REVIEW ARTICLE

Drug Safety 2003; 26 (7): 483-518
0114-5916/03/0007-0483/$30.00/0

Benefit-Risk Assessment of Antileukotrienes in the Management of Asthma

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Contents

Abstract

Antileukotrienes are a relatively new class of anti-asthma drugs that either block leukotriene synthesis (5-lipoxygenase inhibitors) like zileuton, or antagonise the most relevant of their receptors (the cysteinyl leukotriene 1 receptor [CysLT1]) like montelukast, zafirlukast or pranlukast. Hence, their major effect is an anti-inflammatory one. With the exception of pranlukast, the other antileukotrienes have been studied and marketed in the US and Europe for long enough to establish that they are useful drugs in the management of asthma. Their effects, significantly better than placebo, seem more pronounced in subjective measurements (i.e. symptoms scores or quality-of-life tests) than in objective parameters (i.e. forced expiratory volume in 1 second or peak expiratory flow rate). Also, there is some evidence that these drugs work better in some subsets of patients with certain genetic polymorphisms – probably related to their leukotriene metabolism – or patients with certain asthma characteristics. There are a small number of comparative studies only, and with regard to long-term asthma control differences between the agents have not been evaluated. Nevertheless, their overall effect appears comparable with sodium cromoglycate (cromolyn sodium) or theophylline, but significantly less than low-dose inhaled corticosteroids. Antileukotrienes have been shown to have a degree of corticosteroid-sparing effect, but salmeterol appears to perform better as an add-on drug. Montelukast is probably the most useful antileukotriene for continuous treatment of exercise-induced asthma, performing as well as salmeterol without inducing any tolerance. All antileukotrienes are taken orally; their frequency of administration is quite different ranging from four times daily (zileuton) to once daily (montelukast). Antileukotrienes are well tolerated drugs, even though zileuton intake has been related to transitional liver enzyme elevations in some cases. Also Churg-Strauss syndrome (a systemic vasculitis), has been described in small numbers of patients taking CysLT1 antagonists. It is quite probable that this disease appears as a consequence of an 'unmasking' effect when corticosteroid dosages are reduced in patients with severe asthma once CysLT1 antagonists are introduced, but more data are needed to definitely establish the mechanism behind this effect. Overall, however, the benefits of antileukotrienes in the treatment of asthma greatly outweigh their risks.

Asthma is one of the most important diseases in terms of prevalence, morbidity and resource consumption,[1,2] so the introduction of new drugs is always welcomed. Antileukotrienes, including receptor antagonists and synthesis inhibitors, are the only new anti-asthma drug class to be launched in the past decade. These new agents raised great expectations as they are directed against the most potent of all asthma mediators, the leukotrienes. These substances are synthesised by many cells from the arachidonic acid in the phospholipid bilayer of the cell membrane in response to a variety of stimuli including allergens.[3]

The present review includes the information retrieved from PubMed from the publication of the first trials in 1990 up to May 2002. Each antileukotriene, i.e. montelukast, zafirlukast, pranlukast and zileuton, was included as a keyword and the search was then narrowed to retrieve only clinical trials. For the most part the papers included here describe controlled clinical trials. However, some information from uncontrolled clinical trials has been included when a specific area has not yet been covered by a controlled trial. A second search was performed to gather information about Churg-Strauss syndrome and its relation to the antileukotrienes. Again, each antileukotriene was included as keyword, narrowing the search to only those papers that included the syndrome as another keyword. In section 9, where this condition is discussed, more general papers on the syndrome itself have been used in order to provide a general idea of this illness.

1. Pharmacology of Antileukotrienes

1.1 Mechanism of Action

Leukotrienes are mediators formed from arachidonic acid, a compound that is a normal constituent of the phospholipid bilayer of many biological membranes, especially the nuclear membrane. There are two kinds of leukotrienes: the dihydroxy acid leukotriene B4 (LTB4) and the cysteinyl leukotrienes (CysLT) C4 (LTC4), D4 (LTD4) and E4 (LTE4).

LTB4 has a specific receptor and acts mainly as a neutrophil chemoattractant. CysLTs operate through two different receptors, CysLT1 and CysLT2 receptors. The first seems to be the most important for the induction of the asthmatic reaction as it increases vascular permeability (an effect also elicited through CysLT2), induces contraction and finally hypertrophy of smooth muscle and also stimulates mucosal secretion and eosinophil recruitment.[3-5]

Recently, the discovery of a special LTC4 high affinity binding site has been described.[6] Its function seems to differ from the contraction effects on bronchial smooth muscle elicited by LTC4 and LTD4 through CysLT1. This could explain why the CysLT1 antagonists do not have exactly the same potency as each other in blocking the effects of LTC4 and LTD4 on this receptor.[6,7]

Arachidonic acid, released by phospholipase A2 from membranes in response to different activating signals including receptor activation, physical stimuli (i.e. cold or hyperosmolar milieu), or antigen-antibody reactions, interacts with 5-lipoxygenase (5-LO)-activating protein (FLAP), which helps to transfer it to 5-LO. This interaction results in the formation of 5-hydroxyperoxyeicosotetraenoic acid (5-HPETE), which is transformed to the unstable intermediate leukotriene A4 (LTA4) also by 5-LO. In neutrophils and monocytes LTA4 is predominantly converted to LTB4 by a hydrolase. In eosinophils, mast cells and basophils the intermediate leukotriene is conjugated with reduced glutathione by LTC4 synthase. LTC4 is carried out of the cell and then transformed to LTD4 and LTE4.[4,8,9]

There are two different ways of interfering with the action of leukotrienes. One is by inhibiting their production by inhibiting 5-LO or FLAP activity (inhibitors) and the other is by blocking their receptors (antagonists). The available antagonists are, for the moment, directed against the one receptor demonstrated to play a role in asthma symptoms, CysLT1, and they act in a competitive way. The 5-LO blockers also inhibit production of LTB4.

CysLT1 antagonists that are currently commercially available are zafirlukast, pranlukast, and montelukast. The only marketed 5-LO inhibitor is zileuton.

1.2 Clinical Pharmacokinetics and Bioavailability

All antileukotrienes are orally administered, are absorbed in the gastrointestinal tract and are extensively metabolised in the liver. Most of the drug is excreted by the biliary system and a small amount in the urine. CysLT1 antagonists have a longer mean plasma half life than zileuton (montelukast 2.7–5.5 hours,[10] zafirlukast 8–16 hours,[11,12] zileuton 2.5 hours[13] and pranlukast 1.45–3.28 hours).[14,15]

For zafirlukast, the recommended dose in adults is 20mg every 12 hours; in children the dose is 10mg

twice daily. The drug is approved for use in children over 12 years of age in the European Union, and from the age of 7 in other countries. Co-administration of zafirlukast with food rich in proteins or fats reduces its availability by 40%. Described interactions with other drugs include: warfarin, terfenadine, erythromycin, theophylline and aspirin (acetylsalicylic acid). There is no interaction with oral contraceptives. Liver insufficiency and older age decrease clearance of the drug, but renal impairment does not affect drug pharmacokinetics.[11,12]

Montelukast is administered once daily at approved doses of 10mg for adults, 5mg for children (aged 6–14 years) and 4mg for preschool children (aged 2–5 years). A sprinkle formulation is also approved in some countries for use in children from the age of 1 year. The availability of this CysLT1 antagonist is not affected by food in adults and only minimally in children.[16] Age or sex do not influence availability.[17,18] At recommended doses there are no interactions between montelukast and warfarin,[19] terfenadine, theophylline,[20] prednisone, digoxin[21] or oral contraceptives. Phenobarbital (phenobarbitone) reduces plasma concentrations of montelukast.[22,23]

Pranlukast is marketed in Japan and South Korea and its development has ceased in the US and Europe.[24] However, pranlukast was also recently launched in Latin America. The approved dose is 450mg every 12 hours. Information about its interaction with other drugs is very sparse in the international literature, but it is quite well established that plasma concentrations reached after evening doses are considerably higher than those attained after morning doses.[14,25] Age does not affect pranlukast pharmacokinetics.[15]

Zileuton is the only 5-LO inhibitor marketed to date. The recommended dose is 600mg every 6 hours.[26,27] There are no interactions between zileuton and prednisone,[28] terfenadine,[29] digoxin[30] or sulfasalazine and its metabolites, sulfapyridine and *N*-acetyl-sulfapyridine,[31] but it must be administered with caution when associated with theophylline[32] or warfarin.[33] Neither age[34] nor concomitant food intake[35] nor time of the day[36] influence zileuton pharmacokinetics. Renal impairment is not a limitation for the administration of zileuton,[37] but liver insufficiency is a contingency that must be taken into account when this drug is used.[38]

2. Effects of Antileukotrienes on Asthma Pathogenesis

Even though this is not their predominant method of action, both CysLT1 antagonists and the 5-LO inhibitor have both short-[39-42] and long-term bronchodilator effects;[43] this is also the case for montelukast when the drug is administered intravenously.[44]

2.1 Bronchial Hyperreactivity

All antileukotrienes have undergone evaluation in extensive bronchial challenge tests attaining a good efficacy. For instance, zafirlukast can blunt bronchoconstriction induced by inhaled LTD4 in normal individuals[45] and in patients with asthma[46] and also when study subjects are receiving inhaled corticosteroids.[47] This effect has also been shown for pranlukast in normal volunteers[48] and for montelukast in patients with asthma.[49]

Antileukotrienes have also proven their efficacy in allergen challenge tests. Zafirlukast has been able to prevent early bronchial reactions to several allergens.[50-53] The late phase reaction was also diminished in one of these trials, and this effect was enhanced when zafirlukast was taken concomitantly with loratadine.[50,54] Given by the inhaled route, the drug has also been shown to be efficacious in blocking the early, but not the late, bronchial response to allergen challenge.[55,56] Similar results, with variable attenuation of the late phase response, have been found for pranlukast[57-59] and montelukast.[60] Zileuton also blocks the early phase response but not the late phase response, probably due to its short half life.[61]

As to ways of measuring non-specific bronchial hyperresponsiveness and its treatment, zileuton has been shown to decrease bronchoconstriction due to inhalation of histamine,[62] pranlukast has been shown to blunt the response to inhaled methacholine

in patients with allergic asthma[59,63] and in patients with aspirin-intolerant asthma,[64,65] as has montelukast in patients with mild asthma[66] and zafirlukast in asthma patients homozygous for the glycine-16 β_2-adrenoceptor genotype.[67]

Bronchial responses to inhalation of platelet-activating factor have been shown to be attenuated by zileuton[68] and zafirlukast[69] in asthmatic patients, and by pranlukast in transgenic mice.[70] Montelukast has been shown to efficaciously block the bronchial response to inhaled adenosine monophosphate (AMP) in atopic asthma patients both with[40] and without[71] concomitant use of inhaled corticosteroids.

