



Leukotriene Modifiers Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
montelukast (Singulair®) ¹	generic, Merck Sharp & Dohme	<ul style="list-style-type: none"> ▪ Prophylaxis and chronic treatment of asthma in adults and children 1 year of age and older ▪ Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older ▪ Relief of symptoms of seasonal allergic rhinitis (SAR) patients 2 years of age and older ▪ Relief of symptoms of perennial allergic rhinitis (PAR) in patients 6 months of age and older
zafirlukast (Accolate®) ²	generic, Par	<ul style="list-style-type: none"> ▪ Prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older
zileuton (Zyflo®) ³	Chiesi	<ul style="list-style-type: none"> ▪ Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older
zileuton ER (Zyflo CR®) ⁴	generic, Chiesi	<ul style="list-style-type: none"> ▪ Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older

OVERVIEW

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.⁵ These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli. In the United States (U.S.), asthma affects approximately 25.7 million people. It is one of the most common chronic childhood diseases, affecting approximately 7 million children.⁶

The 2018 Global Initiative for Asthma (GINA) guidelines advise assessment of asthma control (well controlled, partly controlled, or uncontrolled), as well as future risk of adverse outcomes (fixed airflow limitation and medication side effects).⁷ Asthma severity is assessed retrospectively based on the level of treatment required to control symptoms and exacerbations. Severity should be assessed after the patient has been on a regular controller treatment for several months and should rule out improper inhaler technique and treatment nonadherence. GINA recommends a stepwise approach to asthma treatment. Step 1 and Step 2 describe options for mild asthma with as-needed short-acting beta₂-agonist (SABA) with or without low-dose inhaled corticosteroid (ICS). Step 3 includes low-dose ICS and long-acting beta₂-agonist (LABA) as the preferred controller options for moderate asthma. For severe asthma, Step 4 recommends medium- to high-dose ICS plus LABA. The addition of sublingual immunotherapy (SLIT) may be considered in asthmatic adults with allergies to house-dust mites who exhibit allergic rhinitis who have asthma exacerbations despite treatment with ICS. Step 5 advises consideration of monoclonal antibody therapy and other add-on therapies in select patients. At each step, alternative controller options are described, including leukotriene receptor antagonists during step-up and step-down therapy. “Difficult-to-treat asthma” patients are relatively insensitive to the effects of glucocorticosteroids and may be unable to achieve asthma control due to factors such as comorbidities, poor adherence, and allergen exposure. Treatment-resistant or refractory asthma refers to patients whose symptoms remain poorly controlled despite high doses of inhaled corticosteroids, a second controller and management of comorbid conditions, or patients who have deterioration of asthma control when treatment is stepped down. The

National Asthma Education and Prevention Program (NAEPP) and GINA guidelines recommend ICS as the cornerstone for the treatment of asthma while leukotriene modifiers are included as potential alternatives or add-on therapy in some patients, including those with aspirin-sensitive asthma.^{8,9} GINA states that leukotriene modifiers are less effective than ICS, but may be appropriate for initial controller treatment for patients who are unable or unwilling to use ICS, intolerant to ICS, or who also have allergic rhinitis. Limited data exist to support the use of leukotriene modifiers in acute asthma. Leukotriene modifiers are also used as add-on therapy in patients receiving ICS to reduce the dose of the ICS in patients with moderate to severe asthma, and to potentially improve asthma control in patients whose asthma is not controlled with low or high doses of ICS. In the NAEPP and GINA guidelines, leukotriene modifiers may be used as an alternative controller treatment in asthma, including in children under 4 or 5 years.^{10,11} In adults and adolescents aged over 12 years and children ages 5 or 6 to 11 years, leukotriene modifiers are not the preferred adjunctive therapy to ICS compared to the addition of LABA; the additive benefits of leukotriene modifiers have not shown to be as significant as the additive benefits of LABAs.¹²

GINA recommends a SABA for the treatment and prevention of exercise-induced bronchoconstriction (EIB); however, tolerance to SABA therapy can develop with regular use. Montelukast (Singulair) is FDA approved for acute prevention of EIB and is an acceptable alternative to ICS.¹³ The American Academy of Allergy, Asthma and Immunology (AAAAI) states that leukotriene modifiers are effective when used intermittently or daily to provide prophylaxis for asthma and EIB, and do not lead to tolerance.¹⁴ Although the effectiveness of leukotriene modifiers varies among patients and rarely results in complete protection, these agents may decrease the time to recovery from EIB when given prophylactically before exercise.

