REVIEW ARTICLE

DRUG THERAPY

Asthma

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According to survey data for which the diagnosis of asthma was based on a physician's assessment, it is estimated that approximately 7% of Americans have current asthma.[1,2] The disease affects people of all races and ethnic groups worldwide, from infancy to old age, with slightly more boys than girls affected and, after puberty, more women than men. Dramatic increases in the prevalence of atopy and asthma have occurred over the past few decades in Westernized countries[3] and more recently in less-developed nations.[4] Estimates suggest that as many as 300 million persons are affected worldwide.[5]

In the 1970s and 1980s, severe asthmatic exacerbations (as indicated by emergency department visits and hospitalizations for asthma) and asthma-related mortality rose steeply in the United States. Yet despite the persistently high prevalence of disease, the most recently available data indicate improved outcomes, with fewer annual hospitalizations for asthmatic attacks and fewer asthma-related deaths.[6] Among the possible explanations for these favorable trends are the more widespread preventive use of inhaled corticosteroids and the introduction over the past 10 to 15 years of new, highly effective medications and improved medication formulations for the treatment of asthma.

Airway obstruction in asthma and the consequent symptoms of cough, shortness of breath, chest tightness, and wheezing are caused by some combination of airway smooth-muscle constriction and inflammation of the bronchi. The former can be severe, leading to life-threatening narrowing and closure of airways, even in the absence of mucous plugging. Both abnormal smooth-muscle contractility[7] and excess smooth-muscle mass[8] may contribute. Airway inflammation in asthma consists of mucosal, submucosal, and adventitial edema; cellular infiltration, particularly by eosinophils (and in some cases, neutrophils) and activated helper T lymphocytes[9] as well as mast cells that (unlike mast cells in other eosinophilic airway diseases) infiltrate smooth-muscle bundles[10]; increased airway secretions, including secreted mucus, desquamated lining cells, and intraluminal eosinophils; capillary engorgement; hyperplasia of smooth muscle; and deposition of excess collagen, particularly immediately beneath the basement membrane of the epithelium.[11,12]

Traditionally, drugs used to treat asthma were categorized according to their predominant effect — relaxation of airway smooth muscle (bronchodilators) or suppression of airway inflammation (antiinflammatory drugs). Newer medications (e.g., the leukotriene modifiers) and drug combinations (e.g., inhaled corticosteroids combined with long-acting β-adrenergic agonists) have dual effects, resisting such traditional dichotomization. Now, asthma medications are classified according to their roles in the overall management of asthma (quick relief or long-term control), a model that is particularly useful when speaking to patients about their asthma medicines.

All patients with asthma should have available a quick-relief bronchodilator for use as needed. Consensus opinion suggests that when quick-acting bronchodilators are

needed for symptom relief more than 2 days per week (or more than twice a month for nighttime awakenings caused by asthmatic symptoms), controller medications should be prescribed.[2,13]

QUICK RELIEF

Quick-acting β-adrenergic agonists administered by inhalation are the most effective therapy for rapid reversal of airflow obstruction and prompt relief of asthmatic symptoms. Most widely used are the short-acting, β_2-selective, adrenergic agonists: albuterol (commonly known as salbutamol outside the United States), levalbuterol, and pirbuterol (Table 1). Metaproterenol delivered by metered-dose inhaler has recently been withdrawn from the market.

The short-acting β-agonists all have an onset of action in 5 minutes or less, with a peak effect in 30 to 60 minutes and a duration of action of 4 to 6 hours.[14] With regular use of a bronchodilator (four or more times daily), the potency (as measured by the increase in maximal expiratory flow) does not decline, but the duration of action is slightly shortened.[15,16] Because a regular schedule of administration four times a day does not improve outcomes, as compared with as-needed administration[17] (and, in patients with certain genotypic variants of the β-receptor, may have a deleterious effect),[18,19] the short-acting β-agonists are recommended for use only as needed for relief of symptoms (or before anticipated exposure to known asthmatic triggers, especially exercise). The practice of administering a short-acting β-agonist before using an inhaled corticosteroid to improve delivery of the corticosteroid to the lower airways has been abandoned as unnecessary.[20] Similarly, there is no need for patients to wait more than 10 to 15 seconds between puffs when a dose of two or more puffs is recommended.[21]

