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The Use of Leukotriene Receptor Antagonists to Treat Allergic Rhinitis

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Introduction

Allergic rhinitis (AR) is an IgE-mediated hypersensitivity reaction of the nasal mucosa to allergens such as animal dander, pollen, dust mites or mold. Symptoms of AR include sneezing, itching of the nose and palate (pruritus), clear nasal discharge (rhinorrhea), and nasal congestion. Allergic rhinitis is often associated with itchy, swollen, watery eyes (allergic conjunctivitis) as well as constant clearing of the throat and snoring.[1] Asthma is a common concomitant disease state with more than 90 percent of asthma patients reporting at least one AR symptom and approximately 85 percent of asthma patients reporting at least four AR symptoms.[2] Allergic rhinitis may affect people seasonally or year round depending on the allergen. Complications of untreated AR include ear infections, sinusitis, recurrent sore throats, cough, headache, difficulty sleeping, fatigue, irritability, and poor school performance.[3] Approximately 26 percent of the U.S. population is affected by AR[2] and an estimated 80 million people suffer from nasal/ocular symptoms for more than a week every year.[4] Allergic rhinitis sufferers consume over $6 billion in prescription medications a year.[1] One study estimates that AR sufferers miss 3.5 million work days and more than 2 million school days per year.[5] According to a recent Harvard study, AR costs U.S. employers $5.4 billion annually in sick days and may be as high as $7.7 billion if loss of productivity is included in the calculation.[6]

Pharmacological therapies have included intranasal cromolyn, oral and topical antihistamines, oral and topical decongestants, and oral and topical corticosteroids. The newest FDA approved AR agent is montelukast. It is a leukotriene receptor antagonist (LTRA) approved in January 2003 for the treatment of seasonal AR. It is marketed by Merck as Singulair® and was originally approved in February 1998 for the treatment of asthma.[7] A second member of the same class of agents whose off-label uses include treatment of AR is zafirlukast (Accolate®).[8] It was approved for the treatment of asthma in September 1996 and is marketed by AstraZeneca. Pranlukast (Ultair®) is a third LTRA, but it is not marketed in the U.S. This article will address the pharmacology, AR clinical trials, adverse effects, dosing, and costs of the two LTRAs available in this country, montelukast and zafirlukast.

Pathogenesis of Allergic Rhinitis

The inflammatory reaction of AR occurs in two phases denoted as early-phase and late-phase. Early-phase symptoms occur within minutes of exposure to a sufficient amount of allergen. These symptoms, such as watery rhinorrhea, sneezing, itching and the sensation of congestion, are due to vasodilation, increased vascular permeability, stimulation of mucus-producing glands and neuronal stimulation. Many mediators are involved including histamine, platelet activating factor, prostaglandins, cytokines, tryptase, and leukotrienes, with histamine as a prominent factor in the early-phase response. Chemotactic factors released during the early-phase attract additional inflammatory mediators to the nasal mucosa, particularly basophils, neutrophils, eosinophils and T lymphocytes.

Table 1. Pharmacokinetics (PK) of leukotriene receptor antagonists for special populations[8, 11-13]

Population	Montelukast	Zafirlukast
Children 2-5 y	4 mg tablet is similar to 10 mg tablet in adults	No indication for this age group
Children 6-14 y (MTK) Children 5-11 y (ZFK)	5 mg tablet is similar to 10 mg tablet in adults	10 mg tablet is similar to 20 mg tablet in adults
Adolescents ≥15 y (MTK) Adolescents ≥12 y (ZFK)	10 mg tablet is similar to 10 mg tablet in adults	20 mg tablet is similar to 20 mg tablet in adults
Elderly > 65 y	Small decrease in clearance	Clearance reduced by 50-60%
Hepatic Insufficiency	CL reduction dependent on loss of hepatic fx	CL reduction dependent upon loss of hepatic fx
Renal Insufficiency	No clinical affect on PK	No clinical affect on PK

MTK=montelukast, ZFK=zafirlukast, CL=clearance

This second wave of mediators is responsible for the late-phase response hours later, which is characterized primarily by nasal obstruction, but also includes a sustained perpetuation of the rhinorrhea, sneezing and itching from the early-phase. The cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4, produced by eosinophils during the late-phase, play a key role in the perpetuation of nasal symptoms, especially congestion.[9] Many studies have shown increased concentrations of leukotrienes in nasal lavages after allergen challenge.[10] Montelukast and zafirlukast selectively bind to cysteinyl leukotriene receptors without agonist activity. Blockade of the cysteinyl leukotriene receptor inhibits both upper and lower airway inflammation mediated by various allergens, thus the drugs may be used for both asthma and AR.[8, 11-13]