Allergic rhinitis (AR) is an inflammatory condition that presents with nasal congestion, rhinorrhea, sneezing, and/or itching.¹⁵ In 2012, 17.6 million adults and 6.6 million children were reported to have allergic rhinitis (AR).¹⁶ The AAAAI and the American College of Allergy, Asthma, and Immunology (ACAAI) published updated guidelines for the treatment of seasonal allergic rhinitis (SAR) in 2017.¹⁷ For initial treatment of moderate to severe SAR in patients 15 years and older, the guidelines recommend monotherapy with intranasal corticosteroids (INCS) given their demonstrated clinical benefit over other agents. The authors note that montelukast (Singulair) is the only leukotriene modifier approved for AR and can be considered for patients with co-morbid asthma, another FDA-approved use of montelukast. The guidelines also recommend combination therapy with intranasal antihistamines when INCS monotherapy fails and acknowledge that many patients require multiple agents for relief from symptoms of AR. Other agents that have been used in the treatment of AR include first-generation antihistamine nasal sprays, mast-cell stabilizers (cromolyn), anticholinergics (ipratropium), and, in refractory cases, systemic corticosteroids. Additional clinical practice guidelines for the management of AR from the American Academy of Otolaryngology, Head and Neck Surgery in 2015 are similar in recommending INCSs over leukotriene receptor antagonists as first-line treatment for patients with AR.¹⁸

PHARMACOLOGY^{19,20,21,22}

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are inflammatory mediators produced from arachidonic acid metabolism and are released from a variety of inflammatory cells including mast cells, eosinophils, basophils, and macrophages. They are the most potent bronchoconstrictors yet identified in humans.^{23,24} Leukotriene-mediated effects include airway edema, smooth muscle contraction, mucous secretion, microvascular permeability, and altered cellular activity associated with the inflammatory process.

Montelukast (Singulair) and zafirlukast (Accolate) are leukotriene receptor antagonists (LTRAs) that selectively inhibit the cysteinyl leukotriene receptor. Montelukast inhibits at the LTD₄ receptor, and zafirlukast inhibits at the LTC₄ and LTE₄ receptors. The LT receptor is found on airway smooth muscle cells, airway macrophages, eosinophils, and certain myeloid stem cells. Physiologic effects of the LTRAs in asthma include mild bronchodilation, as well as reductions in allergen-, exercise-, and sulfur-dioxide-induced bronchoconstriction.²⁵ There is also evidence of an anti-inflammatory effect.^{26,27} Zileuton is an inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB₄, LTC₄, LTD₄ and LTE₄) formation.

Although the inflammatory response of AR is mediated primarily by immunoglobulin E (IgE), some data show that LT may also be of importance in inflammatory upper airway disease.²⁸ In genetically predisposed individuals, initial exposure to an allergen causes increased production of IgE antibodies that bind to and sensitize resident mast cells through specific receptors. Upon subsequent exposure to the same substance, these receptors are cross-linked, leading to degranulation and the release of histamine, LT, and other inflammatory and immune mediators in the nasal mucosa. These products of mast cell degranulation effect the immediate hypersensitivity reaction (sneezing, itching, rhinorrhea, and nasal congestion).²⁹

PHARMACOKINETICS^{30,31,32,33}

Drug	Bioavailability (%)	Half-Life (hours)	Protein Binding (%)	Metabolism
montelukast (Singulair)	63–73	2.7–5.5	> 99	extensive via CYP450 and CYP2C9
zafirlukast (Accolate)	unknown (reduced with food intake by 40%)	0.5–5	> 99	extensively metabolized via CYP2C9; several inactive metabolites
zileuton (Zyflo)	unknown	2.5	93	metabolized via CYP1A2, CYP2C9 and CYP3A4; O-glucuronidated and N-dehydroxylated metabolites; several active and inactive metabolites
zileuton ER (Zyflo CR)		8–16		

Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis have a decreased rate of metabolism of montelukast, resulting in a 40% increase in bioavailability and a slight prolongation of half-life.

Because of its primarily hepatic metabolism, the clearance of zafirlukast is reduced in patients with hepatic impairment. In patients with stable alcoholic cirrhosis, the bioavailability of zafirlukast is increased by 50% to 60%. Administration of zafirlukast with food reduces bioavailability by 40%; thus, it is recommended that zafirlukast be given on an empty stomach.

Pharmacokinetics of zileuton ER remains unchanged by hemodialysis. Relative bioavailability of zileuton ER to zileuton immediate-release tablets with respect to C_{max} and AUC under fed conditions were 0.45 (90% confidence interval [CI], 0.41 to 0.49) and 0.76 (90% CI, 0.7 to 0.83), respectively.

CONTRAINDICATIONS/WARNINGS^{34,35,36,37}

Zileuton and zileuton ER are contraindicated in patients with active liver disease or persistent alanine aminotransferase (ALT) elevations of 3 times or more the upper limit of normal (ULN).

Cases of life-threatening liver failure have been reported in patients treated with zafirlukast. The manufacturer recommends physicians consider the value of liver function testing.