In patients with moderate or severe airflow obstruction, a log-linear dose–response curve for bronchodilation can be demonstrated for short-acting β-agonists administered at very high doses (up to 4000 μg of albuterol by metered-dose inhaler).[15] Dose-dependent, sympathomimetic-type side effects, including tremor, anxiety, heart pounding, and tachycardia (but not hypertension), are common, and a small dose-dependent decrease in serum potassium and magnesium levels is detectable. However, at the usual dose (two puffs per administration), unpleasant stimulatory side effects are uncommon. Although their effectiveness may be diminished somewhat, inhaled β-agonist bronchodilators are not contraindicated in patients who are simultaneously taking beta-blockers.[22,23]

The decision about which of the various short-acting β-agonists to use is based largely on cost and the patient's or physician's preference. Pirbuterol is the only one available in a breath-actuated metered-dose inhaler, a device meant to optimize medication delivery by releasing a spray of medication only on the patient's initiation of inspiration. Levalbuterol, the purified D-rotatory isomer of albuterol, was developed for the purpose of eliminating side effects, which some argue are limited to the S-rotatory isomer.[24] However, when delivered by metered-dose inhaler, levalbuterol has an efficacy and side-effect profile that is indistinguishable from that of the racemic mixture of molecules in albuterol.[25] Albuterol has been made available in a metered-dose inhaler free of chlorofluorocarbons (CFCs), and CFC-containing albuterol inhalers were taken off the market on December 31, 2008.[26] Like CFCs, the alternative propellant, hydrofluoroalkane (HFA), is inert in the human airway, but unlike CFCs, it does not contribute to depletion of the stratospheric ozone layer. For more information on HFA-containing metered-dose inhalers, see the Supplementary Appendix, available with the full text of this article at NEJM.org. A Supplementary Video, also available at NEJM.org in an article by Hendeles et al.,[26] demonstrates the use of an HFA albuterol inhaler. The HFA inhalers are equipotent to the CFC-propelled inhalers,[27] can be used with valved holding chambers (spacers) in patients with poor inhalational technique,[28] and provide bronchodilation comparable to nebulized albuterol when a sufficient number of puffs is administered and inhalational technique is good.[29]

Short-acting β-agonists that are to be swallowed, in either tablet or liquid form, should be discouraged, despite their seeming convenience (especially for very young children). They take longer to start working, are less potent, and are associated with more frequent side effects than inhaled short-acting β-agonists.[30] Similarly, anticholinergic bronchodilators such as ipratropium are not recommended (or approved by the Food and Drug Administration [FDA]) for quick relief of asthmatic symptoms. They take longer to start working (20 to 30 minutes) and cause less bron-

Table 1. Short-Acting β-Adrenergic Agonists.*

Drug	Brand Name	Formulation	Dose	No. of Doses per MDI Canister	Rating in Pregnancy†	Comments
Albuterol	Ventolin (GlaxoSmithKline), ProAir (Teva), Proventil (Schering–Plough)	MDI–HFA	90 μg/puff	200	C	CFC-driven albuterol MDIs were taken off the market on December 31, 2008; generic albuterol HFA inhalers are not yet available
	AccuNeb (Dey), generic	Liquid for nebulization	0.63, 1.25, or 2.5 mg/vial; 5 mg/ml		C	
	Proventil Repetabs, Vospire ER (DAVA Pharmaceuticals)	Extended-release tablets	4 or 8 mg		C	
	Proventil, generic	Tablets	2 or 4 mg		C	
	Generic	Syrup	2 mg/5 ml		C	
Levalbuterol	Xopenex (Sepracor)	MDI–HFA	45 μg/puff	200	C	Single stereoisomer derived from albuterol
		Liquid for nebulization	0.31, 0.63, or 1.25 mg/vial		C	
Metaproterenol	Alupent (Boehringer Ingelheim), generic	Liquid for nebulization	10 or 15 mg/vial; 50 mg/ml		C	Less β_2 selectivity than albuterol; manufacture of metaproterenol MDI was discontinued in July 2008
	Alupent, generic	Tablets or syrup	10 or 20 mg; 10 mg/5 ml		C	
Pirbuterol	Maxair (Graceway)	MDI–CFC	200 μg /puff	400	C	Breath-actuated MDI

* CFC denotes chlorofluorocarbons, HFA hydrofluoroalkane, and MDI metered-dose inhaler.
† A pregnancy rating of C indicates that a risk to the fetus cannot be ruled out.

chodilation than inhaled β-agonist bronchodilators.[31] Anticholinergic bronchodilators should be used only in the rare case of a patient with intolerance to all β-agonist bronchodilators or for the treatment of severe asthmatic attacks[32] or asthmatic attacks induced by beta-blockers.[2]

A novel approach to asthma management, not yet adopted in the United States, combines a short-acting β-agonist with an inhaled corticosteroid in a single device, administered as needed for symptom relief. Use of the device has been associated with favorable outcomes in patients with mild asthma, as compared with the use of albuterol alone as needed.[33] Similarly, the long-acting β-agonist bronchodilator with a quick onset of action (formoterol) is being used in combination with an inhaled corticosteroid in a single inhaler for both maintenance and rescue therapy.[34,35] The safety of this approach in a broad and diverse patient population remains to be ascertained.