2.2 Bronchial Inflammation

Several trials involving all antileukotrienes have clearly demonstrated that these drugs have anti-inflammatory properties. Montelukast has been shown to reduce both peripheral blood[72,73] and sputum eosinophils in short[74] and long-term trials.[75] Peripheral eosinophil counts decreased in children under treatment with montelukast.[76] Zafirlukast has shown the same effect in a long-term study,[77] and furthermore, after segmental antigen challenge, there was a reduction in lymphocyte and basophil counts in bronchoalveolar lavage fluid of patients undergoing short-term treatment with this drug.[78] Segmental challenges have been also used to evaluate the anti-inflammatory properties of zileuton, with positive results.[79,80] Similar effects have been shown for pranlukast regarding peripheral and sputum eosinophil counts.[81,82] In addition to cellular mediators of inflammation, concentrations of eosinophil cationic protein in the blood and sputum have been shown to decrease in response to pranlukast.[82-84]

Zafirlukast and pranlukast intake also leads to a reduction in exhaled nitric oxide in adult asthmatic patients.[67,83,85,86] Montelukast has been shown to set off the same effect in children.[87,88]

The possibility that antileukotrienes might prevent airway remodelling, opens an important field for the future development of these drugs.[89]

3. Efficacy of Antileukotrienes in Exercise-Induced Asthma

3.1 Zafirlukast

Several studies comparing zafirlukast with placebo in exercise-induced asthma allow the conclusion that this drug is efficacious in treating this condition, which appears quite as expected given the significance of leukotrienes as mediators of exercise-induced asthma. In adult asthmatic patients either receiving β_2-adrenoceptor agonists (β_2-agonists) or inhaled corticosteroids or both, 14 days of treatment with zafirlukast 20mg or 80mg twice daily reduced both the area under the forced expiratory volume in 1 second (FEV_1)-time curve and the maximum fall in FEV_1. For the FEV_1 time curve, differences over placebo were significant with tests performed at 2 and at 8 hours after drug administration; for the FEV_1 fall, results after the 8-hour test rendered a higher benefit compared with placebo than results achieved at earlier time points. It is quite possible that this result is due to the known phenomenon of a refractory phase initiated at the time of the 2 hour test and prolonged until the 8-hour test.[90] The higher dose (80mg twice daily) afforded better protection than the lower dose (20mg twice daily) although the difference was not significantly different according to the 95% CI. In asthmatic children aged 6–14 years, zafirlukast at different doses has also shown its superiority over placebo regarding the maximum FEV_1 fall, the area under the curve, and recovery time for return to basal FEV_1.[91]

Only one trial in exercise-induced asthma comparing a single dose of zafirlukast with other antileukotrienes has been published to date. The results suggest that zafirlukast efficacy is somewhat lower than that of montelukast and also that of salmeterol, even though differences did not reach statistical significance.[92] In this study, efficacy was maintained through 12 hours for all drugs except zileuton. No trial comparing zafirlukast to other anti-asthma drugs in exercise-induced asthma for an extended time period has been conducted to date.

3.2 Montelukast

Of the antileukotrienes, montelukast has been the most extensively studied in exercise-induced asthma. It is quite a potent drug for the prevention of exercise-induced bronchospasm, and is at least as potent as salmeterol.[93,94]

Taken for two consecutive days and at different doses, montelukast showed a dose-related protection in exercise tests 24 hours after the last dose. Protection was significant and about was 25% greater than that achieved with placebo for the two higher doses (10 and 50mg once daily).[95] When taken at even higher doses in another study (50mg twice daily or 100mg once daily), protection appears to be even better (up to +50% as compared with placebo; $p < 0.001$).[96] When montelukast was taken once daily for 12 weeks at the recommended dosage of 10 mg/day and a number of exercise tests were performed during the treatment phase (at 4, 8, and 12 weeks), montelukast again proved to be an efficacious 'controller drug', reducing the area under the FEV_1-time curve by about 50% (for placebo the reduction was about 10%), and the recovery time by about 30% (for placebo this value was about 9%). Maximum FEV_1 fall was also blunted demonstrating efficacy (39% for montelukast and 17% for placebo).[97]

At least two studies have compared montelukast with other anti-asthma drugs in exercise-induced asthma. In one of them, already mentioned, montelukast was compared with zafirlukast, zileuton and salmeterol at usual doses. Montelukast proved to be as potent as salmeterol and slightly more efficient than zafirlukast after a single dose of each drug, at 1, 2, 4, 8 and 12 hours after drug administration. All four drugs were significantly better than placebo.[92] Another study evaluated the effects of regular treatment with twice daily salmeterol or once daily montelukast at the usual doses for 8 weeks. The study included 191 patients with previously documented exercise-induced asthma. Results of exercise tests at day 3 after beginning of treatment were significantly better for either one of the two treatments as compared with placebo. The protective effect attained by montelukast did not change significantly throughout the study period, whereas the protective effect of salmeterol decreased with time. At week 8, the percentage of inhibition of maximum FEV_1 fall was 57% for montelukast and 33% for salmeterol ($p < 0.002$).[93] Previously a very similar trial with almost the same number of patients had yielded comparable results.[94] In these studies, exercise tests were carried out at the end of the dose administration intervals. According to Nelson et al.[98] and Simons et al.[99] salmeterol tolerance might be due in part to the timepoints chosen to perform the exercise tests, as tolerance seems to be directly related to the time elapsed from the time of the last dose taken.

In yet another study on protection against unspecific bronchoprovocation, montelukast has also been shown to reduce the bronchial response to dry cold air (as a surrogate of exercise-induced asthma) in asthmatic children aged 3–5 years.[100]

3.3 Pranlukast

Pranlukast has mainly been studied in Japan, some trials have been published in the international literature. Only one study on the effect of pranlukast on exercise-induced asthma is available to us, and only in abstract form;[101] no placebo control group was included. The whole paper was published later in 2000 but in Japanese. In this trial, the usual twice daily doses of 450mg were administered to 11 patients for 14 days, and the authors found a reduction of the maximum fall in FEV_1 from 50% below baseline before treatment to 30% below baseline after treatment.

To the best of our knowledge no comparison of pranlukast with other anti-asthma drugs is available regarding exercise-induced asthma.

3.4 Zileuton

Zileuton has proven its efficacy in the prevention of exercise-induced asthma in a placebo-controlled trial. As compared with placebo, a reduction of 40% in the maximum FEV_1 fall after exercise testing was documented. The study included 24 subjects with exercise-induced asthma who received the active drug or placebo, respectively, for 2 days prior to the

test. Zileuton was given at recommended doses (600mg four times daily).[102]

The comparison study by Coreno et al.,[92] already mentioned earlier, included zileuton in comparison with two CysLT receptor antagonists (montelukast and zafirlukast) and salmeterol. Zileuton was more efficient than placebo at 1 and 4 hours after drug administration, but no different from placebo at 8 and 12 hours, as was to be expected given its short half-life. At 1 and 4 hours the degree of protection achieved by zileuton was similar to that of zafirlukast (57% reduction of FEV_1 maximum fall) and worse than that of montelukast or salmeterol (both 70% reduction).

4. Efficacy of Antileukotrienes in Long-Term Asthma Control Compared with Placebo

4.1 Zafirlukast

Zafirlukast has been quite extensively studied as a preventer of asthma symptoms. Most of the trials have included patients with moderate asthma and have studied several endpoints. In one of the earliest trials, four patient groups ($n = 4 \times 66$) were treated with placebo or different doses of zafirlukast twice daily for 6 weeks (10, 20, and 40 mg/day). The highest dose significantly improved asthma symptoms in terms of fewer night time awakenings, lower daytime asthma scores, less salbutamol (albuterol) use and FEV_1 increase.[103] A very similar design was used in a more recent study including asthmatic children aged 5–11 years. Doses were 5, 10, 20 and 40mg twice daily, and contrary to the results of the adult trial, the greatest improvements were attained at the two lowest doses (5 and 10mg twice daily) with no additional clinically significant benefits at higher doses.[104] Even at these low doses, zafirlukast significantly improved almost all outcome measurements as compared with placebo (i.e. FEV_1 change from baseline, peak expiratory flow rate [PEFR] morning, evening and variability, rescue medication), except symptom scores and night awakenings. Only when a subset of patients with one or more night awakenings per week was analysed, was zafirlukast shown to perform significantly better than placebo in these endpoints.[105]

Three large trials,[77,106,107] including a total of 1362 patients who were treated with zafirlukast 20mg twice daily or placebo for 13 weeks, have been published to date (and a further two were included in an integrated analysis by Barnes and Miller[105] but they have not been published independently). In all of them, study outcome variables such as symptom scores, β_2-agonist use, FEV_1, and PEFR proved to be significantly more favourable in the active than in the placebo group. In the trial by Fish et al.[106] treatment effects on clinical symptoms were more pronounced than those on pulmonary function test results. For example, daytime symptoms decreased by 28% with zafirlukast, and by 16% with placebo and night-time awakenings decreased by 41% with zafirlukast and only by 3% with placebo. β_2-Agonist use was reduced much more in the active treatment group (–28%) than in the placebo group (–2%). With regard to FEV_1, the difference between groups was much smaller: +6% with zafirlukast and +1% with placebo (table I). This trend of a more marked effect on clinical symptoms

Table I. Efficacy of zafirlukast (ZK) at the recommended dose of 20mg twice daily compared with placebo (P) according to data from follow-up studies including large numbers of patients. The numbers represent percentage increase or decrease relative to baseline in each treatment or placebo group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Daytime symptom score		Night awakenings		β_2-Agonist use		QOL	
	(wk)	ZK	P	ZK	P	ZK	P	ZK	P	ZK	P
Fish et al.[106]	13	+6	+1	−28	−16	−41	−3	−28	−2	NA	NA
Nathan et al.[77]	13	+11	+10	−23	−16	−42	−24	−27	−14	+18	+13
Kemp et al.[109]a	13	+16	+12	−23	−11	−29	+4	−23	+7	NA	NA

a Corticosteroid naive patients.