Neuropsychiatric events have been reported in some patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton ER (Zyflo CR). In 2009, the FDA required that manufacturers of these products include a precaution about behavior and mood changes in each product's prescribing information.³⁸ The reported neuropsychiatric events include post-marketing cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), tics, and tremor. The Food and Drug Administration (FDA) recommends that prescribers should consider discontinuing these medications if neuropsychiatric symptoms occur.

Patients with asthma on therapy with montelukast (Singulair) may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast and these underlying conditions has not been established.

Patients with phenylketonuria (PKU) should be informed that the 4 mg and 5 mg montelukast chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4 mg and 5 mg chewable tablet, respectively.

DRUG INTERACTIONS^{39,40,41,42}

Drug	Aspirin	Cytochrome P-450 Enzyme Inducers	Erythromycin	Propranolol	Theophylline	Warfarin
montelukast (Singulair)	--	X (May decrease montelukast levels – monitor for decreased clinical response to montelukast)	--	--	--	--
zafirlukast (Accolate) ⁴³	X (Increases plasma levels of zafirlukast by 45%)	No formal studies done but use with caution	X (Decreases plasma levels of zafirlukast by 40% – monitor for decreased clinical response to zafirlukast)	--	X (Decreases mean plasma levels of zafirlukast by 30%)	X (Increases half-life of warfarin and mean prothrombin time by 35% – monitor INR closely)
zileuton, zileuton ER (Zyflo, Zyflo CR)	--	--	--	X (Increase in propranolol concentration, AUC, and half-life; may potentiate bradycardia; monitor vital signs closely)	X (Increases theophylline levels and risk of theophylline toxicity; reduce theophylline dose by 50% when initiating zileuton; monitor theophylline levels closely)	X (Increases INR monitor INR closely if adding or discontinuing zileuton)

Phenobarbital, which induces hepatic metabolism, decreased the area-under-the-curve (AUC) of montelukast approximately 40% following a single 10 mg dose of montelukast. No dosage adjustment for montelukast is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with montelukast.

Patients with known aspirin sensitivity should continue avoiding aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) while taking montelukast. Although montelukast is effective in improving airway function in patients with asthma with documented aspirin sensitivity, it has not been shown to shorten a bronchoconstrictor response to aspirin and other NSAIDs in aspirin-sensitive asthmatic patients.

Studies conducted in healthy subjects between zileuton immediate-release and prednisone and ethinyl estradiol (oral contraceptive), which are metabolized by CYP3A4 isoenzymes, have shown no significant interaction. However, it is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with zileuton extended-release.

Co-administration of zafirlukast dosed at 40 mg twice daily in a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

Co-administration of zafirlukast or zileuton with warfarin results in a clinically significant increase in prothrombin time (PT). Patients on concomitant warfarin and zafirlukast or warfarin and zileuton ER therapy should have their PT/INR monitored closely and warfarin dose adjusted accordingly.

Co-administration of zafirlukast with fluconazole, a moderate CYP2C9 inhibitor, resulted in increased plasma levels of zafirlukast, by approximately 58%. The clinical significance of this interaction is unknown. Zafirlukast exposure is likely to be increased by other moderate and strong CYP2C9 inhibitors.

CYP450 Isoenzyme System

Drug	Substrate	Inhibitor	Inducer
montelukast (Singulair)	CYP3A4* CYP2C9†	--	--
zafirlukast (Accolate)	CYP2C9	CYP3A4 CYP2C9	--
zileuton, zileuton ER (Zyflo, Zyflo CR)	CYP1A2‡ CYP3A4	CYP2C9 CYP1A2	--

* Selected 3A4 substrates: dihydropyridine calcium channel blockers, cisapride, cyclosporine

† Selected 2C9 substrate: warfarin

‡ Selected 1A2 substrate: propranolol

ADVERSE EFFECTS^{44,45,46,47}

Drug	Abdominal Pain	Dyspepsia	Hepatic Enzyme Elevation	Myalgia	Nausea / Vomiting
montelukast (Singulair) n=1,955 (n=1,180)	2.9 (2.5)	2.1 (1.1)	AST/ALT 1.6/2.1 (1.2/2)	reported	reported
zafirlukast (Accolate) n=4,058 (n=2,032)	1.8 (1.1)	1.3 (1.2)	ALT 1.5 (1.1)	1.6 (1.5)	3.1/1.5 (2/1.1)
zileuton (Zyflo) n=475 (n=491)	4.6 (2.4)	8.2 (2.9)	ALT > 3x ULN: 1.9 (0.2)	3.2 (2.9)	5.5 (3.7)
zileuton ER (Zyflo CR) n=199 (n=198)	≥ 1 (< 1)	≥ 1 (< 1)	ALT > 3x ULN: 1.8–2.5 (0.5–0.7)	7 (5)	5 (2)

ULN = upper limit of normal

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

In children, the most common adverse effects reported with montelukast in more than 2% of patients and at a frequency greater than placebo were otitis, pharyngitis, influenza, fever, sinusitis, cough, upper respiratory infection, headache, and diarrhea. With zafirlukast, adverse effects occurring more frequently than in placebo, and in greater than 2% of pediatric patients, were headache (4.5% versus 4.2%, respectively) and abdominal pain (2.8% versus 2.3%, respectively).