Pharmacokinetics

The pharmacokinetics profiles for the LTRAs are not affected by race or gender. Both zafirlukast and montelukast are administered orally and have rapid absorption, within 3-4 hours. Both are highly bound to plasma proteins (>99%) and have minimal distribution across the blood-brain barrier. Zafirlukast and montelukast are hepatically metabolized by the cytochrome P450 2C9 and 3A4/2C9 systems, respectively. At therapeutic concentrations, zafirlukast is also an inhibitor of CYP3A4 and CYP2C9. Montelukast, on the other hand, is not an inhibitor of CYP450 isoemzymes. Both drugs are primarily excreted via the biliary route.[8, 11-13]

The pharmacokinetics of the LTRAs for special populations are summarized in Table 1. As long as smaller doses are administered, the plasma concentrations profiles of LTRAs in children are similar to that of healthy young adults. With healthy young adults as the standard, the pharmacokinetics of LTRAs differ in the elderly and patients with hepatic insufficiency.[8, 11-13]

The oral bioavailability of a 10 mg montelukast tablet is not affected by food in adults, so it may be taken without regard to meals. The bioavailability of 4 mg and 5 mg chewable tablets in children and adolescents is reduced by 37% when taken with a meal. In spite of the reduced bioavailability, there is no reduction in the clinical efficacy, so it may also be taken without regard to meals.[11] The bioavailability of zafirlukast, on the other hand, is reduced by approximately 40% when taken with meals, so it should be taken one hour before or two hours after a meal.[8]

Clinical Trials

Donnelly et al. compared zafirlukast to placebo for relief of acute seasonal AR. In this randomized, double-blind, parallel-group trial, 164 people with documented symptomatic ragweed allergy spent eight hours a day for two consecutive days in an outdoor park during ragweed season in Iowa. After 3 hours on the first day, they were randomized to receive a single dose of 10, 20, 40, or 100 mg zafirlukast or placebo. Subjects self-assessed their symptoms (none, slight, mild, moderate, or severe) hourly at the park and every 2 hours at home for 2 days. Inhaled ß-agonist use was allowed during the trial for relief of symptomatic bronchoconstriction. Zafirlukast relieved nasal congestion and rhinorrhea more effectively than placebo ($p \leq 0.05$). Sneezing was also reduced ($p \leq 0.05$), an unexpected result since sneezing is

Table 2. Efficacy of leukotriene receptor antagonists in seasonal allergic rhinitis[5, 9,13-16]

Reference	Design	Duration	Treatment	N	Results
Donnelly et al. 2002[13]	R, DB, PC, PG	2 days	ZFK 10, 20, 40, 100mg PBO	164	ZFK > PBO
Flowers et al. 1990[15]	DB, PC, C	not specified	MTK 10mg PBO	12	MTK = PBO
Philip et al. 2002[10]	R, DB, PC, PG	2 weeks	MTK 10mg LTD 10mg PBO	1302	LTD = MTK > PBO
Lis et al. 2001[18]	R, DB, PC, PG	2 weeks	MTK 10mg + LTD 10mg MTK 10mg LTD 10mg PBO	907	MTK + LTD = monotherapy with either agent > PBO
Meltzer et al. 2000[16]	R, DB, PC, PG	2 weeks	MTK 10mg + LTD 10mg MTK 10mg MTK 20mg LTD 10mg PBO	453	MTK + LTD > monotherapy with either agent = PBO
Wilson et al. 2001[19]	R, SB, PC, C	2 weeks	FXD 120mg MTK 10mg LTD 10mg PBO	37	FXD = MTK + LTD > PBO
Pullerits et al. 1999[17]	R, DB, PC, PG	7 weeks	ZFK 40mg BCM 400mcg PBO	32	BCM > ZFK = PBO
Wilson et al. 2001[20]	R, SB, PC, DD, C	2 weeks	MTK 10mg Inhaled BDS 400mcg + intranasal BDS 200mcg	12	BDS > MTK > PBO
Wilson et al. 2001[21]	R, SB, PC, C	2 weeks	MTK 10mg + CTZ 10mg MTS 200mcg PBO	22	MTS = MTK + CTZ > PBO
Wilson et al. 2001[22]	R, SB, PC, DD, C	2 weeks	MTK 10mg + CTZ 10mg Inhaled BDS 400mcg + intranasal BDS 200mcg	21	BDS = MTK + CTZ > PBO
Wilson et al. 2000[23]	R, SB, PC, PG	4 weeks	CTZ 10mg + MTK 10mg CTZ 10mg + MTS 200mcg CTZ 10mg + PBO	38	CTZ = CTZ + MTK = CTZ + MTS > PBO

