included.

Keywords: asthma, leukotriene antagonists, montelukast, zafirlukast, omalizumab, bronchial thermoplasty

INTRODUCTION

Although the treatment of asthma has evolved significantly in the past 100-plus years, from the use of “Asthma cigarettes” at the beginning of the 20th Century, to the monoclonal antibody omalizumab today,

few, if any, pharmaceutical classes have disappeared completely from use. Indeed, only 2 completely new classes of drug have been approved since the 1960s.¹ Despite great progress in describing the underlying pathophysiology of asthma, it remains an incompletely understood syndrome with distinct phenotypes.^{2,3} Furthermore, this knowledge has yet to substantially impact management of this disease: As it has since antiquity,⁴ treatment remains nonspecific and driven by self-reported symptoms more than any other factor. Inhaled corticosteroids (ICS), in use for over 40 years, remain the cornerstone of therapy.^{5,6}

Although treatment of breathlessness with various inhaled agents is recorded in accounts from ancient China and Egypt,^{4,7} the term asthma first appears in *The Iliad* as Homer describes Hector’s rapid or panting breathing pattern as he lies exhausted on the field of battle after defeat at the hands of Ajax.⁸ The term is used frequently in the works of Hippocrates, though it is arguably as a symptom, interchangeable with

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dyspnea, and not a disease. The earliest clear description of asthma as a single clinical entity is in the vivid writings of the greek philosopher/physician Aretaeus in the first century AD; "The cheeks are ruddy and the eyes protuberant, as if from strangulation; a rale can be heard ... voice is liquid and without resonance; a desire of much and of cold air ... they breathe standing, as if desiring to draw in all the air they can possibly inhale." He broadly defines the disease: "If from running, gymnastic exercises, or from any other work, the breathing becomes difficult it is called asthma."⁷ In the 19th century, the "modern" concept of the disease was refined by Dr Henry Salter. An asthmatic himself, Salter recognized the role of bronchospasm mediated by airway smooth muscle and described asthma as "paroxysmal dyspnea of a peculiar character with intervals of healthy respiration between attacks."⁹

The 21st century "working" definition, courtesy of the National Institutes of Health (NIH), is slightly less succinct: "Asthma is a chronic inflammatory disorder of the airways in which many cells ... play a role: in particular, mast cells, eosinophils, neutrophils ... T lymphocytes, macrophages, and epithelial cells. ... this inflammation causes recurrent episodes of coughing ... wheezing, breathlessness, and chest tightness. These episodes are usually associated with ... airflow obstruction that is often reversible, either spontaneously or with treatment."⁶ The socioeconomic effect of asthma is not trivial: Asthma affects approximately 80% of the US population, or over 22 million people,^{6,10} with an estimated annual treatment cost of 18 billion dollars for the adult population alone.¹¹

The clinical presentation, evaluation, and differential diagnosis of suspected asthma is a broad topic unto itself.^{5,6,12} The purpose of this review is to discuss modern or "novel" treatment options for asthmatic patients, address drugs in development with relevant pharmacology, and review newer therapies (ie, approved or developed within the last 2 decades) already in clinical use.

ASTHMA CLASSIFICATION AND GUIDELINES

Typically, asthma has been classified by severity, with categories such as 'mild intermittent,' 'mild persistent,' 'moderate persistent.'⁶ However, beyond the initial evaluation of a patient who is not on long-term therapy, the conventional classification schema is not as clinically useful as more dynamic assessments of treatment response. Indeed, the categories of severity were never intended to be applied to patients on long-term therapy and, in fact, have not been well validated even in their target population.¹² Unfortunately, in practice,

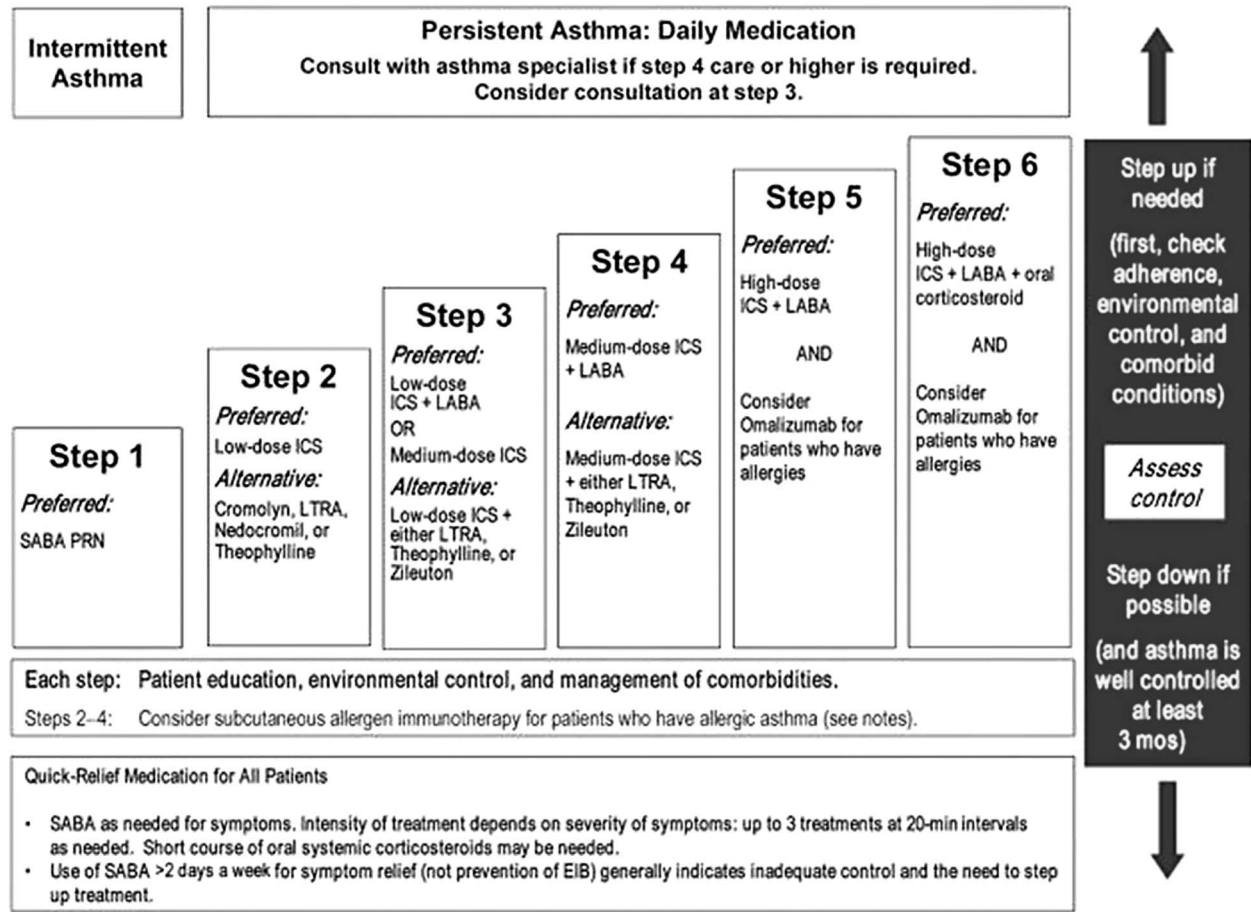
they were frequently used inappropriately to assess patients on therapy,¹³ resulting in underestimation of disease severity and consequent undertreatment.^{12,14} With increasing recognition of this issue, the most recent guidelines (see below) have de-emphasized these conventional severity assessments. The treatment of asthma is geared toward "control," or minimizing the symptoms and acute exacerbations of asthma as these can lead to airway remodeling and irreversible loss of pulmonary function. Therefore, it is recommended that once long-term therapy has been initiated, patients be classified by the level of treatment (measured in 'steps') they require to maintain good control of their symptoms, and the quality and durability of that control.^{5,6,13} The conventional classifications of disease severity have been virtually eliminated from the World Health Organization guidelines entirely,⁵ whereas in the NIH-sponsored guidelines,⁶ they are recommended only for the initial evaluation of patients that are either treatment naive or are being considered for inclusion in clinical trials.

At present, there are 2 sets of asthma guidelines in widespread use. The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3⁶ was last published in 2007. The Global Initiative for Asthma (GINA) guidelines were last updated in 2010.^{5,15} Although not entirely correct, these are sometimes referred to as the "American" (NAEPP) and "European" (GINA) guidelines, based on their authorship by the National Institutes of Health (NIH) and World Health Organization, respectively.

In both sets of guidelines, ICSs and beta-agonists are the cornerstones of therapy, with other agents added on in "steps": If the patient does not demonstrate good disease control, then the therapeutic regimen is increased to the next step up in the algorithm (see below for the definition of control). Once control is achieved, stepping down to the lowest level of medication required for maintenance is recommended. Tables 1 and 2 summarize the different steps in both sets of adult guidelines, and Table 3 summarizes the definitions of control.^{5,6}

The differences between these 2 guidelines, at least where the basic treatment algorithms are concerned, are generally quite subtle and pertain primarily to pediatric patients and the initiation of a long acting beta agonist (LABA). The GINA guidelines also more explicitly endorse the use of multiple-drug regimens, such as an inhaled steroid, LABA, and leukotriene antagonist simultaneously, a common clinical practice for severe asthma. The stepwise progression of therapies are otherwise quite similar. (For specific reference, any treatment guidelines discussed henceforth are those of the NAEPP, and for adults, unless otherwise noted.)