The most commonly reported adverse reactions (occurring at a frequency of $\geq 5\%$) in zileuton ER-treated patients and at a frequency greater than placebo-treated patients were sinusitis (6.5% versus 4%, respectively), nausea (5% versus 1.5%, respectively), and pharyngolaryngeal pain (5% versus 4%, respectively). Post-marketing experience with zileuton has shown cases of sleep disorders and behavioral changes.

Monitoring

Assess serum alanine aminotransferase (ALT) before treatment begins, once a month for the first 3 months, every 2 to 3 months for the remainder of the first year, and periodically thereafter for patients receiving long-term zileuton or zileuton ER therapy.

SPECIAL POPULATIONS^{48,49,50,51}

Pediatrics

Safety and efficacy of zileuton and zileuton ER in children under 12 years of age have not been established.

Montelukast is indicated for prophylaxis and chronic treatment of asthma in children 1 year of age and older; acute prevention of EIB in patients 6 years of age and older; relief of symptoms of seasonal AR in children 2 years of age and older; and relief of symptoms of perennial AR in children 6 months of age and older.

Zafirlukast is indicated for prophylaxis and treatment of asthma in children 5 years of age and older.

Pregnancy

Montelukast and zafirlukast are Pregnancy Category B. Congenital limb defects have been rarely reported in the offspring of women being treated with montelukast during pregnancy. A causal relationship between these events and use of montelukast has not been established.

Zileuton and zileuton ER are Pregnancy Category C.

Hepatic Impairment

Use of zileuton or zileuton ER is contraindicated in patients with active liver disease and in patients with elevated hepatic enzymes ≥ 3 times the upper limit of normal.

Zafirlukast is primarily metabolized in the liver and is contraindicated in patients with hepatic impairment including hepatic cirrhosis. A dose reduction may be warranted in patients with stable alcoholic cirrhosis, since the C_{max} and AUC may be 50% to 60% greater than those of normal adults.

Renal Impairment

Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis metabolize montelukast at a slower rate. However, no dosage adjustment is required in patients with mild to moderate hepatic insufficiency. There are no data regarding administering montelukast in patients with severe hepatic insufficiency.

There are no apparent differences in the pharmacokinetics of zafirlukast or zileuton between renally-impaired patients and normal subjects. In addition, pharmacokinetics of zileuton ER remain unchanged by hemodialysis. Therefore, dosing adjustment in patients with renal dysfunction or undergoing hemodialysis for zileuton ER is not necessary.

Elderly

Montelukast has a similar pharmacokinetic profile in the elderly and younger adults. The half-life is slightly increased in the elderly; however, no dose change is needed.

The oral clearance of zafirlukast decreases with age. There is an approximately a 2- to 3-fold increase in drug exposure as evidenced by peak plasma concentration (C_{max}) and area-under-the-curve (AUC) in persons greater than 65 years of age compared to younger adults.

DOSAGES^{52,53,54,55}

Drug	Dosage in Adults	Dosage in Children	Availability
montelukast (Singulair)	Asthma and perennial allergic rhinitis, seasonal allergic rhinitis: 10 mg daily* (≥ 15 years) Exercise-induced bronchoconstriction: 10 mg 2 hours prior to exercise, no more frequently than every 24 hours* (≥ 15 years)	Asthma and perennial allergic rhinitis,: 5 mg daily* (6–14 years); 4 mg daily* (6 months–5 years) Seasonal allergic rhinitis: 5 mg daily* (6–14 years) 4 mg daily* (2–5 years) Exercise-induced bronchoconstriction: 5 mg 2 hours prior to exercise, no more frequently than every 24 hours* (6–14 years)	4 mg granule packets; 4 mg and 5 mg chewable tablets; 10 mg tablets
zafirlukast (Accolate)	20 mg twice daily† (≥ 12 years)	10 mg twice daily† (5–11 years)	10 mg and 20 mg tablets
zileuton (Zyflo)	600-mg tablet 4 times a day‡ (≥ 12 years)	--	600 mg film-coated tablets
zileuton ER (Zyflo CR)	1,200 mg twice daily (≥ 12 years)	--	600 mg extended-release tablets

* When used for asthma and allergic rhinitis, montelukast should be given once daily in the evening.

† Zafirlukast should be taken at least 1 hour before or 2 hours after meals.