LONG-TERM CONTROL

Achieving good long-term control of asthma (infrequent asthmatic symptoms, an unrestricted level of activity, normal or near-normal lung function, and rare asthmatic attacks requiring emergency care) requires a multifaceted approach: avoidance of environmental stimuli that can provoke bronchoconstriction and acute and chronic airway inflammation; monitoring of changes in disease activity; in some cases, allergen immunotherapy; and drug therapy. The use of controller medications should be intensified (or stepped up) until good asthma control is achieved, including a reduction of the number of asthmatic attacks requiring systemic corticosteroids to no more than one yearly. Inhaled corticosteroids constitute the drug class that has had the greatest effect in helping patients achieve well-controlled asthma.

INHALED CORTICOSTEROIDS

Corticosteroids have proved effective in the treatment of asthma, as they have in many other inflammatory diseases, because of their multiplicity of antiinflammatory activities, including a broad effect on the transcription (both up-regulation and down-regulation) of many genes.[36,37] In airway-biopsy specimens from patients with asthma who have had prolonged treatment with inhaled corticosteroids, the histologic abnormalities that are typical of asthma have been shown to diminish. Changes include fewer mast cells, eosinophils, T lymphocytes, and dendritic cells in the mucosa and submucosa[38]; reduced goblet-cell hyperplasia and epithelial-cell injury[39]; and decreased vascularity.[40]

Along with suppression of airway inflammation, nonspecific bronchial hyperresponsiveness typically decreases by a factor of two to four.[41] Beneficial clinical outcomes include fewer asthmatic symptoms, increased lung function, improved asthma-specific quality of life, and fewer asthmatic exacerbations, including severe attacks resulting in hospitalization[42] or death.[43] Optimistic predictions to the contrary, evidence is for the most part lacking to indicate that long-term use of inhaled corticosteroids can prevent the progressive decline in lung function observed in some persons with asthma.[44,45] Inhaled steroids suppress but do not cure asthmatic inflammation: in a stable phase of the disease, markers of airway inflammation (e.g., exhaled nitric oxide concentrations and sputum eosinophilia) and bronchial hyperresponsiveness return to baseline approximately 2 weeks after the use of inhaled corticosteroids has been stopped.[46,47]

Not all patients benefit equally from inhaled corticosteroids. For instance, current cigarette smokers are less likely to derive the same antiasthmatic effects as nonsmokers.[48] Neutrophilic inflammation of the airways is less likely to respond to treatment than is eosinophilic inflammation. Genetic differences in persons with asthma may also be predictive of nonresponsiveness to corticosteroids.[49]

Most of the currently available inhaled corticosteroids, when swallowed and systemically absorbed from the gastrointestinal tract, undergo extensive first-pass metabolic inactivation in the liver before reaching the systemic circulation.[50] In addition, because in general less than 20% of the delivered dose is deposited onto the airways, only small amounts are available for systemic absorption across the respiratory tract mucosa. With the use of changes in hypothalamic–pituitary–adrenal function as an assay, a systemic effect can be seen with inhaled-corticosteroid administration at doses as low as 88 μg of fluticasone per day.[51] However, virtually no clinically important, long-term adverse systemic effects are observed among adults taking low-to-medium doses. At high doses (usually >1000 μg of beclomethasone per day or the equivalent), the risks of skin bruis-