FEV_1 = forced expiratory volume in 1 second; **NA** = not available; **QOL** = quality of life.

as compared with pulmonary function test results was also seen in the Nathan et al. trial[77] where zafirlukast led to an improvement in FEV_1 by 11% whereas placebo achieved a 10% improvement. Again, in contrast to pulmonary function test results, improvements in daytime symptoms (–23 vs –16%), night-time awakenings (–42 vs –24%), and β_2-agonist use (–27 vs –14%) were apparently more pronounced in the active treatment group. In this trial, a questionnaire on quality of life (QOL) was also included. Here, zafirlukast improved QOL by 18% whereas placebo improved QOL by 13% (table I). The third trial[107] also assessed the impact of zafirlukast treatment on the economic burden of asthma. This trial showed that treatment with the active drug was associated with significantly fewer unscheduled healthcare visits, and significantly fewer days of work or school absenteeism, as compared with placebo. The integrated analysis performed by Barnes and Miller on five 13-week trials[105] performed with zafirlukast 20mg twice daily (versus placebo, including or not other treatment branches) in corticosteroid-naive patients with mild to moderate asthma, led to the conclusion that the risk of an asthma exacerbation (main endpoint) for a patient treated with zafirlukast is approximately half that of a patient receiving placebo (odds ratio [OR] 0.45; 95% CI 0.26–0.76). However, it is important to underline that in two of the trials the rate of exacerbations in the active treatment groups was not different from that in the placebo groups. When subsets of patients according to severity of the disease were analysed, zafirlukast treatment was associated with the best benefit in the less severe cases ($FEV_1 > 65\%$ predicted, or PEFR variability <10%). Curiously, these results contradict a previous publication that reported on exploratory subset analyses using integrated data from four 13-week trials with zafirlukast in patients only treated with salbutamol. Tashkin and colleagues[108] concluded that zafirlukast is incrementally beneficial in the treatment of patients with more moderate asthma who have a worse pulmonary function and a higher need of rescue medication at baseline. Unfortunately, this paper was not included in the analysis by Barnes and Miller.[105] Still, the results of a study on a subset of corticosteroid-naive patients with severe persistent disease support the hypothesis that zafirlukast is effective in patients with severe asthma.[109] In this study, mean FEV_1 improved by 16% in patients treated with zafirlukast, and by 12% in patients receiving placebo; again, the difference between groups regarding symptoms and β_2-agonist use was more pronounced: –23 vs –11% for daytime symptoms, –29 vs +4% for night-time awakenings, and –23 vs +7% for rescue medication use (table I). It seems reasonable to suspect that differences in the definition of the trial endpoints, diversity of included patients coming from different parts of the world, and lack of treatment standardisation prior to the trial may in part explain those conflicting results.

4.2 Montelukast

The first follow-up study compared montelukast with placebo in a group of 29 asthma patients (15 treated with inhaled corticosteroids) for a short period of time (11 days) in a cross-over design. In this study, a very high dose of montelukast (200mg three times daily), compared with placebo, achieved significant improvements of FEV_1 over baseline at day 11 (approximately 14%). Also, β_2-agonist use, and day and night-time symptom scores were reduced.[72] Effects occurred irrespective of concomitant inhaled corticosteroid use.

After that, three large follow-up studies have been carried out comparing montelukast with placebo for a longer period of time. In one of them[110] 343 patients with mild to moderate asthma were randomly distributed to receive montelukast 10, 100 or 200mg once daily, montelukast 10 or 50mg twice daily, or placebo for a 6-week period. All montelukast doses resulted in similar, significant differences compared with placebo in asthma control endpoints: FEV_1 increased by about 10%; β_2-agonist use was reduced by 1 puff/day; morning PEFR was augmented by 18.8 L/min; and also physicians' as well as patients' global evaluations and asthma QOL scores were all significantly better with montelukast as compared with placebo (table II).

A second study[111] included 281 patients with moderate asthma and incorporated three active treat-

Table II. Efficacy of montelukast (MK) at the recommended dose of 10mg once daily in comparison to placebo (P) according to follow-up studies involving large numbers of patients. Numbers represent percentage increase or decrease relative to the baseline in each treatment or placebo group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Daytime symptom score		Night awakenings		β_2-Agonist use		QOL	
	(wk)	MK	P	MK	P	MK	P	MK	P	MK	P
Altman et al.[110]	6	+11	+1	−13	−7	−28	−20	−24	0	NA	NA
Noonan et al.[111]	3	+14	+6	−13	−3	−28	−7	−18	−4	NA	NA
Reiss et al.[112]	12	+13	+4	−20	−13	−41	−20	−28[a]	−12[a]	+16	+8
Knorr et al.[113][b]	8	+8	+3	−15	−10[c]	−28	−23[c]	−17	−7	+15	+7
Knorr et al.[76][d]	12	NA	NA	−37	−27	−37[e]	−31[e]	NA	NA	+12	+10[c]

a Data extracted from a chart in the original paper.

b Children 14–16 years-old, dosage 5 mg/day.

c Statistically non-significant difference between groups.

d Children 2–5 years-old, dosage 4 mg/day.

e Evaluated as a night-time symptoms score.

FEV_1 = forced expiratory volume in 1 second; **NA** = not available; **QOL** = quality of life.

ment branches (2, 10 and 50mg of montelukast once daily) as compared with placebo for 3 weeks. In addition to the usual study endpoints, the subjective evaluation by patients and by doctors, as well as a QOL questionnaire were incorporated in the design. The two higher montelukast doses led to better results than placebo or the lower dose of the drug. Even though improvements were statistically significant, the clinical impact was quite modest. For example, morning PEFR improved 15–22% over baseline, but no improvement was detected in evening PEFR, only 20% of patients and 25% of physicians preferred montelukast 10 or 50mg over placebo and also, although there was a numerical reduction of peripheral blood eosinophil counts, the difference was not significant in relation to placebo.

A third trial,[112] the most ambitious of the three, involved a total of 681 patients with moderate asthma, 408 treated with montelukast 10mg twice daily, and 273 with placebo. The follow-up period was 12 weeks, and study endpoints were the same as in the former trial. Superiority of montelukast compared with placebo regarding FEV_1 was approximately 9% and regarding QOL score was 8%. Daytime and night-time symptom scores were also reduced compared with placebo by 7 and 21%, respectively; β_2-agonist use was also reduced by 16% (table II). A subset analysis of the patients taking inhaled corticosteroids allowed the investigators to conclude that montelukast was as efficacious in this group as in the patients who were not receiving inhaled corticosteroids. With respect to all three studies, it is important to underline that the beneficial effects of montelukast were already documented on the first day of treatment.

Montelukast has also proven its efficacy in children. Two large trials have been conducted in two paediatric age groups: 6–14 and 2–5 years. The first trial included 336 children with asthma that was not well controlled, who were followed for 8 weeks while they received montelukast 5mg or placebo. The beneficial effects of montelukast were found to be significant when compared with placebo, and of a magnitude comparable to those seen in the adult trials: 5% improvement in FEV_1 over placebo; 8% in terms of QOL; and reductions in symptom scores (–7% [daytime] and –5% [night-time]) and β_2-agonist use (−10%) [table II].[113] In the second study,[76] a total of 689 children aged 2–5 years (461 receiving montelukast 4mg once daily, 228 receiving placebo) were followed for 12 weeks (50% on inhaled corticosteroids or sodium cromoglycate (cromolyn sodium). The main aim of the study was to assess the safety of montelukast in this age group, but also its usefulness in preschool asthma was included as a secondary objective. Apart from symptoms and β_2-agonist consumption, caregiver and physician evaluations were included among the study endpoints. There were statistically significant differences between the placebo and the active

groups in terms of daytime (–27 vs –37%) and night-time (–31 vs –37%) asthma symptoms, oral β_2-agonist rescue need, β_2-agonist consumption, days without asthma, etc (no baseline values were provided for these parameters). The caregiver global evaluations for the montelukast and placebo groups were not statistically different; similarly, improvements in QOL scores were numerically greater in the montelukast than the placebo group, but there were no statistical differences between groups (+12 vs +10%, both groups increasing 0.5 points or more) [table II]. The most probable explanation for this fact is the modest impact of the drug in asthma control as compared with placebo. For instance, the additional benefit of montelukast over placebo regarding 'percentage of days without daytime asthma symptoms' was 5%, and a similar magnitude of superiority was achieved in 'percentage of days without β_2-agonist use' (6%).

4.3 Pranlukast

The two trials of pranlukast compared with placebo conducted in the US and Europe were for 4 weeks each and mostly used higher doses of the drug than is usually recommended in Japan (225mg twice daily). The US study included two active treatment branches with pranlukast at dosages of 337.5 and 450mg twice daily,[114] whereas in the European study the doses were lower (225 and 337.5mg twice daily).[115] The European study allowed patients to use inhaled corticosteroids (up to 1000 μg/day beclomethasone dipropionate or equivalent) whereas the US study did not. Study designs were otherwise similar. A total of 135 patients were included in the European study, and 65 in the US study.

The US study found increases in FEV_1 that were numerically greater for the active treatment groups than for placebo (7% for 337.5mg twice daily, 5% for 450mg twice daily, and 2% for placebo), but no statistics were applied due to the small number of patients in each group (about 22 patients).[114] Asthma symptom scores were generally better for the active treatment groups (–15, –19 and –12% in daytime symptom scores and –24, –35 and –22% in night-time symptom scores, for 337.5mg twice daily, 450mg twice daily and placebo, respectively). The use of β_2-agonists was reduced only in the higher dosage group in relation to placebo (–7, –31 and –16%, for 337.5mg twice daily, 450mg twice daily and placebo, respectively) [table III].