‡ Zileuton may be taken with meals and at bedtime for ease of administration.

^{||}Zileuton ER should be taken within 1 hour after morning and evening meals.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

montelukast (Singulair) versus beclomethasone (Vanceril®)

In a multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study, 782 patients ≥ 15 years old with asthma were randomized to receive montelukast 10 mg daily, inhaled beclomethasone 200 mcg twice daily, or placebo for 6 weeks.⁵⁶ The percentage of days of asthma control was almost identical between the montelukast and beclomethasone groups (98% overlap in the distribution). Montelukast was at least equal in efficacy to beclomethasone, and both were greater than placebo on the basis of frequency of asthma attacks, asthma flare-ups, and rescue corticosteroid use. Both treatments were better than placebo at improving forced expiratory volume in 1 second (FEV₁).

montelukast (Singulair) versus fluticasone (Flovent®)

In a multicenter, double-blind, double-dummy, parallel-group design study, 533 patients > 15 years old with persistent asthma were randomized to receive low-dose fluticasone inhalation 88 mcg twice daily or montelukast 10 mg daily.⁵⁷ Compared to montelukast, fluticasone resulted in significantly greater improvements at endpoint in morning pre-dose FEV₁ ($p < 0.001$), forced mid-expiratory flow ($p < 0.001$), forced vital capacity ($p = 0.002$), and peak expiratory flow rate (PEFR) ($p < 0.001$). At endpoint, fluticasone was more effective than montelukast at decreasing rescue albuterol use ($p < 0.001$), asthma symptom scores ($p < 0.001$), and nighttime awakenings due to asthma ($p = 0.023$). Fluticasone increased the percentage of symptom-free days compared with montelukast ($p < 0.001$). Adverse event and asthma exacerbation profiles for fluticasone and montelukast were similar.

In a 48-week, parallel-group, multicenter study with a 12-week, double-blind period, followed by a 36-week, open-label period, it was investigated if montelukast is as effective as low-dose fluticasone in controlling mild persistent asthma as determined by rescue-free days.⁵⁸ The subjects enrolled within the study were 15 to 85 years of age with mild persistent asthma ($n = 400$) and were randomized to oral montelukast 10 mg once nightly or inhaled fluticasone 88 mcg twice daily. The results showed that the mean percentage of rescue-free days were similar between treatments after 12 weeks (fluticasone, 74.9%; montelukast, 73.1% [95% CI, -3.2 to 6.8%]) but not during the open-label period (fluticasone,

77.3%; montelukast, 71.1% [95% CI, 0.8 to 11.7%]). Fluticasone and montelukast significantly improved symptoms, quality of life (QoL), and symptom-free days during both treatment periods; however, greater improvements occurred with fluticasone in lung function during both periods and in asthma control during open-label treatment. The study concluded that, in patients with mild persistent asthma, rescue-free days and most asthma control measures improved similarly with fluticasone and montelukast over the short term, but with prolonged open-label treatment, asthma control improved more with fluticasone.

A randomized, double-blind, 12-week study was performed to evaluate the efficacy, safety, and health outcomes of low-dose fluticasone propionate inhalation powder propionate versus montelukast in 342 children (6 to 12 years of age) with persistent asthma.⁵⁹ The children were given fluticasone propionate inhalation powder 50 mcg twice daily or montelukast chewable 5 mg once daily for a period of 12 weeks. The results showed that, compared with montelukast, fluticasone propionate inhalation powder significantly increased mean percent change from baseline FEV₁ (p=0.002), morning peak expiratory flow (PEF) (p=0.004), evening PEF (p=0.020), and percent rescue-free days (p=0.002) at endpoint, and fluticasone significantly reduced nighttime symptom scores (p<0.001) and mean total (p=0.018), and nighttime (p<0.001) albuterol use. The number of subjects that withdrew was greater with montelukast (21%) than with fluticasone propionate inhalation powder (13%). Adverse events reported with both therapeutic regimens were comparable. The study concluded that fluticasone propionate inhalation powder was significantly more effective than montelukast in improving pulmonary function, asthma symptoms, and reducing rescue albuterol use. Parent- and physician-reported satisfaction ratings were higher with fluticasone propionate inhalation powder treatment, and asthma-related costs were lower.

montelukast (Singulair) versus fluticasone/salmeterol (Advair®)

A 12-week, randomized, double-blind, double-dummy, multicenter trial compared inhaled fluticasone/salmeterol twice daily to montelukast 10 mg daily in patients ≥ 15 years of age.⁶⁰ When compared to patients in the montelukast group, the fluticasone/salmeterol group had significantly better pulmonary function scores, more symptom-free days, more rescue-free days, and fewer nighttime awakenings (p=0.011). Patients in the fluticasone/salmeterol group had significantly reduced asthma scores (p<0.001) and rescue albuterol use (p<0.001) versus the montelukast group.