Table 2. Inhaled Corticosteroids.*

Drug	Brand Name	Formulation‡	Dose per Inhalation	No. of Doses per Canister	Rating in Pregnancy†	Patient Age	Comments
			μg			yr	
Beclomethasone	Qvar (Teva)	MDI–HFA	40 or 80	100	C	≥5	Prepared as an aerosol solution (rather than suspension), with smaller particle size
Budesonide	Pulmicort (AstraZeneca)	DPI or suspension for nebulization	DPI: 90 or 180; suspension for nebulization: 250 or 500	DPI: 60 or 120; suspension for nebulization: prefilled single-dose vials	B	DPI: ≥6; suspension for nebulization: 1–8	Built-in dose counter
Ciclesonide	Alvesco (Sepracor)	MDI–HFA	80 or 160	60	C	≥12	Prepared as an aerosol solution, activated by airway esterases, approved for twice-daily use
Flunisolide	Aerobid (Forest Laboratories)	MDI–CFC	250	100	C	≥6	Available with menthol flavoring as Aerobid-M
Fluticasone	Flovent (GlaxoSmithKline)	MDI–HFA or DPI	MDI–HFA: 44, 110, or 220; DPI: 50 or 100	MDI–HFA: 120; DPI: 60	C	≥4	Built-in dose counter with both MDI and DPI
Mometasone	Asmanex (Schering-Plough)	DPI	110 or 220	30; 30, 60, 120	C	≥4	Approved for once-daily use; built-in dose counter
Triamcinolone	Azmacort (Abbott)	MDI–CFC	75	240	C	≥6	Built-in small-volume spacer
In combination with LABA							
Budesonide with formoterol	Symbicort (AstraZeneca)	MDI–HFA	80 or 160 (with 4.5 μg of formoterol)	120	C	≥12	2 Puffs twice daily; built-in dose counter
Fluticasone with salmeterol	Advair (GlaxoSmithKline)	MDI–HFA or DPI	MDI–HFA: 45, 115, or 230 (with 21 μg of salmeterol); DPI: 100, 250, or 500 (with 50 μg of salmeterol)	MDI–HFA:120; DPI: 60	C	MDI–HFA: ≥12; DPI: ≥4	MDI–HFA: 2 puffs twice daily; DPI: 1 inhalation twice daily; built-in dose counter

* Fluticasone and mometasone are more potent, microgram for microgram, by a factor of approximately 2:1 than beclomethasone, budesonide, and flunisolide. The most recently released inhaled corticosteroid, ciclesonide, is an ester prodrug — inactive until hydrolyzed to desisobutyryl-ciclesonide by esterases endogenous to airway epithelium. Preliminary data suggest that ciclesonide is associated with a lower incidence of oral candidiasis than fluticasone[58] and is not associated with growth retardation in children when given in conventional doses.[59] Mometasone has been approved for once-daily use, although it is likely that other inhaled corticosteroids can also be administered once daily for patients with mild, well-controlled asthma.[60,61] CFC denotes chlorofluorocarbons, DPI dry-powder inhaler, HFA hydrofluoroalkane, LABA long-acting β-agonist, and MDI metered-dose inhaler.

† A pregnancy rating of B indicates that there is no evidence of fetal risk in humans, and a rating of C that a risk to the fetus cannot be ruled out.

‡ Other formulations are available outside the United States.

ing, cataracts,[52] elevated intraocular pressure,[53] and accelerated loss of bone mass[54] increase. In children, growth retardation is a concern. Expected growth decreases by an average of approximately 1 cm in the first year after instituting inhaled corticosteroids in growing children,[45,55] but evidence from studies in prepubescent school-age children suggests that even when these children continue to receive long-term treatment with inhaled corticosteroids, they ultimately reach their normal predicted height.[45,56]

Pharyngeal and laryngeal side effects of inhaled corticosteroids include sore throat, coughing on inhalation of the medication, weak or hoarse voice, and candidiasis. Rinsing the mouth after each administration of the medication and using a valved holding chamber when it is delivered with a metered-dose inhaler are two techniques that can minimize the risk of oral candidiasis (thrush). (Use of the valved holding chamber also reduces the amount of medication available for systemic absorption from the oropharynx.) Cough can usually be overcome by changing either the inhaled corticosteroid medication or the delivery system. Dysphonia, generally intermittent, is thought to be due to laryngeal edema and mucosal thickening or possibly myopathy.[57] It usually resolves with temporary cessation of the medication and may also do so with a change in aerosol generation and flow pattern (e.g., switching from a dry-powder inhaler to a metered-dose inhaler with valved holding chamber.)

When first introduced for the treatment of asthma in the mid-1970s, the inhaled corticosteroid beclomethasone was prescribed for use four times daily, and each puff of medication from a metered-dose inhaler sold in the United States contained only 42 μg of medication. Since then, additional corticosteroid preparations have become available, including drugs that are more potent, deliver a larger dose per inhalation, and are recommended for use once or twice daily, features that have contributed to improved efficacy and compliance (Table 2).

There are differences among the various inhaled corticosteroids.[62,63] For the most part, choices are based on the convenience of the dosing schedule (once or twice daily) and method of delivery (metered-dose inhaler, dry-powder inhaler, or suspension for nebulization), the starting dose and flexibility in making dose adjustments, the cost to the patient, and observed side effects. Only minor differences in the products' therapeutic outcomes have been found.