The results of the European study were similar.[115] There was an FEV_1 increase in the active treatment groups as compared with placebo, but when measurements were carried out at the end of the dose administration intervals, statistical significance was only reached for the lower dose group (+12, +8 and +4% for 225mg twice daily, 337.5mg twice daily and placebo, respectively). Daytime symptoms score was significantly better for the higher dose group (–15, –22 and –7%, for 225mg twice daily, 337.5mg twice daily and placebo, respectively); also, night-time score was significantly better only for the higher dose group (–7, –28 and +7%, for 225mg twice daily, 337.5mg twice daily and placebo, respectively), and the use of rescue

Table III. Efficacy of pranlukast (PK) compared with placebo (P) according to data from follow-up studies. The numbers represent percentage increase or decrease relative to baseline in each treatment or placebo group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Daytime symptom score		Night-time symptom score		β_2-Agonist use	
	(wk)	PK	P	PK	P	PK	P	PK	P
Grossman et al.[114]a,b	4	+7	+2	–15	–12	–24	–22	–7	–16
Barnes and Pujet[115]a	4	+8	+4	–22	–7c	–28	+7	–10	+4c
Yoo et al.[116]d	4	+1	0c	–28	–10	–24	–12	NA	NA

a Values for pranlukast 337.5mg twice daily.

b No statistics were applied in this study due to the small number of patients.

c No statistically significant difference between groups.

d Values for pranlukast 225mg twice daily.

FEV_1 = forced expiratory volume in 1 second; **NA** = not available.

β_2-agonists was only significantly reduced in the higher dosage group (−4, –10 and +4%, for 225mg twice daily, 337.5mg twice daily and placebo, respectively) [table III].

In a more recent trial in Asia, pranlukast 225mg twice daily was evaluated versus placebo for 4 weeks in a group of 197 patients with mild to moderate asthma.[116] At the end of the treatment period, most endpoints were significantly better for the active treatment group, although the size of the effect over the placebo group was modest: +1% in FEV_1, +7% in morning PEFR, +6% in evening PEFR, and +18% and +12% in morning and evening asthma symptom scores. According to the authors, the small impact of pranlukast on pulmonary function in these patients might be due in part to their good asthma control at the time of entry into the trial (table III).

Although placebo was not used for a control group, there is a recent clinically interesting trial that focuses on the response to pranlukast from a different point a view.[117] There were three different groups of patients in this study: patients with mild to moderate asthma, patients with severe asthma without oral prednisolone, and patients with severe asthma taking oral prednisolone. Patients received either conventional treatment alone (but it was not clearly stated what 'conventional' meant), or conventional treatment plus pranlukast 225mg twice daily. Between 11 and 14 patients were treated with additional pranlukast in each group, and 8 patients each were treated with conventional therapy alone. At 16 weeks after the beginning of the treatment period, patients were classified into a responder group and a non-responder group, dependent on their PEFR that was to have increased at least 15% from baseline, or not. Interestingly, the proportion of responders was lower when the disease was more severe: 79, 67 and 27% for each group from milder to more severe asthma. Responders were followed for 4 years and the effect of the drug was maintained throughout all this time. As only responders were included in the follow-up, data are not strikingly convincing, but what is important is the fact that the beneficial effect of pranlukast was maintained for the whole 4 year period with virtually no adverse events. However, it must be taken into consideration that the concept of responders and non-responders is a mere theoretical construct as there is always a continuum of responses and the cut-point is arbitrary. In another paper,[118] the same group of investigators reported that the effect of pranlukast on PEFR was greater in patients with moderate asthma (receiving beclomethasone dipropionate 800 μg/day) than in patients with more severe asthma (receiving beclomethasone dipropionate 1600 μg/day, but not oral corticosteroids). In a third group of patients with severe asthma receiving beclomethasone dipropionate (1600 μg/day) plus oral prednisolone (5 to 20 mg/day), additional treatment with pranlukast had no effect. The results of these studies reinforce the concept that first, there are responders and non-responders to antileukotrienes, and second, that the severity of asthma is a factor that might help predict the likelihood of a positive response.

4.4 Zileuton

There have been three large long-term follow-up trials comparing zileuton with placebo up to 1996. In the first of these[119] 139 patients with mild to moderate asthma were randomly assigned to receive zileuton 600mg or 400mg four times daily or placebo for 4 weeks. The two active treatment branches led to significantly better results than placebo in terms of: FEV_1 (+13, +11 and +3%, for 600mg four times daily, 400mg four times daily or placebo, respectively); morning PEFR (+4, +8 and 0%, for 600mg four times daily, 400mg four times daily or placebo, respectively); evening PEFR (+7, +4 and +2%, for 600mg four times daily, 400mg four times daily or placebo, respectively); and β_2-agonist use (–24, –17 and –6%, for 600mg four times daily, 400mg four times daily or placebo, respectively) [table IV]. In the second trial[120] 373 patients received either one of the two zafirlukast doses mentioned above or placebo, and were followed for 25 weeks. At the end of the treatment period, FEV_1 increased by 15, 12 and 7%, for 600mg four times daily, 400mg four times daily or placebo, respectively. The corresponding numbers for morning

Table IV. Efficacy of zileuton (ZL) at the recommended dose of 600mg four times daily compared with placebo (P) according to data from follow-up studies including large numbers of patients. The numbers represent percentage increase or decrease relative to baseline in each treatment or placebo group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Daytime symptom score		Night-time symptom score		β_2-Agonist use		QOL	
	(wk)	ZL	P	ZL	P	ZL	P	ZL	P	ZL	P
Israel et al.[119]	4	+13	+3	−37	−17	NA	NA	−24	−6	NA	NA
Liu et al.[120]	25	+15	+7	−36	−21	−31	−5	−30	−7	NA	NA
Israel et al.[121]	13	+13	+5	−28	−16	−33	−18	−26	−13	+18	+9

FEV_1 = forced expiratory volume in 1 second; **NA** = not available; **QOL** = quality of life.

PEFR were +30, +14 and +5%, for daytime symptom scores they were −36, –31 and –21%; and for nocturnal symptom scores they were –31, –31 and –5%. β_2-Agonist use was reduced significantly only in the 600mg dose group as compared with placebo (–30 vs –7%) [table IV].

A very similar, third clinical trial was performed in 401 patients who were followed for 13 weeks.[121] In addition to the outcome variables that were quite similar to those of the above-mentioned studies, a questionnaire on QOL was included. Here, three months of treatment with zileuton led to a significant improvement in asthma control. At the end of the 13 weeks FEV_1 improved by 10 and 13% in the 400mg and 600mg four times daily zileuton groups, respectively, but only 5% in the placebo group. Morning and evening PEFR increased in the same magnitude (5, 4 and 1%, for 600mg four times daily, 400mg four times daily or placebo, respectively). Daytime symptom score decreased significantly only in the 600mg group (−28, –21 and –16%). Nighttime symptom score for patients who had had a baseline score of >1 (i.e. the more symptomatic patient group) also decreased significantly in the 600mg group vs placebo (–33 vs –18%). QOL overall score improved significantly in the zileuton 600mg group (+18%, 0.8 units), but not in the 400mg group (+12%, 0.6 units) as compared with placebo (+9%, 0.4 units) [table IV].

Although it did not include a placebo group, there is a very interesting study by Lazarus et al.[122] in which 2947 asthmatic patients (FEV_1 at least 35% predicted) received zileuton (600mg four times daily) plus usual asthma therapy (n = 2458) or just usual therapy alone (n = 489) for 12 months. The number of asthma exacerbations during the study period did not differ between groups (45 and 49% for the zileuton and the usual treatment groups, respectively), and hospital admissions were similar for both groups (3.2 vs 4.1%). However, significantly less patients receiving additional zileuton required oral corticosteroid rescue therapy (23 vs 30%) or visits to the emergency department (7.7 vs 11.5%). Also in other endpoints (no baseline values provided), the addition of zileuton led to significant improvements, such as with respect to time missed usual activities, performance impairment, sleep interruption or β_2-agonist use.

5. Comparison of Antileukotrienes to Other Anti-Asthma Agents

5.1 Zafirlukast

Regarding comparison of zafirlukast with sodium cromoglycate, there is information available on two studies which have only been published in abstract form. In one of them (referenced by Adkins and Brogden[12]), 287 asthmatic patients were randomly assigned to receive either zafirlukast 20mg twice daily, or sodium cromoglycate aerosol 1.6mg four times daily, or placebo. Both active treatments were better than placebo in reducing symptoms or rescue medication use, but no differences were found between them. In the second study[123] that evaluated a total of 258 patients, no differences were found between zafirlukast 20mg twice daily, dry powder inhaled sodium cromoglycate 40mg daily or placebo. The authors tried to explain this lack of demonstrable effect of both active drugs with the very mild character of the asthma in the patients included in this trial.

Several clinical trials comparing zafirlukast with inhaled fluticasone propionate have been published recently. At least two of them have been carried out in patients previously receiving inhaled β_2-agonists alone. In one of them,[124] 451 patients received either a low dose of fluticasone propionate (88μg twice daily) or zafirlukast at the usual dose (20mg twice daily) for 12 weeks. In almost all study endpoints fluticasone propionate was at least twice as effective as zafirlukast (statistically significant). For instance, data giving percentage change from baseline were, for fluticasone and zafirlukast, respectively, +17 vs +8% for FEV_1, +14 vs +3% for morning PEFR, +10 vs +3% for evening PEFR, –39 vs –17% for combined symptom score and –52 vs –30% for salbutamol use (table V).

Another clinical trial evaluated the effect of zafirlukast at the recommended dose (20mg twice daily) in comparison to fluticasone propionate (88μg twice daily) in a similar way, but only for 4 weeks, in a sample of 294 patients whose asthma had previously been insufficiently controlled by β_2-agonists alone.[125] The double-blind study period of 4 weeks was followed by an open period of 4 weeks when all patients received fluticasone propionate at the same dose. Results of the double-blind period were numerically again in favour of fluticasone propionate in all endpoints, but to a lesser extent than in the study mentioned above: +16 vs +13% for FEV_1, +8 vs +5% for morning PEFR, +5 vs +4% for evening PEFR, –34 vs –28% for combined asthma symptom score and –41 vs –25% for salbutamol use, with fluticasone and zafirlukast, respectively (table V). Statistically significant differences were only reached for morning PEFR and asthma symptom score. When patients receiving zafirlukast were switched to fluticasone propionate in the open study period, they experienced additional benefits in pulmonary function tests but not in symptom scores or salbutamol use.