Table 1. Treatment steps for adult patients, from the NAEPP expert report 3.



Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta₂-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta₂-agonist

Treatment algorithm

Once a patient has been diagnosed with asthma, a typical (NAEPP, adult) treatment algorithm proceeds thusly⁶: At step I, a patient is treated with as-needed short-acting beta-agonists alone. As a general rule, the need to use a so-called “rescue inhaler” such as albuterol more than twice a week is considered to be inadequate asthma control and indicates a need to “step up” the treatment regimen.

At step II, a low-dose ICS is started. See Table 4 for comparative ICS dosing. LABAs are not recommended for monotherapy owing to concern about the safety of LABAs without concomitant ICS use.^{16–19}

At step III, the ICS is increased to ‘medium dose,’ or dual therapy with low-dose ICS and a LABA is initiated. Other agents such as leukotriene (LT) receptor antagonists (LTRAs) can be used at any step above I but are not considered “preferred” therapeutic options.

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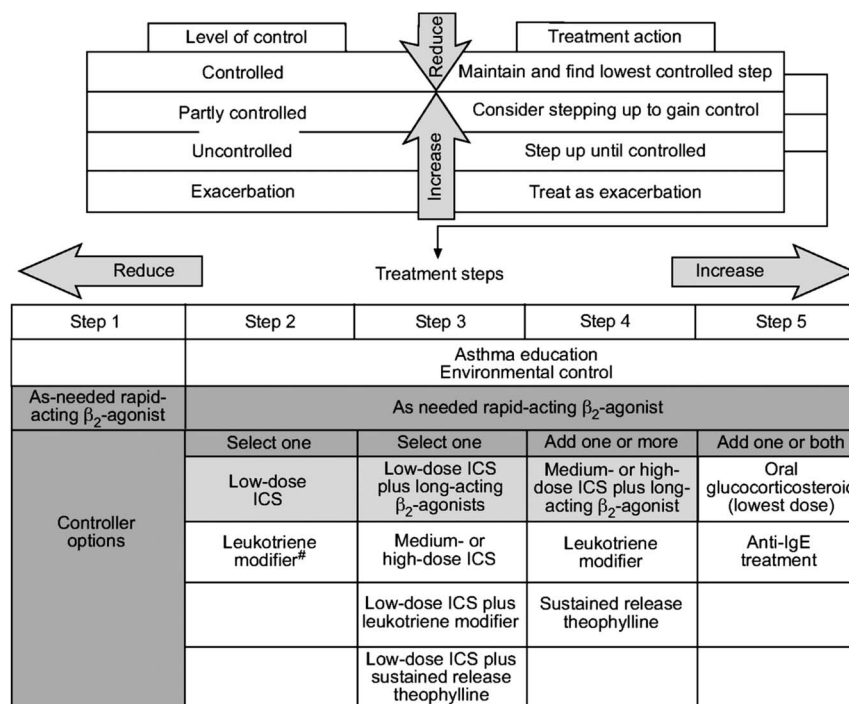
Step 4 preferred therapy is medium-dose ICS plus a LABA, increasing to high-dose ICS at step 5. At this point, omalizumab should also be considered for patients with allergies. The GINA guidelines advocate for expanded multi-drug regimens at step 4 as shown in Table 2.

Finally, at step 6, triple therapy with high-dose ICS plus LABA plus another agent such as an LTRA should be given a trial. However, once this step is reached, there are essentially no clinical trials to guide therapy and the recommendations are based solely on expert opinion.

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Agents from a multitude of pharmacologic classes, many of which will be discussed later, have been tested or are presently at various stages of

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Table 2. Treatment steps for patients 5 years of age to adults. From the GINA guidelines.

development. However, as of this writing, there are only 2 “modern” (ie, developed in the last few decades) therapeutic classes that have been approved by the Food and Drug Administration (FDA) for the treatment of asthma: LTRAs and a single monoclonal antibody, omalizumab. The newest “class” of treatment approved by the FDA is actually nonpharmacologic: bronchial thermoplasty (BT).

Leukotriene-receptor antagonists

Although the vast majority of medications approved for asthma in the recent past were essentially improvements on established classes (eg, ICS/LABA combinations), LTRAs, starting with zafirlukast²⁰ in 1997, were the first truly new class of FDA-approved medications since the cromones (cromolyn, nedocromil) in the 1960s. LTRAs are well established as controller medications for asthma and are included in both the NAEPP and GINA guidelines as previously discussed. Unlike the other commonly used controller medications, LTRAs are orally administered, and thus, the inherent problems with technique and compliance found with inhalers are avoided.^{21,22} Montelukast,²³ with once daily dosing, is one of the top 10 highest selling drugs in the United States, second only to fluticasone/salmeterol (Advair)²⁴ among asthma medications. They act by competitively antagonizing cysteinyl leukotriene receptor 1 (CysLT1), preventing the binding of leukotrienes D4 and E4.

There are 2 LTRAs commonly prescribed in clinical practice: montelukast (Singulair)²³ and zafirlukast (Accolate),²⁰ though montelukast, as noted above, is more widely used (a distantly related third compound, zileuton, works by a separate mechanism and is not generally recommended due to concerns about hepatotoxicity⁶). Montelukast is also the only agent in the class approved for patients under 5 years of age. Their chemical structures are shown in Figure 1.

Pharmacology/biochemistry of LTRAs

Cysteinyl LTs have a myriad of proven and theoretical roles in human diseases,^{25–28} which are outside the scope of this discussion and are reviewed elsewhere.²⁹ In human airways, they predominantly exert proinflammatory effects by binding to the CysLT1 receptor. These receptors are in airway smooth muscle cells and resident white blood cells.³⁰ Antagonism of CysLT1 results in a blunted bronchoconstrictor response to antigen.

In patients with asthma, the number of cells expressing CysLT1 is increased: Eosinophils, neutrophils, mast cells, macrophages, B lymphocytes, and plasma cells located in the bronchial mucosa all express this receptor, but T lymphocytes do not.³¹ These cells are not only found in increased number in asthma patients compared with healthy controls but multiply even further during acute exacerbations. They are expressed to a lesser extent in bronchial smooth muscle^{30,31} and also in the nasal mucosa (including the epithelium and

Table 3. Assessment of asthma control in patients age 12 to adult. From the NAEPP expert panel report 3.

Components of Control		Classification of Asthma Control (≥12 yrs of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV ₁ or peak flow	>80% Predicted/ personal best	60–80% Predicted/ personal best	<60% Predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	0 ≤0.75* ≥20	1–2 ≥1.5 16–19	3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see Figure 4 and 5 for treatment steps)		• Maintain current step. • Regular followups every 1–6 mo to maintain control. • Consider step down if well controlled for at least 3 mo.	• Step up 1 step and Reevaluate in 2–6 wk. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and Reevaluate in 2 wk. • For side effects, consider alternative treatment options.

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

Key. EIB, exercise-induced bronchospasm; ICU, intensive care unit.

inflammatory cells) of patients with various types of chronic rhinitis and atopy.^{32,33} It should be noted that a second receptor, CystLT2, is also highly expressed in the nasal mucosa and is not antagonized by the clinically available LTRAs.³⁴ The CystLT2 receptors are not as strongly expressed in human airways, however,^{35,36} and their role in the pathogenesis of asthma is unclear. They are expressed in bronchial eosinophils and macrophages,^{35,37} but until recently, there were no specific antagonists to these receptors with which to evaluate their contribution to human disease. Recent data indicate they may be the predominant mediators of the actions of LTs in the cardiovascular system.³⁸ The CystLT1 receptors are thought to be the most potent mediators of bronchoconstriction yet described.³⁹ In addition, they have been experimentally shown to

impair mucociliary clearance, increase mucus secretion, and increase microvascular permeability, leading to pulmonary edema.^{27,40} CystLT1 receptors have also been implicated in smooth muscle hyperplasia and airway remodeling.⁴¹

Adverse reactions and interactions

The most noteworthy adverse events that have been reported for this class are hepatic failure, an increased incidence of Churg–Strauss syndrome (CSS), and neuropsychiatric symptoms including suicide. The FDA has issued a warning for this last potential adverse event, though the evidence for a causal link with increased risk of suicide is limited.^{42,43} In fact, a study recently published noted a trend towards a lower risk of suicide.^{44a}

Table 4. Comparative doses for inhaled corticosteroids.

Drug	Low daily dose			Medium daily dose			High daily dose		
	Child 0–4 yrs of age	Child 5–11 yrs of age	≥12 yrs Of age and adults	Child 0–4 yrs of age	Child 5–11 yrs of age	≥12 yrs Of age and adults	Child 0–4 yrs of age	Child 5–11 yrs of age	≥12 yrs Of age and adults
Beclomethasone, HFA, 40 or 80 µg/puff	NA	80–160	80–240	NA	>160–320	>240–480	NA	>320	>480
Budesonide DPI, 90, 180, or 200 µg/inhalation	NA	180–400	180–600	NA	>400–800	>600–1200	NA	>800	>1200
Budesonide inhaled: inhalation suspension for nebulization (mg)	0.25–0.5	0.5	NA	>0.5–1.0	1.0	NA	>1.0	2.0	NA
Flunisolide: 250 µg/puff	NA	500–50	500–1000	NA	1000–1250	>1000–2000	NA	>1250	>2000
Flunisolide HFA 80 µg/puff	NA	160	320	NA	320	>320–640	NA	>640	>640
Fluticasone: HFA/MDI: 44, 110, or 220 µg/puff	176	88–176	88–264	>176–352	>176–352	>264–440	>352	>352	>440
DPI: 50, 100, or 250 µg/inhalation	NA	100–200	100–300	NA	>200–400	>300–500	NA	>400	>500
Mometasone DPI: 200 µg/inhalation	NA	NA	200 µg	NA	NA	400 µg	NA	NA	>400 µg
Triamcinolone acetone: 75 µg/puff	NA	300–600	300–750	NA	>600–900	>750–1500	NA	>900	>1500

From the NAEPP expert panel report 3.