N=number of patients, R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, ZFK=zafirlukast, PBO=placebo, C=crossover, MTK=montelukast, LTD=loratadine, SB=single-blind, FXD=fexofenadine, BCM=beclomethasone, DD=double-dummy, BDS=budesonide, CTZ= cetirizine

thought to be histamine-mediated. The 20 and 40 mg doses relieved symptoms more consistently than either the 10 or 100 mg doses. Overall, there was greater symptom relief on the second day.[14]

Flowers et al. compared montelukast to placebo in a double-blind, placebo-controlled crossover antigen-challenge study of 12 participants with documented symptomatic ragweed and grass pollen allergies. A solution of ragweed or mixed grass pollen extract was delivered intranasally to the subjects. There was no clinical difference between montelukast and placebo in relief of rhinorrhea, nasal congestion, throat irritation or sneezing.[15]

Philip et al. examined the daily administration of montelukast 10 mg, loratadine 10 mg, and placebo for relief of seasonal AR. In spring 2000, 1302 people were evaluated in a randomized, double-blind, parallel-group study at 50 study centers in the U.S. and Canada. Subjects rated and recorded their daytime and nighttime symptoms. Both nasal symptoms (nasal congestion, rhinorrhea, nasal pruritus and sneezing) and ocular symptoms (tearing,

Table 3. Adverse effects of leukotriene receptor antagonists compared to placebo[8, 11-13, 19]

Adverse Effect	Montelukast vs. Placebo		Zafirlukast vs. Placebo	
Headache	18.4%	18.1%	9.9%	9.0%
Nausea	<1%	<1%	2.6%	2.2%
Diarrhea	3.1%	3.1%	2.3%	1.8%
Abdominal pain	2.9%	2.5%	1.6%	1.2%
Dyspepsia	2.1%	1.1%	1.3%	1.2%
Rash	1.6%	1.2%	<1%	<1%
Cough	2.7%	2.4%	<1%	<1%
Fever	1.5%	0.9%	1.6%	1.1%

ocular pruritus, redness and puffiness) were assessed during a 3- to 5-day placebo run-in period followed by a two-week double-blind treatment period. Montelukast provided significant relief compared to placebo ($p \leq 0.001$), as did loratadine ($p \leq 0.001$ for daytime symptoms, $p \leq 0.003$ for night-time symptoms). A statistical comparison between montelukast and loratadine was not incorporated into this study. However, according to the authors, mean changes from baseline numerically favored montelukast over loratadine for the night-time symptoms score (difficulty going to sleep, night-time awakenings, congestion upon awakening); while daytime nasal, eye, and daily composite scores numerically favored loratadine."[10]

The Montelukast Study Group published a randomized, placebo-controlled comparison of combination therapy with montelukast and loratadine vs. monotherapy with each agent. Subjects were randomized into 5 treatment groups and received montelukast 10 mg, montelukast 20 mg, loratadine 10 mg, montelukast 10 mg + loratadine 10 mg, or placebo. The study consisted of 453 subjects participating in a 1-week placebo run-in period followed by a 2-week treatment period. Neither montelukast nor loratadine monotherapy was rated significantly more effective than placebo at relieving daytime nasal symptoms. Combination treatment gave better results than monotherapy with either agent. [16]

Pullerits et al. published the results of a randomized, double-blind, placebo-controlled, parallel-group trial comparing zafirlukast 20 mg bid, intranasal beclomethasone 200 mcg bid, and placebo. Thirty-two patients with documented seasonal grass pollen AR participated in this 50-day study. Patients began using their randomly assigned treatment three weeks prior to the beginning of grass pollen season and continued throughout the grass pollen season. Symptoms of sneezing, rhinorrhea, nasal itch, and blockage were rated and recorded daily by each subject. There was no significant difference between zafirlukast and placebo. However, subjects consistently rated the beclomethasone treatment superior to both zafirlukast and placebo on daily symptom relief. In addition, six weeks after the study began, nasal biopsies were evaluated for eosinophil cationic protein (labeled with mouse antihuman EG2 antibody) as a marker of activated eosinophils. The beclomethasone treatment group showed a significantly smaller increase in EG2-positive cells than did the placebo group. The increase in EG2-positive cells was not significantly different between the placebo and the zafirlukast groups.[17] The results of these and other pertinent studies are summarized in Table 2.