Another 12 week trial[126] including 338 patients evaluated fluticasone propionate and zafirlukast at the same doses as the other studies, but added a placebo arm. In addition to pulmonary function and symptom endpoints, QOL was also measured. This time fluticasone propionate efficacy was again about twice that of zafirlukast in every study endpoint, including the QOL score. Magnitudes of the differences were as follows for fluticasone propionate, zafirlukast, and placebo, respectively: +23 vs +15 vs +10% for FEV_1, +14% vs +4% vs +2% for morning PEFR, +9 vs +3 vs +1% for evening PEFR, –49 vs –27 vs –30% for symptom score and –58% vs –40% vs –25% for salbutamol use (table V). In contrast to fluticasone propionate zafirlukast was not significantly better than placebo regarding FEV_1, and morning and evening PEFR.

There are more comparative study data from a trial[127] comparing the same drugs in patients previously receiving low to moderate doses of inhaled corticosteroids (up to 800 μg/day of beclomethasone dipropionate or equivalent). Two hundred and twen-

Table V. Efficacy of zafirlukast (ZK) at the recommended dose of 20mg twice daily compared with fluticasone propionate (FP) 88μg twice daily according to data from follow-up studies including large numbers of patients. The numbers represent percentage increase or decrease relative to baseline in each treatment group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Combined symptom score		β_2-Agonist use		QOL	
	(wk)	ZK	FP	ZK	FP	ZK	FP	ZK	FP
Bleecker et al.[124a]	12	+8	+17	−17	−39	−30	−52	NA	NA
Nathan et al.[125a]	4	+13	+16[b]	−28	−34	−25	−41[b]	NA	NA
Busse et al.[126a]	12	+15	+23	−27	−49	−40	−58	NA	NA
Kim et al.[127c]	6	+1	+9	+14	−23	+14	−34	+0.1[d]	+0.6[d]

a Patients only receiving short-acting β_2-agonists.

b Statistically non-significant difference between groups.

c Patients previously receiving beclomethasone dipropionate 800 μg/day or equivalent.

d Points in the test (0.5 is considered a clinical significant difference).

FEV_1 = forced expiratory volume in 1 second; **NA** = not available; **QOL** = quality of life.

Table VI. Efficacy of montelukast (MK) at the recommended dose of 10mg once daily in comparison with inhaled corticosteroids (ICS) or ICS plus salmeterol (SM) according to follow-up studies involving large numbers of patients. Numbers represent percentage increase or decrease relative to the baseline in each treatment group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	FEV_1		Daytime symptom score		Night awakenings		β_2-Agonist use		QOL	
	(wk)	MK	ICS	MK	ICS	MK	ICS	MK	ICS	MK	ICS
Malmstrom et al.[73]a	12	+7	+12	−17	−26	−31	−46	−24	−40	+19	+26
Busse et al.[129]b	24	+14	+22	−36	−56	−50	−65	−44	−61	NA	NA
Pearlman et al.[130]c	12	+13	+25	−46	−62	−60	−79	−45	−70	+29	+40

a The ICS was beclomethasone dipropionate 200μg twice daily.

b The ICS was fluticasone propionate 88μg twice daily.

c The ICS was fluticasone propionate 100μg + SM 50μg twice daily.

FEV_1 = forced expiratory volume in 1 second; **NA** = not available; **QOL** = quality of life.

ty one patients were randomly assigned to receive inhaled fluticasone propionate 88μg twice daily, and 216 patients to receive zafirlukast 20mg twice daily for 6 weeks. The group treated with fluticasone propionate improved in all study endpoints with the following magnitudes as compared with the zafirlukast group: +9 vs +1% for FEV_1, +5 vs +0.8% for morning PEFR, +4 vs +0.6% for evening PEFR, –23 vs +14% for combined symptom score and –34 vs +14% for salbutamol use. In the QOL questionnaire applied, fluticasone propionate achieved an improvement of 0.6 points whereas zafirlukast only reached 0.1 points (0.5 points are considered clinically meaningful). Hence, again, there was a clear therapeutic superiority of fluticasone propionate versus the antileukotriene (table V).

In a crossover design study, with bronchial histamine challenges carried out after 2 weeks of treatment with either fluticasone propionate 100μg twice daily or zafirlukast 20mg twice daily in a group of 30 patients, the mean provocational concentration of histamine causing a 20% fall in FEV_1 was 1.61 mg/mL in the fluticasone propionate group, and 0.99 mg/mL in the zafirlukast group. Taking baseline differences into account, the difference between treatments was equivalent to 0.77 doubling doses of histamine ($p = 0.037$).[128] From this study it seems reasonable to conclude that the inhaled corticosteroid also provides better protection regarding unspecific bronchial hyper-responsiveness than the antileukotriene.

5.2 Montelukast

Two studies have compared the efficacy of montelukast with beclomethasone dipropionate. In the first of them,[73] 895 mild-to-moderate asthma patients were randomly assigned to receive either montelukast 10mg once daily, or inhaled beclomethasone dipropionate 200μg twice daily, or placebo for 12 weeks (table VI). In terms of lung function, beclomethasone dipropionate treatment increased FEV_1 by 12.4% more than placebo at the end of the study, whereas montelukast increased FEV_1 by 6.7% more than placebo (both differences were statistically significant). The percentage of asthma exacerbation days was reduced to half with montelukast and to one-third with beclomethasone dipropionate as compared with placebo. Similar differences of superiority over placebo were found in other study endpoints such as morning or evening PEFR, reduction in β_2-agonist use (–40% for beclomethasone dipropionate vs –24% for montelukast), night awakenings per week (–1.9 vs +1.2) or QOL score (+0.58 vs +0.37 points). Differences between beclomethasone dipropionate and montelukast were significant in all studied parameters. However, the onset of action of montelukast was quicker as compared with beclomethasone dipropionate. Adherence to therapy was comparable in the three groups.

In contrast, in a 6-month open-label comparative study[131] (montelukast 5mg once daily vs beclomethasone dipropionate 100μg three times daily) in children aged 6–11 years adherence to the orally administered antileukotriene proved to be better

than to the inhaled corticosteroid. Montelukast achieved adherence of 82%, whereas beclomethasone dipropionate only reached 45% in highly compliant children (defined as having taken the medication as indicated >95% of days). Expressed as percentage of used over prescribed doses the difference was not so apparent (97.6% for montelukast vs 93.0% for beclomethasone dipropionate). Parents' satisfaction scores were favourable with regard to montelukast in terms of 'convenience', 'ease of administration', and 'taken as instructed'. Montelukast also scored better in the patients' satisfaction score with regard to 'taste'. Study endpoints related to asthma control were not different between treatments. This lack of difference between an antileukotriene and an inhaled corticosteroids may probably be due to a better effect of montelukast in mild asthma than in moderate or severe disease.

A review of the open extension studies performed with montelukast versus beclomethasone dipropionate included the above-mentioned study in children and two more carried out in adults.[132] From the adult studies (montelukast 10mg once daily vs beclomethasone dipropionate 200μg twice daily) with a duration of up to 2 years, it was concluded that the therapeutic effects of beclomethasone dipropionate were higher, although, in the course of time, they tended to align with the effects of montelukast. The authors argue that this phenomenon might be due to the reduced adherence to the inhaled corticosteroids with time, reflecting the 'real life' situation. Still, it must be underlined that these studies were extension studies involving patients who were quite well controlled after the blinded clinical trial period and this control could in part explain the effects of the drugs thereafter.

Montelukast (10mg once daily) has also been compared with fluticasone propionate at a low dose (88μg twice daily) in a group of 533 patients who were symptomatic while taking β_2-agonists alone and who were followed for 24 weeks (table VI).[129] No placebo group was included. All study endpoints were significantly better for fluticasone propionate than for montelukast as compared with baseline. Some examples are: FEV_1 (+22 vs +14% increment); evening PEFR (+14 vs +7%); percentage of symptom free days (+32 vs +18%); salbutamol use reduction (–3.1 vs –2.3 puffs/day); and symptom score (–53 vs –36%). Upon comparative analysis of costs in another study, it was concluded that fluticasone propionate treatment is cheaper than montelukast treatment over a 9-month period ($US640 vs $US1028) [1999 values].[133]

The combination of fluticasone propionate 100μg/salmeterol 50μg twice daily has been compared with montelukast 10mg once daily.[130] Patients whose asthma was not well controlled with short-acting β_2-agonists alone (n = 432) were randomised to receive either fluticasone propionate/salmeterol or montelukast (no placebo group) for 12 weeks. There was a significant improvement over baseline with both treatments, but as expected, improvements were greater in the group treated with the combination therapy compared with montelukast, for example: FEV_1 (+25 vs +13% increase over baseline); evening PEFR (+16 vs +8%); percentage of rescue-free days (+44 vs +18%); percentage of symptom-free days (+33 vs +21%); nighttime awakenings (–79 vs –60%), symptom score (–62 vs –46%), and β_2-agonist use (–70 vs –45%) [table VI].

5.3 Pranlukast

No full paper has yet been published in the international literature comparing the effects of pranlukast with other anti-asthma agents. Only two abstracts from 1997 may give some clues with regard to such comparisons. In one study both pranlukast 300mg or 450mg twice daily were found to be as efficacious as beclomethasone dipropionate 84μg four times daily over a 12-week period.[134] Also, nedocromil (3.5mg four times daily) was compared with pranlukast 150, 300 and 450mg twice daily. No effect on FEV_1 was determined with nedocromil, whereas with pranlukast FEV_1 increased in a dose-dependent fashion.[135]

5.4 Zileuton

Data are available from only one trial comparing zileuton with another anti-asthma drug on a long-

term basis, and this comparison is with theophylline.[42] More than 100 patients with moderate asthma were followed for 14 weeks, and treatments with two different doses of zileuton (400 and 600mg four times daily) were evaluated versus theophylline. All treatments led to improvements in FEV_1 from baseline, and they were fairly similar: +30% for the higher zileuton dose, +34% for the lower zileuton dose, and +34% for theophylline. Theophylline appeared numerically more efficacious reducing daytime symptom scores (–30 and –28%, respectively, for the two zileuton doses vs –40% for theophylline) and night-time symptom scores (–25% and –30 vs –40%), but differences were not statistically significant. Also, the reduction of β_2-agonist use appeared more pronounced, although not statistically significant, for theophylline (–24% and –19 vs –31%) at the end of the study. Adverse events were similar in the three groups.