The CSS, also known as allergic granulomatosis and angiitis, is an antineutrophil cytoplasmic antibody associated small vessel vasculitis. Both peripheral eosinophilia and asthma are hallmarks of the disease.^{44b} This syndrome is of particular note, as many asthma therapies from different classes have also been implicated as potential causes of CSS⁴⁵: high-potency ICSs such as fluticasone (alone or in combination with LABA), LTRAs, and omalizumab.⁴⁶ LTRAs have arguably been the most closely associated and studied over the past decade.⁴⁷

The traditional view, termed the *formes frustes* of CSS, is that the CSS is a preexisting condition that had been unknowingly suppressed by oral steroid use in a patient with severe asthma. Once a new therapy allows steroids to be tapered off, the CSS becomes “unmasked” and manifests clinically.^{46,48–50} In 3 of the original 4 reported cases,⁴⁸ oral steroids were tapered off without the substitution of a different agent. In subsequent case reports or series, patients were started

on an LTRA before the diagnosis of CSS, leading to the question of causality. This remains controversial.^{47,51,52}

Zafirlukast and montelukast are metabolized by the Cytochrome P450 (CYP450) system and thus have a number of potential drug–drug interactions. The most noteworthy interaction of either LTRA is that of zafirlukast with warfarin, as zafirlukast increased the prothrombin time by 35% in one drug interaction study.⁵³ Montelukast, on the other hand, was shown not to interact significantly with warfarin.⁵⁴

The most potent effect of montelukast in vitro was on the CYP450 subgroup CYP2C8.⁵⁵ However, drug–drug interaction studies, performed using zafirlukast and montelukast with pioglitazone and rosiglitazone, commonly used examples of CYP2C8 metabolized drugs, showed that this effect did not occur in vivo.^{56,57}

Montelukast and zafirlukast are both pregnancy category B. Zafirlukast should be taken on an empty stomach, at least 1 hour before eating. Montelukast,

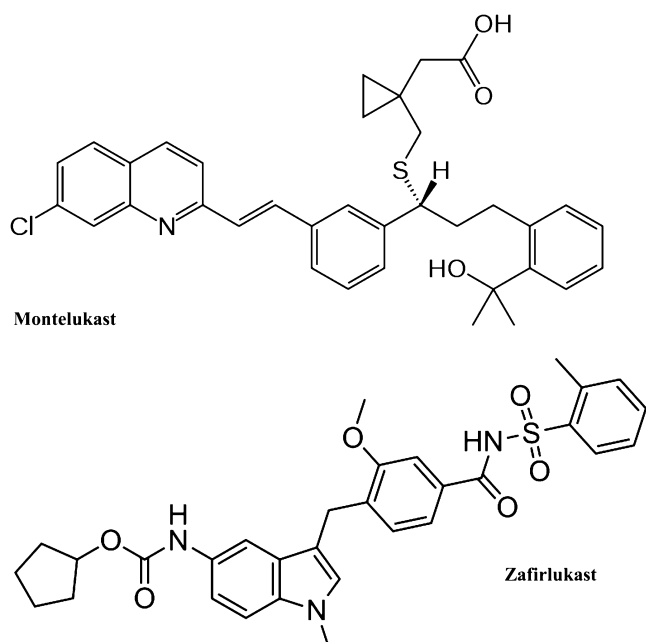


FIGURE 1. Chemical structures of leukotriene receptor antagonists. Montelukast. Zafirlukast.

however, can be taken without respect to meals. For example, montelukast is available in a granular formulation for administration to infants and small children (eg, dissolved in infant formula or sprinkled on foods such as applesauce).

Clinical use

As previously discussed, LTRAs are recommended in the NAEPP guidelines as alternate therapy at steps 2 and above for all patients, and a preferred agent at step 3 for children ages 5–11 years already on ICS. Again, montelukast is the only LTRA approved for children under 5 years of age and is additionally a ‘preferred’ add-on medication at steps 4 and above in that population. These recommendations are based largely on the following evidence:

Ostrom et al⁵⁸ compared inhaled fluticasone with oral montelukast in a randomized, double-blinded trial in 342 children ages 6–12 years of age. Fluticasone was statistically superior to montelukast in essentially every outcome measured, at only one-third the cost per patient. The Pediatric Asthma Controller Trial (PACT)⁵⁹ was a 3-armed study comparing twice-daily fluticasone alone, montelukast alone, or the “PACT combination” of fluticasone once daily plus salmeterol twice daily (this combination was the study drug). Twice daily fluticasone was statistically superior to montelukast monotherapy in all measured outcomes. The “PACT combination” was superior to montelukast

in the primary-end point of asthma control days but not many secondary end points. A recent follow-up analysis of the data from this trial also revealed that compared with montelukast, fluticasone was both lower in total cost and more cost effective in all subgroups studied.⁶⁰

In adults, the Mild Asthma Montelukast versus Inhaled Corticosteroid (MIAMI)⁶¹ trial compared low-dose fluticasone with montelukast in adults with mild persistent asthma. Fluticasone gave significantly better results, especially in those patients with greater baseline severity of disease.

In the Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy study,⁶² adult patients who were not well controlled on ICS monotherapy (800 µg/d of budesonide) were randomized to either doubling the dose of ICS or addition of montelukast, the first trial to examine these 2 options head to head. There was no difference in efficacy between the 2 arms.

Finally, in the first randomized controlled trial (RCT) to directly compare LTRAs with LABAs, Busse et al⁶³ compared zafirlukast and salmeterol. Roughly 80% of the patients in each group were on concomitant ICS therapy. The patients in the salmeterol group had statistically significantly less use of albuterol and greater improvement in spirometry and reported symptoms than those in the zafirlukast group. Subsequent trials and multiple Cochrane reviews^{64,65} have confirmed these findings.

Current guidelines do not recommend LTRAs as a preferred first-line controller agent in any population.^{5,6} Instead they are recommended as add-on or alternative therapy, with the conventional wisdom holding that ICS are the mainstay of asthma controller therapy and that addition of a LABA to ICS was likely a more effective approach overall in patients who required >1 controller medication.^{65–68} However, a recent pair of randomized trials by Price et al,⁶⁹ challenge this thinking. The intent of these so-called pragmatic trials was to demonstrate that under “real world” conditions (ie, outside the confines of a tightly controlled RCT), LTRAs were equivalent not only to the addition to LABA to an ICS (the “Add-on therapy trial”), but also equivalent to ICS as first-line controller therapy (“First line controller trial”). The primary outcome of both trials was the score on the Mini Asthma Quality of Life Questionnaire. Although both trials met their primary outcome at 2 months, they approached but did not meet the criteria for equivalence at 2 years. Secondary outcomes were not significantly different between the 2 groups. Although acknowledging the inherent limitations of pragmatic trials, the authors concluded that based on their

results, LTRAs could be considered equivalent to both first line ICS or add-on LABA, as "caution should be applied in extrapolating results from RCT's to the broad population ... treated in the community setting." It has previously been suggested that adherence to oral therapies are generally expected to be higher due to patient preference,⁷⁰ and earlier "real-world" trials such as the Montelukast in Chronic Asthma (MONICA) study have also given positive results.⁷¹

Finally, the addition of LTRAs to standard care in the acute setting has yielded some promising results, at least in adult patients. High-dose (160 mg) oral zafirlukast given in the acute setting was shown to significantly increase the FEV1 compared with placebo. There was a trend toward a decreased need for "extended care" [defined as an emergency department (ED) stay longer than 4 hours or hospital admission], but this effect did not reach significance despite a 34% relative risk reduction.⁷²

Two studies by Camargo et al^{73,74} evaluated the use of intravenous montelukast in the emergency department. In the 2003 study, patients were randomized to standard therapy (albuterol plus or minus 60 mg of oral prednisone) plus either placebo or intravenous montelukast. The patients randomized to montelukast had a statistically significant improvement in spirometry and were also significantly less likely to require treatment with corticosteroids. There was no difference in the number of patients experiencing treatment failure, which was defined analogously to "extended care" in the zafirlukast study above.

In the 2010 study, the treatment protocol was altered and all the patients received oral corticosteroids immediately after the dose of montelukast (or placebo) was given. Again, the improvement in FEV1 was statistically significant between the 2 groups. However, as with the previous trials, no difference in the rate of treatment failure or total dose of nebulized medications was shown. Interestingly, however, when only the US sites in the study were considered, a statistically significant decrease in the need for hospitalization was seen. Other than usual site-to-site variation in admission criteria and various nonclinical factors, the authors did not hypothesize as to why this was the case. Regardless, they felt that LTRAs should be given serious consideration as adjunctive treatment for acute asthma exacerbations in adults.