The use of high-dose inhaled corticosteroids has proved effective for the control of severe persistent asthma.[64] However, the dose–therapeutic-response (improvement in expiratory flow) curve for inhaled corticosteroids is relatively flat, whereas the dose–systemic-absorption curve appears to be linear.[51] As a result, strategies that can achieve asthma control without using high doses of inhaled corticosteroids are desirable, and reduction of the inhaled-corticosteroid dose in patients with well-controlled asthma (referred to as "stepping down" treatment) can often be achieved without diminishing asthma control.[65]

INHALED LONG-ACTING β-AGONIST BRONCHODILATORS

The inhaled long-acting β-agonists, salmeterol and formoterol (Tables 2 and 3), have largely replaced the older long-acting bronchodilators — orally administered, slow-release albuterol and theophylline. Long-acting β-agonists are potent broncho-

Table 3. Inhaled Long-Acting β-Agonist Bronchodilators.*

Drug	Brand Name	Formulation	Dose	Patient Age	Rating in Pregnancy†	Comments
			μg	yr		
Arformoterol	Brovana (Sepracor)	Liquid for aerosolization	15/vial	Adults	C	Approved for COPD but not asthma
Formoterol	Foradil (Schering-Plough)	Single-dose DPI	12/capsule	≥5	C	Rapid onset of action
	Perforomist (Dey)	Liquid for aerosolization	20/vial	Adults	C	Approved for COPD but not asthma
Salmeterol	Serevent (GlaxoSmithKline)	DPI (60 doses per device)	50/inhalation	≥4	C	Multidose DPI

* COPD denotes chronic obstructive pulmonary disease, and DPI dry-powder inhaler.
† A pregnancy rating of C indicates that a risk to the fetus cannot be ruled out.

dilators (with a bronchodilator effect similar to that of the short-acting β-agonists), have sustained activity for more than 12 hours, and because of their high degree of adrenergic β-2 specificity, have few side effects (generally mild sympathomimetic-type stimulation, including occasional muscle cramps and tachycardia).[66] They have none of the food–drug and drug–drug interactions that complicate the use of theophylline, and toxicity from drug overdosing is exceedingly rare, in contrast to the effects of theophylline overdosing.

As with short-acting β-agonists, regular use of long-acting β-agonists results in only mild tachyphylaxis to the maximal bronchodilator effect and the duration of action of these drugs.[66] In contrast, the bronchoprotective effect of long-acting β-agonists (i.e., their inhibition of exercise-induced bronchoconstriction) rapidly wanes with regular use,[67,68] a contrary pharmacologic effect that has not been fully explained. With rare exceptions,[69] the quick symptom relief provided by short-acting β-agonists is not impeded by regular use of long-acting β-agonists.[70] Variation in the structure of the β-adrenergic receptor, as determined by genetic polymorphisms that are common in the U.S. population (15 to 20%), may limit the effectiveness of long-acting β-agonists in some patients.[71]

The fact that long-acting β-agonists can provide sustained improvement in lung function may tempt clinicians to use them as a long-term controller medication without concomitant use of an antiinflammatory inhaled corticosteroid. However, this strategy results in unsuppressed airway inflammation and an unacceptably high rate of asthmatic exacerbations.[47] Long-acting β-agonists should not be used without concomitant antiinflammatory therapy in the treatment of asthma.

As therapy added to or combined with inhaled corticosteroids, long-acting β-agonists have proved effective in reducing daytime and especially nighttime symptoms, improving lung function, reducing the risk of exacerbations, and minimizing the required dose of inhaled corticosteroids.[72] Comparisons of the use of inhaled corticosteroids in combination with long-acting β-agonists and the use of higher doses of inhaled corticosteroids alone show that the combination therapy is associated with more favorable outcomes (while maintaining lower exposure to corticosteroids).[73,74] Pharmacologic evidence provides theoretical support for a favorable interaction between these two classes of medications: in vitro studies show that corticosteroids improve β-receptor–mediated signaling in the lung, and β-agonists enhance the transcription of genes under the influence of corticosteroids.[75] Combination therapy (a long-acting β-agonist combined with an inhaled corticosteroid in a single inhaler) (Table 2) ensures concomitant use of an antiinflammatory drug and optimizes compliance because of greater convenience. Its major disadvantage is that adjusting the dose of inhaled corticosteroids without changing the dose of β-agonist (e.g., increasing the corticosteroid dose during an asthmatic exacerbation) requires changing devices or adding a separate inhaled corticosteroid inhaler.