montelukast (Singulair)/fluticasone (Flovent) versus fluticasone (Flovent)/salmeterol (Serevent®)

A 52-week, 2-period, double-blind multicenter trial enrolled 1,490 patients ages 15 to 72 years with a clinical history of chronic asthma for at least 1 year, a baseline FEV₁ 50% to 90% predicted, a beta₂-agonist improvement of at least 12% in FEV₁, and whose symptoms remained uncontrolled by inhaled corticosteroids.⁶¹ Patients were randomized to receive montelukast 10 mg once daily in the evening or salmeterol 50 mcg twice daily in addition to inhaled fluticasone 100 mcg twice daily. There was no significant difference in the number of patients having asthma exacerbations between the montelukast and salmeterol groups (20.1% and 19.1%, respectively). Improvements in asthma-specific QoL and nocturnal awakenings were also similar between the groups. Both treatments were well tolerated.

A randomized double-blind study enrolled 182 children (ages 6 to 17 years) with uncontrolled asthma while receiving fluticasone 100 mcg twice daily.⁶² The trial compared the efficacy of fluticasone 100 mcg twice daily in combination with each of 3 treatment options: increased inhaled corticosteroids (fluticasone 250 mcg twice daily), addition of salmeterol 50 mcg twice daily, or the addition of montelukast 5 to 10 mg once daily. Patients received each treatment option in random order for 16

weeks. The primary outcome measure was the patient's differential response to the 3 step-up therapies based on use of oral prednisone for acute asthma exacerbations, asthma control days, and FEV₁. A total of 161 patients had evaluable data. The response to salmeterol was most likely to be the best response, as compared with responses to montelukast (relative probability, 1.6; 95% CI, 1.1 to 2.3; p=0.004) and fluticasone step-up (relative probability, 1.7; 95% CI, 1.2 to 2.4; p=0.002). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to salmeterol (p=0.009). White race predicted a better response to salmeterol step-up, whereas African-American patients were least likely to have a best response to montelukast (p=0.005).

montelukast (Singulair) versus placebo

A 12-month, multicenter, randomized, double-blind, placebo-controlled trial of 220 children ages 2 to 14 years of age with intermittent asthma was conducted to determine if intermittent use of montelukast (n=107) would modify the severity of an asthma episode.⁶³ Parents initiated treatment at the onset of each upper respiratory tract infection or asthma symptom onset. Treatment continued for at least 7 days, or until symptoms resolved for 48 hours. There were 681 treatment episodes (montelukast, 345 episodes; placebo, 336 episodes) in 202 patients. The montelukast group had 163 unscheduled health care resource utilization occurrences compared to 228 in the placebo group (odds ratio [OR], 0.65; 95% CI, 0.47 to 0.89). Symptoms were reduced by 14% and nights awakened by 8.6% (p=0.043). Days off from school or childcare decreased by 37% and parent time off from work by 33% (p<0.0001, respectively). A short course of montelukast introduced at first signs of an asthma exacerbation had a positive impact on asthma symptoms and related activities.

zafirlukast (Accolate) versus fluticasone (Flovent)

In a 12-week double-blind study, 338 patients with asthma were randomized to receive fluticasone 88 mcg inhaled twice daily, zafirlukast 20 mg twice daily, or placebo.⁶⁴ Patients ≥ 12 years old taking fluticasone experienced significantly greater improvements in all clinical parameters (symptom scores, percentages of symptom-free and albuterol-free days, albuterol use, and nighttime awakenings) compared with patients taking zafirlukast (p<0.05) or placebo (p<0.05). Fewer fluticasone patients (4%) had an exacerbation requiring oral corticosteroids compared with those taking zafirlukast (12%) or placebo (10%).

In a double-blind study, a total of 440 patients ≥ 12 years old previously treated with inhaled corticosteroids and short-acting beta-agonists were randomized to treatment with fluticasone inhalation 88 mcg or zafirlukast 20 mg twice daily for 6 weeks.⁶⁵ Patients treated with fluticasone experienced greater mean increases in FEV₁ and PEFR during the study than did those treated with zafirlukast (p<0.001 for all endpoints). Fluticasone-treated patients had significantly greater increases in symptom-free days (p<0.001), rescue-free days (p=0.002), nights with uninterrupted sleep (p=0.006), and fewer asthma exacerbations (p=0.005). Fewer fluticasone-treated patients were withdrawn due to lack of efficacy (p<0.001).