The data on pediatric populations, however, are less encouraging. A trial evaluating the use of intravenous montelukast with a design very similar to the Camargo trials, but in patients aged 6–14 years, failed to show any benefit in either the primary or secondary outcomes.⁷⁵ Another study evaluating the use of oral montelukast for acute asthma in 6- to 14-year-olds was

terminated early after an interim analysis demonstrated that there was no benefit.⁷⁶ In a significantly larger RCT evaluating the addition of oral montelukast to standard therapy in 2- to 15-year-olds there was no statistically significant difference between the 2 groups in any outcome measure, with there actually being a slight trend favoring the placebo arm.⁷⁷ Other trials have similarly shown a lack of benefit.⁷⁸

At present, neither the NAEPP nor GINA guidelines list LTRAs as accepted adjunctive treatments for acute exacerbations of asthma.^{5,6} However, the NAEPP guidelines state that although there is insufficient evidence to make recommendations, "Intravenous LTRAs could provide another pathway to rapid bronchodilation during impending respiratory failure," such that intubation could theoretically be avoided. Due to the mixed results just discussed, it does not seem at this time that anyone is actively pursuing FDA approval for IV LTRAs, nonetheless.²

Patient selection

In many patients, LTRAs can significantly improve asthma control, whereas others respond poorly. There is additionally a small subset of patients, who have an excellent response to LTRAs, and in whom they are more effective than even ICS.⁷⁹ The central dilemma surrounding this class is identifying responders and nonresponders, a goal which no method (beyond the age-old practice of giving it to the patient and seeing how they do) has been successful, as the available data are inconclusive and often involve retrospective analysis of other trials: Some comorbidities or patient factors such as age or concomitant allergic rhinitis (for which montelukast is also therapeutically used) were associated with a better response in a post hoc subgroup analysis of the open-label MONICA study,⁸⁰ for example. The excretion of LTE4 in the urine had been explored both as a marker of disease activity in the early stages of development of the class,^{81,82} and a possible predictor of response to LTRA therapy. It had also been suggested by data from the CLIC trial (Characterizing the Response to an LT Receptor Antagonist and an ICS) that exhaled nitric oxide (FeNO, a well-studied marker of airways inflammation⁸³) could predict which patients would respond more to ICS than LTRA. More recently, it was concluded after analysis from the combined data of the PACT and CLIC trials⁸⁴ that there was no demographic factor that reliably predicted response to montelukast (in contrast to the MONICA results). However, a higher ratio of urinary LTE4 to FeNO was associated with a better response to oral montelukast compared with inhaled fluticasone. Although the American Thoracic Society has issued a practice guideline stating that FeNO is useful in the

prediction and monitoring of response to ICS,⁸³ no such recommendation has been made regarding urinary LTE4 or LTRAs by any large organization to date.

Until expert consensus can be reached, or a randomized trial corroborates these associations with either patient characteristics or biomarkers, simple therapeutic trials and patient/physician preference will continue to drive the use of LTRAs. For acute asthma, oral therapy can be considered as an adjunct for severe asthma exacerbations as per the guidelines⁶ but certainly not as an alternative to standard therapy.

Omalizumab

Omalizumab (Xolair) represents the second recently developed novel therapy for asthma, and is the first biologic agent approved by the FDA for use in asthma.⁸⁵ It is a recombinant humanized monoclonal antibody directed against immunoglobulin E (IgE).

Pharmacology/biochemistry of omalizumab

Omalizumab acts at the same high-affinity binding site (known as FcεRI) at which IgE interacts with mast cells and basophils.⁸⁶ Cell-bound IgE forms crosslinks when exposed to allergens. This leads to degranulation of the mast cell or basophil, releasing histamine and other proinflammatory molecules, precipitating bronchospasm in the asthmatic patient. Importantly, this interaction is not thought to be inhibited by corticosteroids.⁸⁷

The FcεRI receptor is located in the IgE constant region. Therefore, omalizumab binds to all types of IgE, regardless of antigen specificity. It also binds only to free IgE molecules, and not those that have already become activated; this precludes any usefulness in the acute setting. Once circulating IgE levels are diminished, there is a measurable decline in sputum and tissue eosinophil counts, along with those of other proinflammatory lymphocytes and the expression of interleukin-4 (IL-4). The FcεRI receptor also becomes downregulated. If therapy is stopped, serum IgE and receptor activity return to previous levels fairly quickly, but there is no evidence of a rebound phenomenon.^{86,88,89}

Adverse reactions and interactions

The most common troublesome side effect reported from omalizumab therapy is injection-site reaction. Hypersensitivity reactions (see below as well) have been the subject of much debate, as there were concerning reports of anaphylaxis in the early trials,⁹⁰ and the FDA has issued a “black box” warning for such reactions.⁸⁵ A joint task force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and

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Immunology, has issued periodic reports, the most recent of which was published in 2011.⁹¹ They noted that such reactions occurred in approximately 0.09% of patients taking the drug. They continued to recommend that patients being administered omalizumab should be treated with the following precautions: (1) informed consent related to these risks, (2) patient education on the signs and symptoms of anaphylaxis, (3) omalizumab patients should have an epinephrine injector (“epi-pen”) on hand for 24 hours postadministration, (4) patients should be observed for 2 hours after the first 3 injections, then for 30 minutes after subsequent injections (or less based on physician judgment).

As with LTRAs, there have been case reports of the CSS associated with use of omalizumab, but an analysis of the 37 cases reported to the manufacturers safety database noted that less than half of them met criteria for diagnosis of the disease, and there was little, if any, evidence for a causal relationship beyond the “unmasking” of preexisting CSS as corticosteroid therapy was being tapered.⁴⁶ Another reported adverse effect of questionable significance is an increased rate (an odds ratio of 2.2) of helminthic infections noted in a trial from Brazil, in patients at high risk for such infections. Of note, the 95% confidence interval was wide and “crossed one” (0.94–5.15); in other words, the likelihood of such infections in patients on omalizumab could have been anywhere from slightly less likely to 5 times more likely than in patients not on therapy.^{92,93}

There was some suggestion in pooled data from initial trials that there might be an increased risk of malignancy associated with omalizumab therapy, though it could be considered a stretch to attribute a causal relationship of this type in trials that lasted a year or less.⁸⁶ Interestingly, when the data were analyzed more closely, the number of cancers in the omalizumab groups in these trials actually matched that of the general population, whereas the placebo groups had an unexplained cancer rate only one-third of what would be expected.⁹⁴

Omalizumab is pregnancy category B. As a monoclonal antibody, no drug–drug interactions are associated with its use.

Clinical use

Three pivotal phase 3 trials led to the approval of omalizumab for the treatment of allergic asthma. In all 3 studies, the patients were on monotherapy with moderate or high-dose ICS (beclomethasone propionate) alone. During the first 16 weeks of therapy, the dose of ICS was kept stable, and then tapered over the subsequent 8 weeks as tolerated. Busse et al⁹⁵ randomized 525 patients aged 12–75 years to either placebo or

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subcutaneous omalizumab every 2 weeks. Compared with placebo, there was a significant reduction in asthma exacerbations (14.6% vs. 23% in the omalizumab and placebo groups, respectively). The patients were more likely to be able to tolerate a taper of the ICS dose, and more patients were able to be taken off ICS as well. Omalizumab was also significantly better in terms of improvements in spirometry, symptom scores, and rescue inhaler use. There was no difference in adverse events between the 2 groups, and no patients experienced hypersensitivity-type reactions. The other adult phase 3 trial⁹⁶ gave strikingly similar results.

In the pediatric phase 3 trial, 334 patients from 6 to 12 years of age on moderate or high dose ICS were randomized to omalizumab or placebo, with an ICS tapering schedule as in the other 2 trials.⁹⁷ However, the results were slightly less impressive: The difference in exacerbations was not statistically significant until after 16 weeks, with 18% of patients in the omalizumab group experiencing an exacerbation compared with 38.5% with placebo. There were significant reductions in ICS and rescue inhaler use. Children in the omalizumab group also missed significantly fewer days of school. Finally, unlike in the adult trials, there were more study drug-related adverse events in the omalizumab (6% vs. 0.9%) group, and there was evidence of hypersensitivity reactions (primarily urticaria). One patient in the omalizumab group was discontinued from the study due to recurrent urticarial reactions. A more recent and significantly larger RCT (576 patients completed the trial) looking at omalizumab use in the same age group over 52 weeks (24 weeks of fixed ICS, followed by 28 weeks of ICS taper) reduced the exacerbation rate by 43% compared with placebo ($P < 0.001$).⁹⁸ The difference actually increased as the study progressed, indicating a treatment effect over time.

Arguably one of the most important studies supporting the clinical utility of omalizumab, the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) trial⁹⁹ examined its efficacy in patients with poor asthma control despite step 4 therapy by the 2002 GINA guidelines. The primary end point was the rate of "clinically significant" exacerbations, requiring treatment with systemic corticosteroids. After post hoc analysis accounted for an unexpected baseline difference in disease severity between groups, the rate of exacerbations was reduced by 26%, which did reach significance ($P = 0.042$). The number needed to treat for 1 year to prevent 1 exacerbation was 2.2. The rate of hospital admissions was also cut in half.