The life-changing benefit that many patients with moderate or severe persistent asthma have experienced with the use of a long-acting β-agonist together with an inhaled corticosteroid must be counterbalanced against the results of the Salmeterol Multicenter Asthma Research Trial (SMART),[76] in which the addition of a long-acting β-agonist to "usual therapy" was associated with an increased risk of fatal and near-fatal asthmatic attacks, as compared with "usual therapy" alone. It has been pointed out that a minority of subjects in SMART were taking inhaled corticosteroids and that no increased asthma-related mortality has ever been reported among patients taking both a long-acting β-agonist and an inhaled corticosteroid.[77,78] Nonetheless, the mechanism by which salmeterol caused a greater number of asthma-related deaths, among both black and white subjects, remains uncertain, and a black-box warning is therefore included in the prescription-labeling information (or package insert) for all products containing either salmeterol or formoterol. In addition, national and international expert panels[2,13] have recommended the use of long-acting β-agonists only for patients in whom inhaled corticosteroids alone either have failed to achieve good asthma control or, for initial therapy, would not be expected to bring about good control. Future guidelines on the treatment of asthma will need to wrestle with appropriate application of the recent observation that once-daily administration of a long-acting β-agonist in combination with an inhaled corticosteroid provides good control in patients with mild persistent asthma.[79]

Features distinguishing the two long-acting β-agonists are both practical and theoretical.[80]

The onset of action of formoterol occurs within 5 minutes, a period similar to that for short-acting β-agonists, whereas salmeterol has a slower onset of action (15 to 20 minutes). For this reason, in some countries other than the United States, a combination formoterol–inhaled-corticosteroid inhaler is recommended both for quick relief of asthmatic symptoms and, when used regularly, for long-term control.[34] Formoterol is a full agonist in its action at the β-receptor, whereas salmeterol is a partial agonist (and partial antagonist). The implication of this pharmacologic distinction, particularly as it might apply to the risk of fatal asthmatic attacks, is uncertain.

LEUKOTRIENE MODIFIERS

The cysteinyl leukotriene-receptor antagonists, montelukast, zafirlukast, and pranlukast (the last not available in the United States) (Table 4), block the action of leukotriene C_4, D_4, and E_4 at the type 1 cysteinyl leukotriene receptor.[81] Bronchodilation occurs within hours of the first dose and is maximal within the first few days after administration.[82,83] Levels of circulating blood eosinophils decrease in response to treatment with leukotriene-receptor antagonists.[82,83] However, when indirect measures of airway inflammation (e.g., sputum eosinophilia and levels of exhaled nitric oxide) are used to determine the outcome, the effect of leukotriene-receptor antagonists on airway inflammation, as compared with that of placebo, has been variable.[84-86]

Leukotriene-receptor antagonists can be administered as tablets once (in the case of montelukast) or twice (in the case of zafirlukast) daily. Montelukast is available in chewable tablets and oral granules (to be mixed with food) for young children. The recommendation to administer montelukast once daily in the evening was based on the timing of its use in the seminal trials submitted to the FDA at the time of application for approval. No data indicate a greater benefit with administration in the evening as compared with dosing at any other time of day.[87]

Zileuton inhibits production of the cysteinyl leukotrienes (and of leukotriene B_4, a potent chemoattractant for neutrophils) by antagonizing the action of 5-lipoxygenase. An extended-release formulation is now available, making twice-daily dosing possible. No clinical trial has directly compared the efficacy of zileuton with that of a leukotriene-receptor antagonist or has tested the effects of their use in combination. Some clinicians have found zileuton to be more beneficial than leukotriene-receptor antagonists in triad asthma (asthma, aspirin sensitivity, and nasal polyposis), in terms of both controlling asthma and shrinking nasal polyps.[88]

Zileuton causes a reversible chemical hepatitis in 2 to 4% of patients. Hepatic function should be monitored monthly for the first 3 months of therapy, about every 3 months for the remainder of the first year, and periodically thereafter. Reports of the emergence of the Churg–Strauss syndrome (an eosinophilic vasculitis with granulomatosis complicating the course of asthma) in patients recently started on a leukotriene-receptor antagonist (often with concomitant tapering of oral corticosteroids)[89,90] may reflect unmasking of preexisting cases of Churg–Strauss vasculitis,[91,92]

Table 4. Leukotriene Modifiers.