A 12-week, randomized, double-blind, double-dummy, multicenter study was conducted in 451 patients ≥ 12 years old with asthma who were symptomatic on short-acting beta-agonists alone.⁶⁶ After an 8 to 14 day run-in period, patients were randomized to treatment with fluticasone inhalation 88 mcg twice daily or zafirlukast 20 mg twice daily. Treatment with fluticasone was more effective than treatment with zafirlukast in increasing morning FEV₁ (p<0.001) and PEFR (p<0.001). Statistically significant differences between the 2 treatments in FEV₁ were noted after the first observation (Week 4) and in PEFR by Week

2. Mean change in percentage of symptom-free days was greater with fluticasone than with zafirlukast ($p < 0.001$), and fluticasone significantly increased the percentage of rescue-free days ($p < 0.001$). Treatment with fluticasone significantly reduced albuterol use by 2.4 puffs per day compared with 1.5 puffs per day and increased the percentage of nights with no awakenings compared with zafirlukast ($p < 0.001$ for both endpoints).

zileuton ER (Zyflo CR) versus placebo

Efficacy of zileuton ER was evaluated in a randomized, double-blind, parallel-group, multicenter, 12-week, placebo-controlled trial of 397 patients ≥ 12 years old with asthma.^{67,68} Patients were randomized to receive two 600 mg tablets of zileuton ER or placebo. Improved FEV₁ after 12 weeks was the primary efficacy endpoint. Zileuton ER improved FEV₁ more than placebo (0.39 L versus 0.27 L, respectively; $p = 0.021$). Secondary endpoints of PEFr and rescue beta agonist use were also supportive of the active treatment.

Seasonal Allergic Rhinitis

montelukast (Singulair) versus loratadine (Claritin®)

A multicenter, double-blind, placebo- and active-controlled trial evaluated the effectiveness and tolerability of montelukast for treating patients ages 15 to 81 years with seasonal AR.⁶⁹ After a 3 to 5 day, single-blind placebo run-in period, 1,302 patients with active AR symptoms were randomly assigned to receive montelukast 10 mg, loratadine 10 mg, or placebo administered once daily at bedtime for 2 weeks during the spring allergy season. The primary endpoint, daytime nasal symptoms score (mean of nasal congestion, rhinorrhea, nasal pruritus, and sneezing scores on a 0 to 3 scale), improved from baseline in both active treatment groups compared to placebo ($p \leq 0.001$ comparing each active treatment with placebo). Although not a statistically significant difference, there was a strong trend towards more improvement with loratadine than with montelukast. Mean changes from baseline in all other diary-based scores, including nighttime and eye symptom scores, were significantly greater for each active treatment than for placebo. QoL scores were also significantly greater for each active treatment than for placebo. Adverse effects for both active treatments were comparable to that of placebo.

Seasonal Allergic Rhinitis and Asthma

montelukast (Singulair) versus placebo

A 4-week, randomized, parallel group, multicenter study was conducted with 433 adult patients who had both chronic asthma and seasonal AR to determine the effectiveness of montelukast 10 mg versus placebo in improving the asthma symptoms during the allergy season.⁷⁰ There was a 1-week, single-blind, placebo run-in period followed by 3 weeks of double-blind treatment. The primary endpoint was mean change from the baseline to Week 3 in the daytime asthma symptom score. Patients recorded daytime and nighttime asthma symptom scores, beta agonist use, and morning/evening PEFr daily using an electronic diary. Compared with placebo, montelukast resulted in significant improvement from baseline in all of the measured areas including the daytime asthma symptom score ($p = 0.002$). Few patients discontinued due to asthma.

To determine the effect of montelukast on asthma during the allergy season in children with persistent asthma and seasonal aeroallergen sensitivity, a 3-week, double-blind, placebo-controlled, parallel-

group, randomized study compared daily montelukast 5 mg chewable tablets and placebo.⁷¹ Patients (n=421) were 6 to 14 years of age with FEV₁ ≥ 60% and ≤ 85% predicted, persistent asthma that is also active during allergy season, and documented sensitivity to seasonal allergens. Montelukast was not significantly different from placebo (least squares mean 9.53% versus 9.15%, respectively; p=0.810) for the primary endpoint, percent change in FEV₁ from baseline. Compared with placebo, montelukast was associated with significantly lower (better) investigator's global asthma evaluation (LS mean 2.71 versus 2.98; p<0.05) and parent/guardian global asthma evaluation (LS mean: 2.63 versus 2.9; p<0.05) scores. Both treatments were well tolerated with no significant differences observed in rates of adverse effects.

Perennial Allergic Rhinitis

montelukast (Singulair) versus placebo

A 6-week, 2-arm, double-blind study was conducted during the winter season following a placebo run-in period to evaluate montelukast 10 mg (n=1,002) and placebo (n=990) in the treatment of perennial allergic rhinitis (PAR) in adults.⁷² The primary endpoint was the daytime nasal symptoms score, defined as the average of scores for nasal congestion, rhinorrhea, and sneezing, as rated daily by patients. A statistically significant improvement in daytime nasal symptoms was noted in the montelukast group (p<0.001). Other endpoints that showed statistically significant improvement in the montelukast group included nighttime symptoms score and each of the 4 nasal symptoms (congestion, rhinorrhea, sneezing, and itching). According to the study, the treatment effects of montelukast were stable and persistent during the entire 6 weeks of treatment.