The major criticism of the aforementioned pivotal phase 3 trials is that patients were suboptimally treated with moderate or high-dose ICS monotherapy,⁹⁷

and indeed many of these trials studied patients who may very well not qualify for omalizumab based on current guidelines.⁵ Here, however, all study patients were on GINA step IV therapy with high-dose ICS and LABA, and >20% of the patients were also on maintenance oral corticosteroids in addition to the high-dose ICS. The results of the INNOVATE trial can best be evaluated by considering the severity of disease in the population studied. Although omalizumab has not been compared head-to-head with other add-on controller medications such as LTRAs, the INNOVATE trial certainly demonstrates its efficacy in patients on otherwise maximal therapy. Few, if any, other agents have comparable data in patients with such difficult-to-control asthma.

However, as with biologic agents used for other diseases such as rheumatoid arthritis, much of the debate over its use centers not on efficacy but on cost effectiveness. Sullivan and Turk¹⁰⁰ evaluated 6 prior cost-effectiveness analyses, noting that 4 of the 6 provided evidence that it was cost effective. In the 2 studies that demonstrated that it was not, it was estimated that each symptom-free day from omalizumab came at a cost of \$523,¹⁰¹ and the cost per quality adjusted life year was a staggering \$821,000.¹⁰² However, the authors of the former analysis nonetheless concluded that in patients with particularly severe asthma at high risk of hospitalization (eg, ≥ 5 times in the past year), omalizumab was likely cost effective.

Noting methodological issues in many of the cost-effectiveness analyses, particularly in the areas of patient selection and response criteria, Sullivan and Turk concluded that omalizumab was cost effective in appropriately selected patients (ie, those who met GINA steps 4/5 criteria and responded to the drug by 16 weeks) and compared favorably with the costs of biologic agents for other diseases such as rheumatoid arthritis or Crohn disease.

The most recent Cochrane review of omalizumab also cited the high cost as a significant concern in questioning its clinical usefulness but refrained from making any direct statement about cost effectiveness.¹⁰³ They, too, noted the need for appropriate patient selection.

Patient selection

Pooled analysis of data from the 2 adult phase 3 trials¹⁰⁴ identified 3 factors most predictive of response: need for emergency treatment of asthma in the past year, use of higher doses of ICS, and lower FEV1 (in essence, the patients with the most severe asthma). In addition, they demonstrated that most of the patients (87%) who showed a response to the drug at 16 weeks had done so by 12 weeks. However, only 61% had by 4

Table 5. FDA-approved dosing tables for omalizumab.

Omalizumab Doses (milligrams) Administered SQ Injection Every 4 Wks (≥ 12 Yrs of Age)					
Baseline IgE IU/mL	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
30–100	150	150	150	150	300
>100–200	300	300	300	300	
>200–300	300	Administered Every 2 Wks			

Omalizumab Doses (milligrams) Administered SQ Injection Every 2 Wks (≥ 12 Yrs of Age)					
Baseline IgE IU/mL	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
>100–200	Administered Every 4 Wks				225
>200–300		225	225	225	300
>300–400	225	225	300	300	
>400–500	300	300	375	375	
>500–600	300	375			
>600–700	375	Do Not Dose			

weeks; patients should therefore be given an extended therapeutic trial of 12–16 weeks before assessing for a positive therapeutic response.

Omalizumab is given as a subcutaneous injection every 2–4 weeks, based on body weight and IgE levels. The total is given biweekly if doses >300 mg are required, as summarized in Table 5. As noted previously, it is recommended at step 5 of both the GINA and NAEPP guidelines.^{5,6} The FDA labeling is for patients with “moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who’s symptoms are inadequately controlled with inhaled steroids.”⁸⁵ In the United Kingdom, patients must be on high-dose ICS, and in many parts of Europe, a LABA as well. In practice, this generally corresponds to patients who meet (all) the following criteria: (1) ≥12 years of age, (2) moderate to severe persistent asthma, (3) inadequate control with ICS (regional variations as noted above), (4) skin or serum allergen testing positive for a year-round allergen such as dust mites,

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molds, animal dander, etc, and (5) an elevation in total serum IgE.

Of note, the recommended range of IgE upon which omalizumab dosing is based lies between 30 and 700 IU/mL (Table 5). This is thought to be the range in which omalizumab has sufficient activity to be effective. However, many centers, including our own, have successfully treated patients with levels above this range; we do not necessarily consider there to be a true ‘ceiling’ on IgE levels above which omalizumab will not be beneficial. In such cases, we use the maximum approved dose of 375 mg every 2 weeks, and monitor for response to therapy as with any other patient.

Bronchial thermoplasty

BT is a nonpharmacologic therapy approved by the FDA in 2010. It is a bronchoscopically performed procedure in which controlled thermal energy (in essence, radiofrequency ablation, Figure 2) is applied to the bronchial wall during 3 serial procedures.¹⁰⁵ The applied energy results in a reduction of airway smooth muscle mass, with the goal of reducing airway contractility and obstruction of airflow. Up to 5-year follow-up data are available demonstrating no significant adverse sequelae at that interval.^{106,107}

Adverse reactions and interactions

All the studies on BT to date have demonstrated an increased risk of asthma exacerbation (and other respiratory complications) in the postprocedure period. For

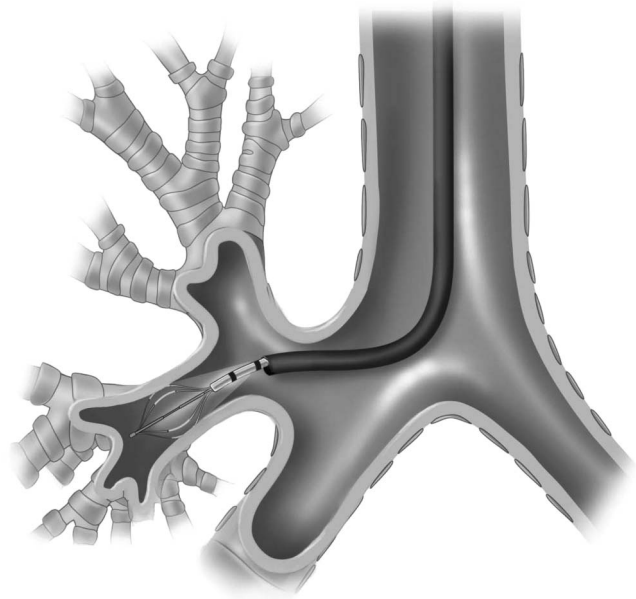


FIGURE 2. BT (image provided courtesy of Boston Scientific Corporation).

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example, 5% of BT patients (compared with 2% in the sham procedure group) in the Asthma Intervention Research 2 (AIR2) trial were hospitalized for “worsening of asthma,” most of them within one day of the procedure.¹⁰⁸ Therefore, BT is not appropriate if the patient has experienced an asthma exacerbation within the prior 4 weeks. Chronic oral corticosteroid therapy is not a contraindication to the procedure, provided the dose has been stable for the same period of time. As with any endoscopic intervention, anticoagulation should be held for the procedure, but no asthma medications need be.

Clinical use

A small early RCT, the Research in Severe Asthma (RISA) trial,¹⁰⁹ demonstrated a short-term increase in asthma-related morbidity but suggested long-term improvement in symptoms. The Asthma Intervention Research (AIR) trial¹¹⁰ was substantially larger and randomized patients in a nonblinded fashion to BT plus ICS/LABA or ICS/LABA alone. Again, there was a short-term increase in respiratory adverse events related to the invasive BT procedure, but compared with the control group, there was a decrease in the incidence of mild exacerbations (the primary end point) compared with baseline. There was also a significant improvement in morning peak expiratory flow (PEF), AQLQ, and ACQ scores compared with controls.

Five-year follow-up data from both trials demonstrated no significant difference in adverse events from years 2 to 5 for the thermoplasty group compared with controls.^{106,107} No follow-up histologic data have been reported from any BT trial.

The pivotal AIR2 trial randomized patients to either BT or a sham procedure.¹⁰⁸ In this study, the patients randomized to the sham procedure had a surprisingly high improvement in AQLQ score from baseline (double that which is considered clinically significant, in fact), which was the primary end point. Although patients randomized to BT did have an even greater improvement, the difference between groups was less than the accepted clinically important absolute score change of 0.5. There was no difference in any of the secondary end points, but there was a statistically significant decrease in ED visits and rate of severe exacerbations. An accompanying editorial¹¹¹ notes that these outcomes were “not considered in the rationale and hypothesis of the study.” It also points out that there are no data on the histologic changes induced by the procedure and that simply placing patients in a strict and monitored study protocol, as was the case in the sham group, was more than sufficient to result in a marked improvement in AQLQ scores.

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Nonetheless, the recently published 2-year follow-up data on patients randomized to the BT group in the AIR2 trial (there was no long-term enrollment of the control group due to ethical concerns) demonstrated a persistence of the therapeutic effect as evidenced by a similar or improved rate of severe exacerbations, hospitalizations, and stable FEV1 values from years 1 to 2.¹¹² A 5-year follow-up is planned, but, again, no histologic data have been collected thus far.

Patient selection

A recent pair of point-counterpoint editorials debated the yet-to-be defined role of BT in current practice. The “pro” editorial, coauthored by members of the AIR study groups, advocated for BT to be used in patients with “truly difficult to control” asthma as add-on therapy at steps 5 or 6.¹¹³ The counterargument, by Michaud and Ernst,¹¹⁴ cautioned that BT “is not yet ready for prime time,” and at this point should only be performed at research centers that will adhere to strict protocols and “all patients ... treated with the procedure must be included in databases that allow for continued evaluation of efficacy and long-term safety.”