6. Inhaled Corticosteroid Sparing Effects of Antileukotrienes

6.1 Zafirlukast

At least one study has shown the ability of zafirlukast to enhance control of asthma symptoms when added to high doses of inhaled corticosteroids.[136] Patients receiving 1000–4000 μg/day of inhaled corticosteroids who had a predefined level of asthma symptoms during the run-in period were assigned to receive zafirlukast 80mg twice daily or placebo for 6 weeks. Addition of zafirlukast was associated with significant improvements in morning PEFR (+6 vs +0.5%), evening PEFR (+5 vs +0.4%), FEV_1 (+9 vs +4%), daytime symptom score (+33 vs +16%), and β_2-agonist use (–21 vs –6%). Also, zafirlukast significantly reduced the risk of an asthma exacerbation. However, the dose used was 4-fold the approved one. No corticosteroid-sparing effect of zafirlukast has been demonstrated to date using licensed doses of the drug.[137]

The first trial comparing salmeterol and zafirlukast as 'add-on treatment' was published in 1999,[138] and it evaluated their effect in patients previously receiving inhaled corticosteroids only. Here, the benefit from adding salmeterol was considerably higher than the benefit from adding zafirlukast. Recently, the data from this study have been added to those of another and their results have been published in a pooled analysis.[139] A total of 429 patients already treated with inhaled corticosteroids (doses not reported) were randomly assigned to receive either additional salmeterol (by metered dose inhaler, 42μg twice daily) or zafirlukast (20mg twice daily) for 4 weeks. Again, the effect of salmeterol was greater than the effect of zafirlukast in most endpoints: daytime symptoms were reduced more efficiently with salmeterol (–34 vs –20%), as was also the case with night-time symptoms (–45 vs –31%) and salbutamol use (–41 vs –25%). Morning (+7.7 vs +5.8%) and evening (3.3 vs 2.8%) PEFR improvements were higher in the salmeterol group, and there was also a superiority of salmeterol regarding the QOL score (+16 vs +12%). Asthma exacerbation numbers matched exactly in the two branches (eight per group); two patients from the salmeterol group withdrew due to a severe asthma attack.

6.2 Montelukast

The corticosteroid-sparing effect of montelukast has been addressed by several studies. In one,[140] four treatment groups were compared once patients (n = 642) had received inhaled beclomethasone dipropionate 200μg twice daily for 4 weeks. The four treatment groups were: (i) montelukast plus beclomethasone dipropionate; (ii) oral placebo plus beclomethasone dipropionate; (iii) montelukast plus inhaled placebo; and (iv) placebo oral and inhaled. Doses were montelukast 10mg once daily and beclomethasone dipropionate 200μg twice daily. Patients receiving both active drugs improved their asthma control significantly in relation to the group taking only beclomethasone dipropionate: +5% in FEV_1, +3% in morning PEFR, –6% in symptom score, –6% in β_2-agonist use. A second study[141] included 226 clinically stable asthma patients receiving high doses of corticosteroids. Patients were randomly assigned to receive add-on montelukast or placebo after reducing the corticosteroid dose on two occa-

sions. Every 2 weeks, the inhaled corticosteroid dose was adapted, i.e. tapered, maintained, or increased, based on a standardised clinical score. The study endpoint was the lowest tolerated corticosteroid dose. As compared with placebo, montelukast allowed a significant reduction of inhaled corticosteroids doses (–47 vs –30%). Also, significantly fewer patients receiving montelukast (16%) required study discontinuation due to failed regain of stability after an increase of inhaled corticosteroids, compared with placebo (30%).

However, not all studies lead to the conclusion that montelukast improves asthma control in patients already receiving inhaled corticosteroids. In patients from a hospital outpatient clinic (median percentage predicted FEV_1 = 60%, interquartile range 48–80%) whose asthma was not well controlled with several treatment combinations (always including inhaled corticosteroids), the addition of montelukast 10mg once daily for a period of 14 days did not make their asthma more stable compared with placebo.[142] Still it can be argued that the room for improvement in these patients was very small and so the conclusions of this study must been interpreted with caution.

In a very recent study,[143] 110 patients with persistent asthma were followed for 1 year to evaluate the corticosteroid-sparing effect of montelukast. Concomitant asthma medication was compared for 1 year before and after the prescription of montelukast. Sixty-two patients maintained treatment with montelukast throughout the year whereas 41 discontinued by their own decision, the rest were lost to follow-up. In both groups (montelukast maintained vs montelukast discontinued) there was a significant decrease in the use of inhaled β_2-agonists (puffs/day): –28% for the montelukast group ($p < 0.05$ compared with the baseline), –12% for the other group (p = NS). However, inhaled corticosteroids doses (fluticasone propionate 220μg or equivalent/day) could only be significantly diminished in the group that discontinued montelukast (–24% compared with baseline) and not in the group that maintained montelukast (–16%). The use of systemic corticosteroids was significantly reduced in both groups (–22 vs –11% for the continued and discontinued montelukast treatments). The authors concluded that montelukast has a marginal utility in persistent asthma.

Although not exactly designed to evaluate the corticosteroid-sparing effect of montelukast, there is an interesting study in children aged 6–14 years with asthma insufficiently controlled by budesonide 200μg twice daily. The addition of montelukast 5mg once daily led to an increase in FEV_1 (+4.6% above baseline vs placebo +3.3% above baseline; p = 0.062), and a significant, although small, decrease in rescue β_2-agonists use (–1.4 vs –1 puffs/day). Montelukast was also significantly superior to placebo regarding PEFR and number of asthma exacerbation days, but not regarding QOL measurements.[144]

The relative corticosteroid-sparing effect of montelukast has also been evaluated in comparison with salmeterol. Even though there are no results yet from the large study Investigation of Montelukast as a Partner Agent for Complementary Therapy trial (IMPACT)[145] announced in 2000, some data have arisen from other trials. For instance, one dose of salmeterol was shown to be equally as effective as one dose of montelukast in a small group of patients with unstable asthma receiving inhaled corticosteroids, in terms of bronchoprotection in an AMP challenge test, and, even more important, the effects of montelukast and salmeterol were additive: the best results were achieved with the combination of montelukast 10mg with salmeterol 100μg.[40] In another study, salmeterol was compared with montelukast in a small group of 20 patients whose asthma was not well controlled with inhaled corticosteroids alone.[146] It was a crossover study and the endpoints included results of an AMP challenge test after each treatment period. Montelukast significantly increased the AMP dose needed to provoke a 20% decrease of FEV_1 (PC_{20}) both after the first and the last dose of the drug, whereas salmeterol treatment led to an increase of the provocative AMP dose after the first dose, too, but not after the last dose. This result will need to be interpreted in terms of induction of a certain degree of tolerance by salmeterol.

Table VII. Efficacy of montelukast (MK) at the recommended dose of 10mg once daily as add-on therapy to inhaled corticosteroids compared with salmeterol (SM) 50μg twice daily according to follow-up studies involving large numbers of patients. Numbers represent percentage increase or decrease relative to the baseline in each treatment group. All groups were comparable at baseline. Unless otherwise stated, differences between groups are statistically significant

Study	Duration	Morning PEFR		Daytime symptom score		Night awakenings		β_2-Agonist use		QOL	
	(wk)	MK	SM	MK	SM	MK	SM	MK	SM	MK	SM
Wilson et al.[146]a	2	+2	+6[b]	−24	−41[b]	−20	−29[b]	−36	−41	NA	NA
Nelson et al.[147]	12	+3	+6	−31	−36[b]	NA	NA	−30	−41	NA	NA
Fish et al.[148]	12	+6	+10	−30	−39	−41	−54	−34	−42	NA	NA

a Only 20 patients in a crossover study.

b Statistically non-significant difference between groups.

NA = not available; **PEFR** = peak expiratory flow rate; **QOL** = quality of life.

Also, only montelukast decreased blood eosinophil counts. Neither treatment reduced exhaled nitric oxide levels. From the clinical and functional points of view, both drugs achieved significant differences from baseline, but there were no significant differences between active treatments – even though results tended to be better with salmeterol – in study endpoints such as morning PEFR (+2% with montelukast vs +6% with salmeterol), evening PEFR (–0.7 vs +2%), daytime rescue medication reduction (–36 vs –41%), or daytime symptom score reduction (–24 vs –41%) and night-time symptom score (–20 vs –29% reduction) [table VII].[146]

A group of 447 patients with insufficiently controlled asthma in spite of receiving low-dose inhaled corticosteroids was randomised to add either salmeterol 50μg twice daily or montelukast 10mg once daily to treatment for 12 weeks to fluticasone propionate 100μg twice daily (table VII).[147] Compared with the baseline values, there were more marked improvements in the salmeterol group with regard to FEV_1 (+15% for salmeterol vs +8% for montelukast), evening PEFR (+4 vs +2%), and salbutamol use in puffs/day (–41 vs –30%); all differences were statistically significant. No difference was found regarding daytime symptom scores (–36 vs –31%). In a larger trial,[148] 948 asthma patients receiving inhaled corticosteroids and still symptomatic were randomised to receive either add-on montelukast 10mg once daily or salmeterol 50μg twice daily. Salmeterol achieved statistically significantly better results over baseline in morning PEFR (+10 vs +6% increase), patient-rated symptoms (−39 vs −30%), salbutamol use in puffs/day (–42 vs –34% reduction) and percentage of symptom-free days (+16 vs +6%) [table VII]. In another study[149] on the socioeconomic burden of asthma, treatment with inhaled corticosteroids plus salmeterol was associated with a significant reduction in hospital event rates in comparison with inhaled corticosteroids plus montelukast (hospitalisations 2.5 times more likely with montelukast add-on therapy). Also, addition of salmeterol to inhaled corticosteroids was associated with significantly lower total asthma care costs compared with montelukast (−63%) in this study, which was carried out for 24 months in patients continuously enrolled in any of 14 United HealthCare plans.[149]

6.3 Pranlukast

In a study involving 79 patients with asthma requiring maintenance treatment with high doses of inhaled beclomethasone dipropionate (≥1500 μg/day), corticosteroid doses were halved after a 2-week run-in period, while patients were assigned to receive either pranlukast (450mg twice daily) or placebo, for a 6-week period. FEV_1 (–0.33 ± 0.2l for placebo vs +0.08 ± 0.5l for pranlukast) [baseline value not available] as well as morning PEFR (–10 vs +1%) and evening PEFR (–4 vs +1%) decreased significantly from baseline in the placebo group but were maintained in the active treatment group.[83] There were also significant differences with respect to daytime episodes of asthma, daytime use of β_2-agonists, and – to a less marked extent – to night-time asthma symptoms.