META-ANALYSES

A 2005 meta-analysis summarized the ability to control asthma symptoms for patients unsuccessfully controlled on regular inhaled corticosteroids (ICS) with add-on therapy of either leukotriene receptor antagonists or long-acting beta₂-agonists (LABA) (8 trials).⁷³ The results suggest there are significantly fewer exacerbations requiring systemic corticosteroids in the ICS + LABA group compared to the ICS + leukotriene receptor antagonist group (RR, 0.83; 95% CI, 0.71 to 0.97). Additional outcomes that favor the ICS + LABA group based on this analysis include improved morning and evening PEFr, increased symptom-free days, reduced night awakenings, and less need for rescue beta₂-agonists. The risk of withdrawal for any reason was also significantly lower in the ICS + LABA group compared to the ICS + leukotriene receptor antagonist group (RR, 0.84; 95% CI, 0.74 to 0.96). A more recent Cochrane review of 37 trials evaluating the benefit of adding a leukotriene receptor antagonist to an inhaled corticosteroid found similar results.⁷⁴ Adjunct therapy with an ICS reduced the number of patients with exacerbations requiring oral corticosteroids (RR, 0.5; 95% CI, 0.29 to 0.86). No determination regarding whether a leukotriene receptor antagonist is superior, inferior, or equivalent to a higher dose of ICS could be made.

A systematic review compared the efficacy of inhaled corticosteroids versus montelukast in schoolchildren and adolescents with mild to moderate persistent asthma.⁷⁵ Studies had to have a minimum of 4 weeks of inhaled corticosteroids compared to montelukast or to the combination of montelukast plus inhaled corticosteroids. A total of 18 randomized, prospective, controlled studies with 3,757 patients published from January 1996 to November 2009 were included. The primary outcome was asthma exacerbations requiring systemic corticosteroids. Other outcomes included pulmonary function, withdrawal and/or hospitalization due to acute asthma exacerbation, change in symptoms score, rescue-medication-free days, albuterol use, adverse effects, and adherence. Patients receiving

inhaled corticosteroids had a significantly lower risk for asthma exacerbation than those with montelukast (RR, 0.83; 95% CI, 0.72 to 0.96; p=0.01); post-hoc analysis suggests this effect was independent of quality, sponsorship, and study duration. Children treated with ICS had a significant higher pulmonary function (final FEV₁ percent of predicted, change from baseline FEV₁ percent, final morning peak expiratory flow) and better clinical parameters (albuterol use, symptom score, rescue-medication-free days, withdrawals due to asthma exacerbation) compared to montelukast.

SUMMARY

At this time, high-quality comparative trials of the leukotriene modifiers are lacking. Selection of a particular agent for the treatment of asthma should be based on the patient's age, current drug regimen (assessing the possibility of drug interactions), and tolerability. Leukotriene modifiers offer an alternative controller option in patients with asthma.

The National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) guidelines recommend inhaled corticosteroids as the cornerstone for the treatment of asthma, while leukotriene modifiers are included as potential alternatives or add-on therapy. Leukotriene modifiers are used as add-on therapy in patients receiving inhaled corticosteroids to reduce the dose of the inhaled corticosteroids in patients with moderate to severe asthma, and to potentially improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled corticosteroids. In adults and adolescents over 12 years of age and children ages 5 or 6 to 11 years, leukotriene modifiers are not the preferred adjunctive therapy to inhaled corticosteroids compared to the addition of long-acting inhaled beta₂-agonists. However, they may be used as preferred alternative or add-on controller treatment for asthma in younger children. These agents may be appropriate for initial controller treatment for patients who are unable or unwilling to use inhaled corticosteroids, intolerant to inhaled corticosteroids, or who also have allergic rhinitis. Limited data exist to support the use of leukotriene modifiers in acute asthma.

Zafirlukast (Accolate) is dosed twice daily. Zileuton (Zyflo) and zileuton ER (Zyflo CR) are dosed 4 or 2 times daily, respectively, and pill burden remains a compliance issue for both agents. The precautions associated with liver toxicity associated with zileuton and zileuton ER may warrant a closer evaluation of the risks and benefits for using these drugs. In contrast, montelukast (Singulair) offers a once daily dosing regimen and multiple dosing forms for ease of administration; montelukast is the only leukotriene modifier approved for the treatment of allergic rhinitis (AR).

In AR, montelukast is considered an alternative to first-line therapy with intranasal corticosteroids in patients who suffer from both asthma and AR.

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