BT is FDA approved for patients with severe persistent asthma inadequately controlled on ICS and LABA, but no specific guidelines have been established. However, the criteria used in the AIR2 trial are commonly used in lieu of them (Table 6).¹⁰⁸ In simplified terms, patients can be considered to be appropriate candidates if their asthma is not well controlled despite being on step 4–5 therapy.

Table 6. Notable BT appropriateness criteria from the AIR2 trial.

Regular use of maintenance ICS and LABA
1000 µg/d Of eclomethasone or equivalent
100 µg/d Of salmeterol or equivalent
Other controller medications, including stable oral corticosteroids (<10 mg/d) but excluding immunosuppressants such as methotrexate, were allowed
Non-life threatening or uncontrolled asthma
Stable use of asthma medications for ≥4 wks
<3 Hospitalizations for asthma or pneumonia in the past year
<4 Pulses of oral corticosteroids in the past year
At least 2 d of asthma symptoms during that period
Nonsmoker
No smoking in the past year
<10 Pack-year history
Documented airway hyperresponsiveness
Baseline AQLQ 6.25 or lower

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NOVEL THERAPIES FOR ASTHMA—NOT FDA APPROVED

Treatment of asthma remains a fertile ground for research, and a multitude of new therapies are being developed. Monoclonal antibodies and other biologics, various mast cell inhibitors, antifungal therapy, and novel anti-inflammatories are all at various stages of development.^{115–117} There have also been some intriguing data involving the role of vitamin D supplementation in asthma, and randomized trials are ongoing.¹¹⁸

BIOLOGIC THERAPIES OTHER THAN OMALIZUMAB

Multiple cytokines and their receptors have been evaluated as potential therapeutic targets in asthma. Monoclonal antibodies directed at key mediators of asthmatic inflammation are on the “cutting edge” of asthma research.² Agents developed for other autoimmune diseases are also being studied: for example, tumor necrosis factor- α antagonists developed for rheumatoid arthritis. These will be discussed in a later section. The following is an overview of some of the many investigational biologic therapies being specifically developed for asthma.

Interleukin targeted therapy

The role of the ILs in the pathogenesis of asthma and other disease have been extensively studied,¹¹⁹ and agents specifically targeting IL-4, -5, -9, and -13 have been or are being explored as possible therapies for asthma.¹¹⁶ Daclizumab, an intravenous anti-IL-2 antibody approved for prevention of renal transplant rejection, has been evaluated in a single RCT in patients with poor asthma control despite ICS, with positive results.¹²⁰ However, the IV route of administration makes this agent impractical and no studies evaluating subcutaneous dosing have been reported.¹²¹

IL-4 and -13 act via the same receptor complex (IL-4 α) and may have multiple common pathways and mechanisms of action.¹²² Several biologic therapies targeting IL-4 have been studied (including a soluble IL-4 receptor, altrakincept,¹²³ and pascolizumab, a monoclonal anti-IL-4 antibody¹²⁴), but failed to show efficacy. However, a recombinant human variant of IL-4, pitrakinra, continues through phase II trials in both inhaled and subcutaneous formulations.¹²⁵ It acts as a competitive inhibitor of the IL-4 α receptor itself, thereby lowering the activity of both IL-4 and IL-13. It has been theorized that the redundancy of the IL-4/IL-13 complex may be to blame for the failure of

IL-4-specific therapies. In 2 phase 2a trials, pitrakinra decreased the bronchoconstrictive response to an inhaled allergen challenge compared with placebo. The difference from placebo was statistically significant only for the *nebulized* route of administration.¹²⁶ Tralokinumab (CAT-354),¹²⁷ lebrikizumab, IMA-638, and QAX 576 are monoclonal antibodies specific for IL-13.¹²¹ They are in phase 2 trials for the treatment of both chronic obstructive pulmonary disease (COPD) and asthma.

IL-5 is a key cytokine in the differentiation and maturation of eosinophils. IL-3 and GM-CSF (granulocyte-macrophage colony-stimulating factor) also play a role, but IL-5 is more specific for eosinophils. IL-5 also modulates histamine release by basophils.¹²⁸ Reslizumab and mepolizumab are humanized monoclonal antibodies directed at IL-5, and both are administered by subcutaneous infusion. Early studies on anti-IL-5 therapy demonstrated limited efficacy in unselected patients.^{129–131} However, in patients with increased sputum eosinophils, mepolizumab administration resulted in a statistically significant reduction in AQLQ scores and exacerbations, and both sputum and peripheral eosinophil counts compared with placebo.¹³² In another RCT of mepolizumab, which specifically enrolled patients with refractory asthma and eosinophilic airway inflammation, there was a significant reduction in severe exacerbations requiring oral prednisolone and sputum and blood eosinophilia, but no change in FEV1.¹³³ A recent trial evaluating reslizumab compared with placebo in non-steroid-dependent patients with sputum eosinophilia¹³⁴ demonstrated significant, albeit mild, improvement in FEV1 and a nonsignificant trend toward fewer exacerbations and higher AQLQ scores. Post hoc analysis noted greater improvement in patients with nasal polyps, such that the difference in AQLQ scores became statistically significant. An editorial¹³⁵ postulated that these trials may be the first tentative steps toward therapy directed by specific patient phenotypes.

IL-9 is thought to play a role in asthma pathogenesis primarily by inducing the proliferation and activity of mast cells.¹³⁶ MEDI-528, an anti IL-9 monoclonal antibody, is currently in phase 2 trials of both subcutaneous and intravenous formulations. The initial data has demonstrated only modest success.^{137,138}

Anti T-lymphocyte therapies

T-helper type 2 (Th2) lymphocytes are thought to play a central role in asthma pathogenesis. The anti-IL agents just discussed (specifically anti-IL-4, -5, and -13) block some “downstream” effects of Th2 cell activity. Critically, many existing asthma therapies, *including* ICS,

have limited direct effects on Th2-mediated inflammatory processes, especially in regard to activation and differentiation of the Th2 cells themselves. In fact, in vitro studies have shown that corticosteroids may guide the differentiation of T-lymphocytes toward the Th2 phenotype.¹³⁹

A multitude of other potential therapeutic targets involving Th2 cells have been identified. Several are in varying but early stages of development, although only a few have published human data at this point¹³⁹: CTRH2 (Chemoattractant receptor homologous molecule expressed on Th2 cells) is a G-protein-coupled receptor expressed on a number of inflammatory cells, especially Th2 lymphocytes and eosinophils.

A recently published double-blind phase 2 RCT¹⁴⁰ of OC000459, an oral highly selective antagonist of the CTRH2 receptor, demonstrated statistically significant decreases in AQLQ scores and (only in the per-protocol group) significant increases in FEV1. Of note, these patients had moderate persistent allergic asthma but were not on an ICS.

Therapies directed at Th2 lymphocytes are in the early stages of development and the ultimate benefit of such treatment compared with conventional therapy is yet to be determined.

Immunomodulators

OM-85 (Broncho Vaxom) is an immunostimulant derived from several different pathogenic bacteria of the upper respiratory tract. It has been shown to decrease the number of exacerbations in children (ages 1–6) with a history of wheezing attacks but has not been extensively studied in adults.¹⁴¹

MISCELLANEOUS AGENTS

Any number of agents approved for other diseases have been or are being explored as potential therapies for asthma, with varying success. Inhaled anticholinergic agents are perhaps the most noteworthy examples and will be discussed later.

Many of the other classes of drugs have been found to have limited efficacy or unfavorable risk:benefit ratios but may illustrate therapeutic targets for future drug development, as there is usually a plausible, usually anti-inflammatory, biologic mechanism of action in the existing drug that can potentially be exploited by a more specifically targeted therapy. For example, the inhibition of mast cells by loop diuretics,¹¹⁷ or the antiinflammatory properties of thiazolidinediones (TZDs). TZDs, widely used in the treatment of diabetes, have antiinflammatory effects via their action as peroxisome proliferator-activated receptor gamma

antagonists. Pioglitazone¹⁴² was first suggested for treatment of asthma following a small case series.¹⁴³ An RCT with rosiglitazone, treating smokers with asthma, showed small improvement in lung function compared with ICS.¹⁴⁴ There is at least 1 NIH-sponsored phase 2 trial of pioglitazone currently recruiting patients. Given the ongoing and serious controversy regarding the cardiovascular risk profiles of TZDs¹⁴⁵; however, there may be little enthusiasm for future research in this area.

Other notable agents in this category include inhaled furosemide,^{146,147} inhaled heparins,¹⁴⁸ colchicine,¹⁴⁹ and primarily as possible steroid-sparing agents, cyclosporine A,¹⁵⁰ mycophenolate,^{151,152} methotrexate,^{153,154} IVIG,^{155,156} and gold.^{157,158}

Tumor necrosis factor- α antagonists

Tumor necrosis factor-alpha (TNF- α) is an important cytokine in the innate immune response and has several possible roles in the pathogenesis of asthma.¹⁵⁹ It is found in greater concentrations in the airways of asthmatic patients compared with controls,^{160,161} induces airway hyperresponsiveness and neutrophilia in nonasthmatic subjects,¹⁶² and directly induces histamine release from mast cells,¹⁶³ to name just a few.