Drug	Brand Name	Formulation	Dose	Patient Age	Rating in Pregnancy*	Comments
			mg	*yr*		
Montelukast	Singulair (Merck)	Granules, chewable tablets, or tablets	Granules: 4; chewable tablets: 4 or 5; tablets: 10	Granules: 1–2; chewable tablets: 2–5 for the 4-mg dose, 6–14 for the 5-mg dose; tablets: ≥15	B	Once-daily use
Zafirlukast	Accolate (AstraZeneca)	Tablets	10 or 20	5–11 for the 10-mg dose, ≥12 for the 20-mg dose	B	One tablet twice daily
Zileuton	Zyflo (Cornerstone Therapeutics)	Extended-release tablets	600	≥12	C	Two tablets twice daily (after meals)

* A pregnancy rating of B indicates that there is no evidence of fetal risk in humans, and a rating of C that a risk to the fetus cannot be ruled out.

although the possibility of a causal association remains debated.[93] In general, the leukotriene-receptor antagonists have been considered virtually free of side effects, and one (montelukast) has been approved for the treatment of asthma in children as young as 1 year old. Recent postmarketing reports have described a few cases in which depression and suicidal ideation developed in children taking montelukast. No cause-and-effect relationship has been established, and on review of all available placebo-controlled clinical trials data, the FDA found no increased risk of suicidal ideation or suicide for any of the leukotriene modifiers. The possibility of medication-induced mood and behavioral changes remains under review.[94]

Because of their perceived safety and convenience, leukotriene-receptor antagonists have largely replaced the cromoglycates (cromolyn and nedocromil) as the noncorticosteroid treatment of choice, especially for young children, in whom medication delivery by aerosol is often a struggle. Cromolyn requires administration four times daily by metered-dose inhaler or nebulizer, provides limited long-term asthma control, and unlike leukotriene-receptor antagonists, has never been shown to have an additive benefit when used in combination with inhaled corticosteroids.

Short-term, double-blind, placebo-controlled trials have shown improved lung function, better scores on asthma-related quality-of-life questionnaires, and fewer asthmatic attacks among patients treated with leukotriene modifiers.[82,83,95,96] Persons with asthma who are obese,[97] who smoke cigarettes,[48] or who have associated aspirin sensitivity[88,98,99] may particularly benefit from treatment with leukotriene modifiers. In the future, identification of specific interindividual variations in the genes coding for enzymes along the leukotriene metabolic pathway may prove clinically useful in predicting whether a patient will have a response to treatment.[100] Currently, a therapeutic trial is often used; symptomatic and objective improvement, if they are to occur, are generally observed within the first month of therapy.

Overall, inhaled corticosteroids provide better asthma control than leukotriene modifiers.[86,96,101-103] As a result, an inhaled corticosteroid is the recommended drug of first choice in the treatment of patients with persistent asthma, including children of all ages.[2] Leukotriene-receptor antagonists are an alternative treatment for mild persistent asthma. For patients of any age in whom good asthma control is not achieved with the use of a leukotriene modifier, transition to an inhaled corticosteroid is indicated. For patients with more severe asthma, the addition of a leukotriene-receptor antagonist to a low dose of an inhaled corticosteroid may improve asthma control,[104,105] but other treatment combinations (specifically, an inhaled corticosteroid plus long-acting β-agonist) are more effective.[106,107]

ANTI-IgE THERAPY

The anti-IgE monoclonal antibody, omalizumab, is the first biologic immunoregulatory agent available to treat asthma. It binds to the portion of IgE that recognizes its high-affinity receptor (FcεR1) on the surface of mast cells and basophils. When given intravenously, omalizumab reduces circulating IgE levels by 95% and can result in levels of free IgE of 10 IU per milliliter or less, a target thought to be clinically relevant for inhibiting allergic reactions in the airways.[108] Its use also results in down-regulation of expression of FcεR1 on the surface of mast and other immune-modulating cells (basophils, monocytes, and dendritic cells).[109] In contradistinction to allergen immunotherapy, treatment with omalizumab is not restricted in its effects to any specific allergen or group of allergens.

Omalizumab is administered subcutaneously every 2 or 4 weeks, depending on the dose. The dose is based on the patient's weight and blood IgE level. Reactions at the injection site (e.g., hives) are uncommon, and systemic allergic reactions (i.e., anaphylaxis) occur in 1 to 2 patients per 1000. Most but not all systemic reactions occur within 2 hours after administration of the first few doses. Patients are asked to remain under medical observation for 2 hours after each of their first three injections and for 30 minutes after each subsequent injection and to carry with them for the next 24 hours prefilled epinephrine-containing autoinjectors for self-administration, if needed.[110]

Omalizumab is indicated for the treatment of moderate and severe persistent asthma when inhaled corticosteroids, long-acting β-agonists, and leukotriene modifiers have not provided adequate control or cannot be used because of intolerable adverse effects. The currently approved dosing range for omalizumab limits administration to patients with blood IgE levels between 30 and 700 IU per milliliter; documented sensitization to a perennial aeroallergen (e.g., dust mites, ani-

mal dander, mold, or cockroaches) is an additional criterion for patient selection.