In another trial, 22 patients with asthma (9 atopic, 13 non-atopic) receiving regular inhaled beclomethasone dipropionate were treated with pranlukast 225mg twice daily for 4 weeks. For patients with non-atopic asthma increases in morning and evening PEFR and decreases in symptom scores were observed at the end of the study period, but these improvements were inferior compared with those in the nine atopic patients (increases in morning PEFR +17 vs +12%; increases in evening PEFR +22 vs +12%; symptoms score decreases −59 vs −40% for atopic and non-atopic patients, respectively). The same group of patients was subsequently analysed as two subsets depending on their treatment with oral prednisolone. Patients receiving oral prednisolone (n = 6) showed no improvement, whereas those not treated with oral corticosteroids improved significantly in all study endpoints (e.g. a significant reduction in symptom score of about 60%).[150] Again, pranlukast seems to be more effective in patients with less severe asthma.[118] The concept that allergic patients respond better to pranlukast than non-allergic patients definitely deserves further study, even though differences might be merely related to the asthma severity.

Nevertheless, in severe asthma, add-on pranlukast has also been proven to be of therapeutic benefit. In one study in a small group of 11 very severely affected asthma patients who received maintenance treatment with inhaled beclomethasone dipropionate 1600 μg/day or beclomethasone dipropionate 800–1600 μg/day plus oral prednisolone 2.5–20 mg/day, and still remained symptomatic, it was shown that addition of pranlukast 225mg twice daily for 8 weeks significantly improved asthma control compared with baseline in terms of PEFR (+9.6% morning; +6.1% evening), symptom score (–38%), and β_2-agonist use (–0.7 puffs/day).[151]

Another study is worth mentioning in this context, even though it was not primarily designed to evaluate a corticosteroid-sparing effect. In patients with unstable asthma receiving regular inhaled beclomethasone dipropionate (800μg twice daily), the addition of pranlukast (225mg twice daily) had the same effect as doubling the dose of beclomethasone dipropionate.[118] Compared with baseline, the effect of doubling the inhaled corticosteroids dose on symptom score was –62%, while the effect of pranlukast addition was –67%; percentage predicted morning PEFR increased by +12% and +14%, respectively, and the use of rescue β_2-agonists decreased by −52 and −78%, respectively.

6.4 Zileuton

To the best of our knowledge, no clinical trial specifically designed in order to evaluate the corticosteroid-sparing effect of zileuton in asthmatic patients has been published to date.

7. Efficacy of Antileukotrienes on Subsets of Asthma Patients

Pharmacogenetics has already been introduced to the field of antileukotrienes, and an early study of the relationship between a genetic polymorphism and the response to zafirlukast has recently been published. A single nucleotide polymorphism in the promoter region of the LTC4 synthase has been reported to be present in 76% of patients with aspirin-intolerant asthma and in only 44% of aspirin-tolerant asthma patients. This polymorphism is a substitution of an adenine by a cytosine. Homozygotic wild genotype (AA) has been shown to be associated with a lower production of LTC4, and consequently, a lesser clinical response to the CysLT1 antagonist zafirlukast.[152] Twenty-three patients with severe asthma whose medication had been reduced to inhaled corticosteroids and β_2-agonist on demand only, were treated with zafirlukast 20mg twice daily for 2 weeks. Ten of the patients had the wild allele (AA), and 13 had the variant allele (CC or CA). Zafirlukast treatment increased FEV_1 by 9% above baseline in patients with the variant genotype, while FEV_1 decreased by –12% below baseline in patients with the wild allele (FEV_1 decrease probably due to prior withdrawal of other medications different from inhaled corticosteroids and β_2-agonists). A recently published investigation in Japanese patients with aspirin-induced asthma has not found such an association and the authors argue that if this polymorphism has some

effect on the development of aspirin-induced asthma it is probably in linkage disequilibrium with another causatively important mutation.[153] A very recent study on the genetic polymorphisms of the core promoter region of the 5-LO gene concludes that there is no difference between homozygous wild-type carriers and heterozygotes with respect neither to the bronchodilator response to an antileukotriene nor to the protection offered by antileukotrienes in an AMP bronchial challenge test.[154]

Some further studies primarily addressing aspects different from clinical asthma control deserve some attention. One of them raises the possibility that patients might respond to pranlukast (and perhaps to other antileukotrienes) depending on their individual leukotriene metabolism. In a group of 37 evaluable patients with moderate and severe asthma, pranlukast 225mg twice daily was added to their usual medication for 4 weeks. Patients were then classified into responders and nonresponders according to PEFR and symptom scores before and after the treatment period. Thirteen patients were responders, and 24 were nonresponders. The urinary ratio of LTE4/prostaglandin (PG) $F_{1\alpha}$ on treatment day 1 was significantly lower in the responder than in the nonresponder group. LTE4 is a marker of 'asthmatic activation' and $PGF_{1\alpha}$ is a metabolite of prostacyclin (PGI_2) that protects from airway narrowing. This ratio might translate into a certain type of arachidonic acid metabolism, and so it might finally serve as a predictive marker of the clinical efficacy of leukotriene antagonists,[155] even though one might theoretically have expected a higher LTE4 production in the group of patients responding well to antileukotriene strategies.

A recent study[156] suggests that among allergic individuals there may be two distinct subpopulations with respect to their inflammatory leukotriene responses to allergen challenge. At the start of this study, nine out of the total 18 allergic asthmatic patients responded to ragweed challenge with high bronchioalveolar lavage (BAL) concentrations of CysLT and LTB4 after 24 hours, whereas the remaining nine patients did not. Treatment with zileuton significantly reduced BAL eosinophil counts in the 'high leukotrienes producers', but not in the 'low leukotrienes producers'. The authors hypothesise that leukotriene inhibition may be more effective in a subset of asthmatic patients whose leukotrienes are a major contributory factor causing allergic inflammation.

8. Clinical Safety of Antileukotrienes

Antileukotrienes have a very good safety profile, and except for some liver enzyme elevations that have been described following use of doses higher than the recommended doses, all adverse events reported from clinical trials are comparable to adverse events reported with placebo. The only severe disease that has been associated with antileukotriene use is Churg-Strauss syndrome. Churg-Strauss syndrome, though, is probably not directly connected with the ingestion of antileukotrienes, but it is related to the 'unmasking' withdrawal of corticosteroids when antileukotrienes are added to anti-asthma treatment. This part of the review will be divided into two sections: the adverse effects detected in clinical trials and the relationship between antileukotrienes and Churg-Strauss syndrome.

8.1 Zafirlukast

Very detailed lists of adverse events with zafirlukast can be found in two of the 13-week placebo-controlled trials and in the one 6-week trial. The adverse effects collected in these studies by Fish et al.,[106] Nathan et al.[77] and Spector et al.[103] are collated in table VIII. The third 13 week follow-up trial, published by Suissa et al.[107] did not mention adverse events. Very comprehensively, a review paper by Barnes[157] includes all adverse effects recorded in all placebo-controlled trials performed with zafirlukast. The paper includes adverse events from 5188 patients treated with zafirlukast (at different doses) and 2573 patients treated with placebo from 93 clinical trials. Results in the paper are expressed as histograms, and we have tried to extract the data from these histograms in order to enter them into table VIII, but consequently, numbers are only approximate.

Table VIII. Adverse events seen with zafirlukast (ZK) and placebo (P) in several clinical trials. The numbers given in the last column (Barnes[157]) represent all the adverse events reported in all clinical trials completed up to March 1996 and are extracted from a bar chart so must be considered approximate (see section 8.1 for details). Most of the trials reported adverse events only if they occurred in at least 2% of patients

	Spector et al.[103]		Nathan et al.[77]		Fish et al[106]		Pearlman et al.[104]		Barnes[157]	
	ZK	P	ZK	P	ZK	P	ZK	P	ZK	P
Demographics										
N	200	66	231	223	514	248	205	206	5188	2573
% Female	29.5	30.3	55	59	42.8	41.1	41	44	42.7	45.0
Age range (y)[a]	18–65		≥12		≥12		5–12		7–78	11–77
Dose (mg twice daily)	5–40		20		20		10		5–80	
Adverse events (% of patients)										
Respiratory system										
rhinitis	1.0	1.0	3.5	5.8	3.1	3.2	NR	NR	2.8	3.6
pharyngitis[b]	16.5	23.0	18.6	18.8	24.7	21.4	9.3	13.6	13.0	14.0
sinusitis	NR	NR	NR	NR	3.5	4.8	3.4	5.8	NR	NR
increased cough	NR	NR	NR	NR	3.1	4.4	NR	NR	2.8	2.8
asthma worsening	NR	NR	NR	NR	2.7	6.5	3.9	5.8	7.8	9.0
CNS										
headache	14.0	11.0	10.0	11.3	13.8	11.3	3.9	2.9	10.2	9.5
Gastrointestinal system										
nausea	NR	NR	2.2	3.6	3.1	2.0	NR	NR	2.9	2.1
vomiting	NR	NR	NR	NR	NR	NR	2.9	2.4	1.4	1.0
gastritis	2.0	6.0	NR	NR	NR	NR	NR	NR	NR	NR
abdominal pain	NR	NR	NR	NR	NR	NR	2.0	1.5	1.9	1.7
diarrhoea	NR	NR	NR	NR	2.7	6.5	2.4	1.9	2.7	2.1
Skin										
rash	NR	NR	NR	NR	3.1	3.6	NR	NR	NR	NR
General										
infections	NR	NR	NR	NR	NR	NR	NR	NR	3.6	3.2
flu syndrome	NR	NR	NR	NR	3.3	4.4	2.0	3.4	2.8	3.2
back pain	NR	NR	NR	NR	2.9	3.2	NR	NR	NR	NR
hypertonia	NR	NR	NR	NR	2.9	3.2	NR	NR	NR	NR
myalgia	NR	NR	NR	NR	3.7	3.6	NR	NR	NR	NR
Overall % patients with adverse events	**53**	**63**	**54**	**59**	**68.1**	**64.5**	**37**	**41**	**NR**	**NR**

a Age range applies to total patient population unless otherwise stated.

b Includes upper respiratory tract infection.