Initially, there was a fair amount of enthusiasm about the potential of TNF- α inhibitors, with promising early results using etanercept.^{164–166} However, one of the larger and more widely cited early RCTs, which demonstrated significant benefit with infliximab,^{167,168} was later retracted.¹⁶⁹ In addition, the largest RCT to date, using golimumab, was stopped early due to serious adverse reactions including increased rates of malignancy and serious infections.¹⁷⁰ Given these data, the clinical usefulness of TNF- α inhibitors (and perhaps only etanercept) is currently thought to be limited and may only be helpful in a small, yet-to-be defined subset of patients.¹⁷¹

HMG-CoA reductase inhibitors

The HMG-CoA reductase inhibitors, or statins, are well established in the treatment of cardiovascular diseases. They are also being studied for a number of other diseases due to their anti-inflammatory properties.^{172,173} Some promising results in animal models and humans have been seen with these agents in asthma, including simvastatin^{174,175} and atorvastatin.^{176,177} In addition, three population-based retrospective studies of asthma patients on ICS have been published. All 3 demonstrated that concurrent statin use was independently associated with a lower risk of asthma related ED visits or hospitalizations.^{178–180} The most recent of the 3,¹⁷⁸ which analyzed 1500 patients

from a state Medicaid database, showed a nearly 50% reduction (odds ratio 0.55) in that end point. Multiple trials, including a small phase 3 RCTs of ICS plus simvastatin or placebo (NCT00792337), are ongoing or recently completed but have not yet published their results.¹⁸¹

Antireflux therapy

It has been widely hypothesized that gastroesophageal reflux (GERD), whether overt or silent, may contribute to asthmatic symptoms, and some open label or non-randomized trials support this.^{182–184} However, RCTs comparing treatment with a proton pump inhibitor to placebo in children with poorly controlled asthma did not demonstrate any meaningful clinical benefit.¹⁸⁵ In fact, the largest and most recent RCT not only demonstrated a lack of benefit, there was also an increased incidence of respiratory infections.¹⁸⁶ A large RCT in adults by many of the same investigators found a similar lack of efficacy, but without increased adverse events.¹⁸⁷ There was no difference between patients with symptomatic versus so-called “silent” GERD in either trial.

Anticholinergic agents

The use of anticholinergic agents is an interesting chapter in the history of asthma therapy. Currently, there are no FDA-approved anticholinergic drugs for use in asthma, as will be discussed below. However, at one time, they were considered first-line therapy: In a curious contradiction, no less an authority than Osler, in *The Principles and Practice of Medicine*,¹⁸⁸ suggested the use of so-called “asthma cigarettes.” These generally contained the leaves of one or more belladonna alkaloid-containing plants, which work via an anticholinergic mechanism. Other classic works from that era, such as those of Stedman and Cecil, carried similar recommendations.¹ In fact, asthma cigarettes were still recommended in Cecil’s *A Textbook of Medicine* until the 1950s.¹⁸⁹ However, by the 1970s, such therapies had fallen out of favor, and mention of belladonna alkaloids in any form had disappeared from that text.¹⁹⁰ With the introduction of longer-acting anticholinergics, there is renewed interest in this therapeutic class.

There are 2 commonly prescribed inhaled anticholinergic agents at present: ipratropium and tiotropium. Both are FDA approved for COPD and not asthma, though there are data to support their use in both. Ipratropium, a short-acting agent, either alone or as part of a combination inhaler with albuterol,¹⁹¹ is commonly used in EDs for acute exacerbations of asthma, and is included in the asthma guidelines as such.^{5,6} There are some data for its efficacy as a ‘rescue’ inhaler

as well,^{192,193} but it is usually reserved for that use only in patients who cannot tolerate albuterol due to tachyarrhythmias or other side effects.

Tiotropium (Spiriva) is an inhaled long-acting anticholinergic bronchodilator and is one of the cornerstone therapies for COPD.^{194,195} Although not FDA approved for use in asthma, recent RCTs have shown it to be an effective agent. The TALC (Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid) study demonstrated that addition of tiotropium to patients on low-dose-inhaled beclomethasone was superior to doubling the dose of the ICS. Adding tiotropium was also noninferior to adding a LABA (salmeterol) to the low-dose ICS.¹⁹⁶ A more recent placebo-controlled RCT demonstrated that tiotropium was superior to placebo when added on to ICS/LABA (with or without other agents such as LTRAs) in patients with severe uncontrolled asthma.¹⁹⁷ These results are perhaps not surprising given the aforementioned historical use of anticholinergic agents for asthma over the last 100-plus years.¹ However, as the current guidelines predate these studies, the use of tiotropium in asthma is not addressed therein.

Antimicrobial therapy

Both antibiotic and antifungal agents have been studied as adjunctive therapy in severe asthma.

Severe asthma with fungal sensitization is loosely defined as severe asthma despite standard therapy, with evidence of fungal sensitization (ie, by allergy testing), but without meeting criteria for Allergic Bronchopulmonary Aspergillosis.¹⁹⁸ The Fungal Asthma Sensitization Trial study¹⁹⁹ evaluated the use of itraconazole,²⁰⁰ versus placebo, in the treatment of patients with severe asthma with fungal sensitization. There was a statistically significant improvement with itraconazole in AQLQ score (the primary end point) and morning PEF and serum IgE levels. As fungal colonization was shown to be present in only a minority of patients, the authors postulated that there may be an additional immunomodulatory effect of itraconazole.

The use of antibiotics, and macrolides in particular, has been the subject of study for several years, primarily for acute exacerbations of asthma.²⁰¹ They have an established role in other pulmonary diseases: Azithromycin²⁰² is used commonly to slow the progression of disease and reduce the number of exacerbations in patients with cystic fibrosis. The mechanism of action is thought to be due primarily to a systemic anti-inflammatory effect, and not the drugs antimicrobial properties.^{203,204} A more recent RCT also demonstrated a reduction in the frequency of COPD exacerbations with daily use of azithromycin.²⁰⁵

These same effects suggest a possible role in the chronic treatment of asthma.²⁰⁶ Clarithromycin,²⁰⁷ another macrolide, has been shown to have similar properties. Clarithromycin improved quality of life and reduced the levels of inflammatory markers in the airways of asthmatic patients.²⁰⁸ Another RCT not only showed some benefit²⁰⁹ but also demonstrated no change in serum cortisol levels, indicating no change in the metabolism of endogenous steroids. This is somewhat in opposition to another proposed mechanism of action of clarithromycin in this context; multiple studies suggest that macrolides may inhibit the metabolism of exogenous corticosteroids, thus acting as a steroid-sparing agent, in a sense.^{210,211} A cochrane review similarly challenged this theory.²¹²

Finally, the use of macrolides in their intended function, that of an antibiotic, has also been studied. It has been suggested that *Mycoplasma pneumoniae* and *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* may play an under-recognized role in the pathogenesis of asthma.²¹³ One placebo-controlled RCT demonstrated that, in patients with stable asthma with proven colonization with one of these bacteria (by polymerase chain reaction), 6 weeks of clarithromycin treatment resulted in a statistically significant increase in FEV1 compared with placebo.²¹⁴ A second trial, this time using roxithromycin, also demonstrated improvement in lung function after 6 weeks of therapy. However, the benefit was not durable.²¹⁵ A more recent trial compared treatment with clarithromycin or placebo in patients inadequately controlled on ICS alone, and showed minimal benefit irrespective of whether patients were polymerase chain reaction positive or negative.²¹⁶

In the acute setting, a 2006 multicenter RCT examined the effect of a 10-day course of telithromycin (a ketolide), added on to standard therapy for acute exacerbations of asthma.²¹⁷ Telithromycin use, compared with placebo, resulted in a statistically significant reduction in only 1 of the 2 primary end points, self-reported symptoms (morning PEF was unchanged).

Phosphodiesterase inhibitors

Roflumilast (Daliresp) is an oral phosphodiesterase 4 (PDE4) inhibitor FDA approved for the treatment of COPD associated with chronic bronchitis.²¹⁸ Similar functionally to theophylline, which is a nonspecific inhibitor of PDEs, it exerts a number of anti-inflammatory effects. Their chemical structures (with caffeine included for comparison) can be seen in Figure 3. Although theophylline has a number of poorly understood effects outside of its weak PDE inhibition,²¹⁹ leading to a number of significant drug–drug interactions and side effects such as cardiac arrhythmia, roflumilast is specific to PDE4. However, as noted below, they both hold the label of “narrow therapeutic index” as they share the same gastrointestinal side effects. PDE4 receptors are nearly ubiquitous on inflammatory cells, and inhibition of these receptors, via increased levels of cyclic AMP and GMP, decreases release of LTs, IL-2 and -4, and synthesis of tumor necrosis factor alpha.^{220,221}

Although sometimes derided as “designer” theophylline,²²¹ there are some promising data for the use of roflumilast in asthma: Bateman et al²²² demonstrated significant improvement from baseline in FEV1 and peak expiratory flow measurements in all 3 doses of roflumilast studied. The improvement from baseline in

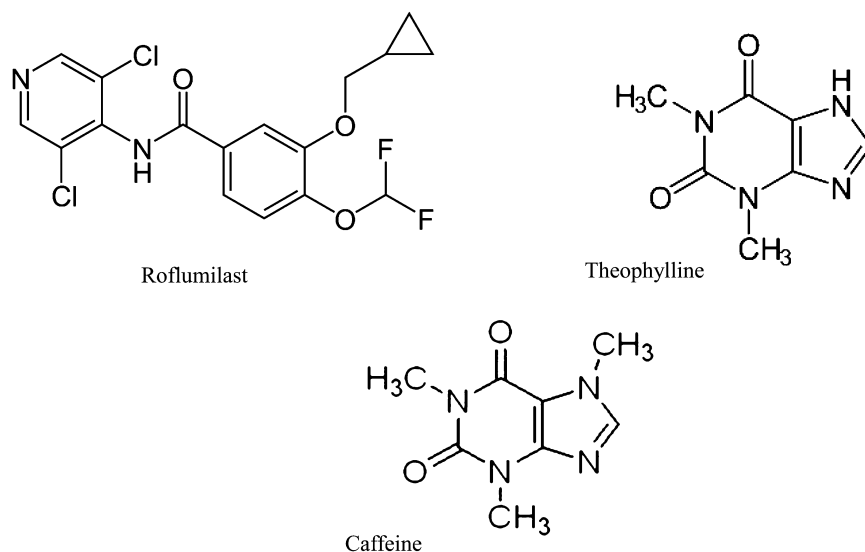


FIGURE 3. Chemical structures of PDE inhibitors and caffeine roflumilast theophylline caffeine.