Omalizumab has been approved for use in adults and children 12 years of age or older. For patients in this age range, the drug has not been shown to be "disease modifying" in the sense that it is not known to prevent long-term changes in lung function or to result in a disease remission (as indicated by drug discontinuation without recurrence of asthmatic symptoms). Treatment with omalizumab has been found to reduce the frequency of asthmatic exacerbations, even among patients already taking many other controller medications.[111] In patients treated with an inhaled corticosteroid alone, the addition of omalizumab, as compared with placebo, permitted a greater reduction of the inhaled-corticosteroid dose, with preserved or slightly improved lung function and with slightly less need for a rescue bronchodilator.[112,113]

One of the greatest drawbacks to the more widespread use of omalizumab is cost, roughly $10,000 to $30,000 per year for the drug alone. Pharmacogenetic markers predictive of a favorable response would be highly desirable, given the large cost of a therapeutic trial lasting 4 to 6 months. Observations to date suggest that traditional clinical characteristics at baseline cannot reliably predict which patients will have a response to anti-IgE therapy.[114]

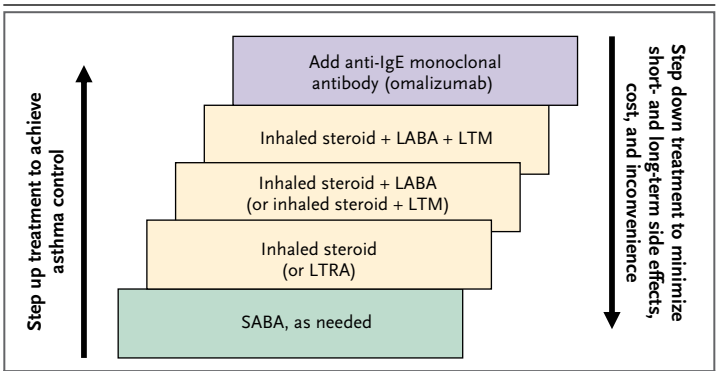

Figure 1. Stepped-Care Approach to Asthma Treatment.

This simplified stepped-care approach to asthma treatment is constructed around the central role of inhaled corticosteroids. For each of the overlapping steps, the dose of the inhaled corticosteroid can be adjusted as needed to achieve the goal of well-controlled asthma while minimizing the long-term risks associated with high doses. LABA denotes long-acting β-agonist, LTM leukotriene modifier, LTRA leukotriene-receptor antagonist, and SABA short-acting β-agonist.

CONCLUSIONS

When asthma symptoms are infrequent, short-lived, and mild, occasional administration of a quick-acting bronchodilator to reverse smooth-muscle constriction in the airways is an acceptable approach. However, as symptoms become more frequent or more severe, the emphasis changes to prevention of symptoms (and of asthmatic attacks) (Fig. 1). By suppressing airway inflammation, an inhaled corticosteroid used once or twice daily reduces the frequency of episodic bronchoconstriction and lessens the risk of asthmatic attacks. In low-to-moderate doses, corticosteroids administered by inhalation are safe for long-term use, even in young children. An alternative to a corticosteroid for mild asthma is a leukotriene-receptor antagonist, which is directed at blocking a specific inflammatory mediator in asthma. Influenza and possibly pneumococcal vaccines are indicated for patients receiving regular controller therapy for their asthma.[115,116]

When symptoms persist despite medication compliance and good inhalational technique, use of a long-acting β-agonist in combination with an inhaled corticosteroid has proved to be the most effective next step, since it addresses both aspects of airway narrowing in asthma: bronchoconstriction and airway inflammation. A novel option for patients with refractory allergic asthma is therapy with an anti-IgE monoclonal antibody.

Asthma control can often be achieved by increasing the dose of inhaled corticosteroids. However, at high doses, the potential for long-term adverse effects becomes a concern. Thus, once control of asthma has been achieved for a period of 3 to 6 months, efforts should be made to reduce the dose of inhaled corticosteroids to the low-to-moderate range. Use of long-acting β-agonists, leukotriene modifiers, and anti-IgE therapy can facilitate a reduction of the dose of inhaled corticosteroids while maintaining asthma control.

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