Adverse Effects

Montelukast's adverse effects have been studied in over 2900 adults and children age six and over for periods of up to two years.[19] Likewise, the adverse effects of zafirlukast have been evaluated in more than 4000 adults and children age 12 and over for periods ranging from 13 weeks to more than a year.[13] The adverse effect profile of LTRAs is similar to that of a placebo (Table 3), with headache being the most commonly reported adverse reaction.[19] Asymptomatic elevations in hepatic enzymes have been reported in 1.5%-1.8% of adults using zafirlukast during post-marketing studies.

Table 4. Leukotriene receptor antagonists dosages for various populations[8, 11]

Population	Montelukast	Zafirlukast
Adults and adolescents	10 mg qd (adolescents ≥ 15 y)	20 mg qd (adolescents ≥ 12 y)
Adolescents and children 6-14 y	5mg qd	Contraindicated for < 12 y
Children 2-5 y	4mg qd	Contraindicated
Children and infants < 2 y	Contraindicated	Contraindicated
Elderly	No dosing adjustment needed	No dosing adjustment needed
Patients with renal impairment	No dosing adjustment needed	No dosing adjustment needed
Patients with hepatic impairment	Use with caution	Use with caution
Pregnant women	No dosing adjustment needed	No dosing adjustment needed
Lactating women	Contraindicated	Contraindicated

There have been rare cases of hyperbilirubinemia or jaundice associated with zafirlukast. It is recommended that liver function enzymes be taken immediately should a patient on an LTRA develop symptoms of hepatic dysfunction. If enzymes are elevated, the LTRA should be discontinued.[8]

Churg-Strauss syndrome, a systemic eosinophilic vasculitis, has been associated with both LTRAs. It is very rare and in most, but not all cases, it is associated with a reduction in oral corticosteroid therapy. Symptoms of Churg-Strauss include eosinophilia, inflammation of blood vessels, especially in the lungs, leading to worsening pulmonary symptoms. It occurs more often in women than in men. A causal relationship between LTRAs and this syndrome has not been established.[8, 13]

Dosing

Montelukast is available as a 10 mg film-covered tablet and 4 mg and 5 mg chewable cherry-flavored tablets. Zafirlukast is available as a 10 mg and 20 mg tablet. Dosages are listed in Table 4. Both LTRAs are Pregnancy Category B.[8, 11]

Drug Interactions

Zafirlukast increases the AUC (63%) and half-life (36%) of S-warfarin, resulting in a 35% increase in prothrombin time. Co-administration of zafirlukast (40 mg/day) and aspirin (650 mg qid) can cause a 45% increase in zafirlukast's concentration. Zafirlukast's inhibition of CYP 3A4 and 2C9 has the potential to increase the concentrations and risk of toxicity of drugs metabolized by one or both of these isoenzymes. No significant effect on oral contraceptives has been observed.[8, 13]

Montelukast has no clinically significant interactions with theophylline, fexofenadine, oral contraceptives, digoxin or warfarin. Phenobarbital can decrease montelukast AUC by approximately 40%. Because montelukast is metabolized via CYP 3A4 and 2C9, there is a potential for interactions with other drugs that are enzyme inhibitors (ketoconazole, erythromycin) or enzyme inducers (carbamazepine, phenobarbital, phenytoin).[11, 12]

Cost

As of March 2003 a survey of three pharmacies in the Gainesville, FL area revealed a difference of over $22 and $41 in quoted zafirlukast and montelukast prices, respectively (Table 5).

Summary

Montelukast and zafirlukast have been used for the treatment of seasonal AR. However, only montelukast has recently received FDA approval for such indication. Leukotrienes play a key role in perpetuation of AR symptoms, especially nasal congestion. The pharmacology of LTRAs, blockade of the cysteinyl leukotriene receptor resulting in inhibition of one pathway of airway inflammation, supports their indication for the treatment of AR. However, clinical trials have provided inconsistent results comparing LTRAs to placebo for improvement of AR.

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Table 5. Retail cost of a 30-day supply of LTRAs in Gainesville, FL area pharmacies

LTRA	Pharmacy #1	Pharmacy #2	Pharmacy #3
Zafirlukast 10mg, #60	$74.46	$85.65	$96.19
Zafirlukast 20mg, #60	$74.46	$85.65	$96.19
Montelukast 4mg, #30	$89.88	$102.95	116.19
Montelukast 5mg, #30	$89.88	$102.95	$116.29
Montelukast 10mg, #30	$83.46	$102.95	$125.09

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