FEV1 was an impressive 400 mL at the maximum dose of 500 mg. However, this result needs to be taken in the context that the patients were not on any other asthma medications other than as-needed albuterol. Headache and gastrointestinal side effects also were far more frequent as the dose escalated. A noninferiority study²²³ also demonstrated statistically significant improvements from baseline in spirometry and self-reported asthma symptoms in patients treated with either inhaled beclomethasone or roflumilast, with no difference between the 2. Again, there was a higher rate of gastrointestinal side effects in the roflumilast arm. There was also a higher rate of dropout due to worsening asthma in the roflumilast arm.

Phase II and III trials are ongoing, but as with COPD, the side-effect profile of this class is a significant concern: The primary drawback is dose-limiting gastrointestinal side effects. There are multiple subtypes of PDE4 receptors, with PDE4-B receptors thought to be the mediators of the beneficial anti-inflammatory properties of these agents, and PDE4-D mediating the primary adverse effect, nausea, in the central nervous system.²²⁴ Inhaled PDE4 inhibitors are now being investigated, in the hope that the therapeutic index can be widened by limiting systemic absorption: GSK256066 is currently in phase II trials. It has been shown to reduce both early and late responses to inhaled allergen challenge.²⁷ This is another contrast with theophylline, in which inhaled administration has been shown to be poorly tolerated with limited efficacy.²²⁵ Other oral PDE4 inhibitors are in early stages of development as well, with more selectivity for the PDE4-B receptor.²²⁶

Phosphodiesterase 5

PDE5 inhibitors such as sildenafil are far more widely known for their use in the treatment of erectile dysfunction. During the development of this class of drugs there were some studies demonstrating a lack of benefit in airways disease with zaprinast, an early PDE5 inhibitor.²²⁷ However, there are some more recent animal data²²⁸ and a single case series²²⁹ demonstrating some intriguing positive effects on airway hyperresponsiveness and spirometric improvements, respectively, with sildenafil. However, another study looking at the combination of L-arginine and sildenafil in a murine model of asthma gave the opposite result.²³⁰

Other Phosphodiesterases

Phosphodiesterases 3 and 7 have also been studied. Studies on PDE3 inhibitors have been mixed, and it has been suggested they may only be beneficial in combination with PDE4 inhibition.²²⁰ A recent study on both PDE7 knockout mice and a murine asthma

model treated with both roflumilast and PDE7 inhibitors did not show any effect of PDE7 on airway hyperresponsiveness. There was a beneficial response to roflumilast. This seems to discount the possibility of PDE7 being a useful therapeutic target for asthma.²³¹

DISCUSSION/CONCLUSIONS

Although it was first described centuries ago, optimal asthma therapy remains an elusive target and a fertile ground for research. The incidence of asthma continues to increase, affecting >22 million people in the United States alone. Despite this, only 3 new therapeutic classes, with a total of four individual drugs approved by the FDA, have been developed specifically for asthma since the 1960s. Existing therapies such as ICSs are effective but underutilized.¹⁰ In addition, some patients cannot maintain good asthma control even with proper use, and there are minor but lingering concerns about complications from chronic use of high-dose ICSs, especially in children.^{232–235} In fact, in the large (>3400 patients) GOAL study (Gaining Optimal Asthma control), asthmatics were closely followed by clinicians experienced in asthma care and had their doses of ICS and LABA titrated to the highest approved dose. Even in such an ideal setting, one-third of patients with severe asthma failed to achieve complete control of their disease with ICS/LABA alone.²³⁶

Outside of such a controlled environment, adherence to inhaled therapy is often poor,⁷⁰ and 1 strategy that has been suggested to combat this is single inhaler maintenance and reliever therapy, or SMART. Multiple studies²³⁷ have demonstrated improvements in asthma control and reduced rate of exacerbations when a budesonide/formoterol combination inhaler is used both as twice-daily maintenance therapy and as-needed “rescue” medication (salmeterol and once daily LABAs such as indacaterol cannot be used with SMART due to potential side effects; theoretically, any ICS can be used, however). This has the benefit of both providing some immediate anti-inflammatory effect with symptom flare-ups, and reducing (or even eliminating) the critical problem of poor adherence with controller medications.

Even with the use of strategies such as SMART to maximize adherence, the preference of most patients for oral medications is undeniable—one need only consider the high prescribing rate for LTRAs compared with other agents that have consistently demonstrated better efficacy in clinical trials (ie, LABAs). Consequently, the lack of oral controller medications that are effective in a majority of patients, but without

the side effect profile of systemic corticosteroids, is an obvious need. Nonsteroid agents, notably omalizumab and LTRAs, are both expensive and only effective in certain patients. Identifying which ones will respond can be difficult, as has been discussed in this review. Recent trials of other novel agents, notably TNF- α antagonists, have been disappointing,¹⁷¹ and results with IL-based therapies have been mixed.¹¹⁶ Future directions for asthma therapy include not only improvements on existing classes, as with the newer ultra-long-acting beta agonists and inhaled versions of oral drugs such as LTRAs and PDE4 inhibitors but also into the new frontiers of medicine such as biologic agents and pharmacogenomics.²³⁸ The current view of asthma is one of different phenotypes, rather than a homogeneous disorder of generalized airway hyper-responsiveness.²³⁹ At least 6 different phenotypes have been identified,³ and unfortunately, in the vast majority of cases, identifying the phenotype of a specific patient, either in terms of symptoms or clinical response to medications, is primarily a process of (therapeutic) trial and error.

The search for genetic or biologic markers that will predict whether or not an individual patient will respond to a particular agent or class of agents is ongoing.²⁴⁰ It may be that the next great asthma breakthrough is not a novel class of medication or therapeutic procedure, but the discovery of a means by which a combination of existing agents can be easily tailored to the individual patient for maximal efficacy with the simplest and safest regimen possible.

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Appendix: Glossary of Frequently Used Terms and Abbreviations

AQLQ: Asthma Quality of Life Questionnaire. A validated 32-item quality of life questionnaire. Each item is given a score from 1 (severe impairment) to 7 (no impairment). A change of 0.5 in the total score is considered clinically significant and is termed the minimal important difference. An abbreviated version (15 items) is known as the mini-AQLQ.²⁴¹

ACQ: Asthma Control Questionnaire. A 7-item questionnaire that unlike the AQLQ is geared specifically toward an assessment of disease control. It omits the “emotional function” components of the AQLQ and includes objective data such as the FEV1 and rescue inhaler use. A modified version omits FEV1 in situations when it is not available. The ACQ is scored from 0 (good control) to 6 (poor control).²⁴¹

CysLT1: Cysteinyl LeukoTriene receptor 1. The site of action of leukotriene receptor antagonists. There is also a type 2, which is not thought to play a role in asthma.

FEV1: forced expiratory volume in 1 second. One of the key parameters of spirometry, assesses the severity of airway obstruction.

GINA: Global INitiative for Asthma. The World Health Organization asthma group.

Modified Pulmonary Index Score: A validated symptom score used to assess the severity of asthma in children. Six categories are evaluated: oxygen saturation, accessory muscle use, inspiratory to expiratory flow ratio, degree of wheezing, heart rate, and respiratory rate.²⁴²

Methacholine: An inhaled agent commonly used clinically to assess the level of reactivity (or hyperreactivity) of the airways to irritant stimuli. It is administered in serial dilutions to give an objective measure of the level of stimulus needed to produce bronchospasm in an individual patient.

NAEPP: National Asthma Education and Prevention Program. The National Institute of Health’s asthma group.

PEF: Measures the airflow from a forced expiration, generally measured by the patient with a pocket-sized meter; it has been shown to correlate well with formal FEV1 testing. Used as a simple at-home measurement (often in the morning) by asthma patients to monitor their level of disease activity. Patients are generally counseled to report a significant decrease from baseline and/or implement a previously discussed treatment plan (referred to as an “asthma action plan” in the guidelines) in response. The use of PEF has not been demonstrated to improve outcomes compared with careful symptom self-monitoring by reliable patients but is commonly recommended for patients with more severe asthma or poor perception of their bronchospasm.⁶

QALY: Quality Adjusted Life Year. A commonly used measure of the relative cost effectiveness of a given intervention. \$50,000 per QALY (the cost of a single year of dialysis) is traditionally cited as the “cutoff” value of a cost-effective therapy.