NR = not reported.

The above-mentioned paper by Barnes[157] also includes data on the effect of zafirlukast on liver enzymes at several doses. Only 1.4% of patients treated with zafirlukast experienced an increase in ALT levels, and in only 0.23% did this liver enzyme level increase lead to withdrawal. The equivalent figures for placebo are quite similar: 1.1 and 0.27%. The corresponding data for AST level increases are 0.8 and 0.17% for zafirlukast, and 0.8 and 0.27% for placebo. Except for pharyngitis (more frequent with the 20mg dose), there were no important differences in clinical symptoms between the lower dose (20mg twice daily) and the pooled higher doses (40mg and 80mg twice daily). Considering that patients included in this database were mostly treated with 20, 40 and 80mg twice daily (with 20mg twice daily being the recommended dose), it can sincerely be concluded that zafirlukast is very well tolerated for all organs and systems, including the liver.

8.2 Montelukast

Like zafirlukast, montelukast has shown a very good safety profile in placebo-controlled clinical trials. A list of the most common adverse events encountered in the main clinical trials with montelukast versus placebo is shown in table IX. The trial by Altman et al.[110] does not offer a specific list of adverse events, but states that upper respiratory tract infection and headache were the most frequent, and that there were no differences between the active treatment and the placebo groups. In fact, laboratory adverse experiences were even more frequent in the placebo (6.9%) than in the montelukast group (3.2%). The adverse events reported by Noonan et al.[111] are quite coincident with this description, and apparently it makes no difference whether the dose of montelukast is as low as 2mg or as high as 50mg once daily. As in the adult trials, upper respiratory tract infection, headache and pharyngitis were the most frequent adverse experiences in the trial performed in children aged 6–14 years.[158] In the study of preschool children, fever and vomiting were the most frequent adverse events after upper respiratory tract infection. In any case, the rates of these adverse events were equivalent in the placebo and the active treatment groups.[76]

Adverse events recorded in all phase IIb and III trials conducted with montelukast were recently published. There is a total of 11 trials, five of them previously published and already commented on above, using different montelukast doses (mostly 10mg once daily) and different durations, and the trials included a total of 1955 patients receiving montelukast and 1180 receiving placebo.[159] These pooled data (not including the trial on preschool children) are summarised in table IX.

Data on increases in ALT and AST levels associated with montelukast are also very reassuring, as the percentage of patients with values above the upper normal limit is low, and equivalent in the montelukast and in the placebo groups (ALT 12.9 vs 11.5%, and AST 6.6 vs 5.6%). In the study with children aged 6–14 years differences between montelukast- and placebo-associated enzyme elevations were somewhat higher for AST (ALT 3.0 vs 2.2%; AST 6 vs 3%).[159] In the study of children aged 2–5 years, no data on transaminase levels are given, but it is reported that there were no significant differences in the number of patients with elevations of AST or ALT between the active treatment and the placebo groups.[76]

8.3 Pranlukast

Information on pranlukast is much more sparse than on the other two CysLT inhibitors. The list of observed adverse events in the three long-term clinical trials published in the international literature are listed in table X. As the table shows, no important differences were found in relation to placebo, but the total number of patients is considerably lower than the number of patients with safety data available for zafirlukast or montelukast. There is one other report that includes unpublished data on file from the phase IIb and III trials conducted in Japan.[160] Unfortunately this paper does not specify the adverse events, but only indicates the body system involved, and so it cannot be included for comparison in table X. In this report, 472 patients are included in the pranlukast group, whereas in the placebo group

Table IX. Adverse events seen with montelukast (MK) and placebo (P) in several clinical trials. The numbers given in the last column (Storms et al.[159]) represent all the adverse events reported in all clinical trials in adults. All trials reported adverse events only if they have occurred in at least 6% of patients, except Storms et al.[159] who reported adverse events above 3% frequency in any of the study groups (as a third group on beclomethasone was included here, it is possible that some of the adverse events for montelukast or placebo are reported when they were <3% because they achieved >3% in the beclomethasone group)

	Reiss et al.[112]		Noonan et al.[111]		Knorr et al.[113]		Knorr et al.[76]		Storms et al.[159]	
	MK	P	MK	P	MK	P	MK	P	MK	P
Demographics										
N	408	273	212	69	201	135	461	228	1180	1955
% Female	56	53	31	35	33	38	61	62	49	52
Age range (y)[a]	15–79		18–63		6–14		2–5		15–78	15–85
Dose (mg once daily)	10		2–50		5		4		10–200	
Adverse events (% of patients)										
Respiratory system										
rhinitis	NR	NR	1	6	NR	NR	NR	NR	0.8	1.4[b]
pharyngitis	5.4	10.6	3	6	13.9	12.6	12	15	5.4	7.0
sinusitis	7.6	8.1	NR	NR	NR	NR	NR	NR	4.0	4.3
upper infection	31.6	35.2	6	4	23.9	29.6	27	28	21.5	24.6[b]
increased cough	NR	NR	NR	NR	6.0	7.4	13	11	NR	NR
bronchitis	NR	NR	NR	NR	NR	NR	NR	NR	2.4	3.6
asthma worsening	11.3	11.7	NR	NR	16.4	22.2	NR	NR	14.1	19.7[b]
CNS										
headache	17.9	20.9	8	15	18.9	21.5			18.4	18.1
Gastrointestinal system										
nausea	NR	NR	NR	NR	NR	NR	NR	NR	2.6	3.6
vomiting	NR	NR	NR	NR	NR	NR	16	20	NR	NR
abdominal pain	NR	NR	NR	NR	5.0	10.4	11	9	2.9	2.5
diarrhoea	NR	NR	1	6	NR	NR	10	8	3.1	3.1
General										
flu syndrome	NR	NR	NR	NR	NR	NR	NR	NR	4.2	3.9
fever	NR	NR	NR	NR	7.5	3.7	27	27	NR	NR
Overall % patients with adverse events	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**66.5**	**71.3**

a Age range applies to total patient population unless otherwise stated.

b Significant between group differences.

NR = not reported.

Table X. Percentage of adverse events seen with pranlukast (PK) and placebo (P) in several clinical trials

	Barnes and Pujet[115]		Grossman et al.[114]		Yoo et al.[116]	
	PK	P	PK	P	PK	P
Demographics						
Number	91	44	22	43	98	99
% female	41	34	37	45	39	45
Age range (y)[a]	18–79		19–61		18–70	
Dose (mg twice daily)	225–337.5		337.5–450		225	
Adverse events (% of patients)						
Respiratory system						
rhinitis	NR	NR	0	9.1	NR	NR
pharyngitis[b]	3.3	0	4.6	18.2	NR	NR
sinusitis	NR	NR	4.6	0	NR	NR
increased cough	2.2	2.3	4.6	4.5	NR	NR
bronchitis	1.1	4.5	NR	NR	NR	NR
respiratory disorder	2.4	3.3	7.0	4.5	NR	NR
dyspnoea	0	4.4	NR	NR	NR	NR
asthma worsening	9.0	9.0	18.6	18.2	NR	NR
CNS						
headache	4.5	2.2	13.9	27.3	1.0	4.0
insomnia	NR	NR	NR	NR	2.0	0
vertigo	NR	NR	NR	NR	1.0	0
Gastrointestinal system						
vomiting	NR	NR	NR	NR	1.0	1.0
abdominal pain	4.4	0		NR	1.0	0
dyspepsia	NR	NR	4.6	0	1.0	8.0
diarrhoea	2.3	2.3	NR	NR	NR	NR
constipation	NR	NR	NR	NR	1.0	3.0
Skin						
pruritus	2.2	2.3	NR	NR	3.0	2.0
rash	NR	NR	NR	NR	4.0	2.0
General						
viral infection	1.1	4.5	4.6	0	NR	NR
flu syndrome	NR	NR	NR	NR	NR	NR
weight increase	NR	NR	0	9.1	NR	NR
Overall % patients with adverse events	**NR**	**NR**	**NR**	**NR**	**15.0**	**15.0**

a Age range applies to total patient population unless otherwise stated.

b Includes upper respiratory tract infection.

NR = not reported.

there are only 83. Only regarding adverse events in the gastrointestinal system there is a relative preponderance of pranlukast versus placebo (4.7 vs 0%), but interestingly, liver and biliary adverse events are reported to be rarer in the active treatment (1.5%) than in the placebo group (4.8%). Also, respiratory problems were more frequently encountered in the placebo group. Further adverse events affected other body systems including urinary, special senses, psychiatric, central and peripheral nervous system, skin or 'general', and they occurred with comparable frequency in the two groups.

With respect to liver enzymes elevations, it seems that pranlukast is well tolerated. There is no specific allusion to ALT or AST level elevations in the two European follow-up studies,[114,115] but it is

stated that no significant changes associated with pranlukast were noted in clinical chemistry safety parameters. Yoo et al.[116] report an ALT elevation rate of 1% in the active treatment group versus 2% in the placebo group.

8.4 Zileuton

Zileuton has also been shown to be well tolerated in terms of clinical adverse events in long-term clinical trials. Those studies that offered a specific list of adverse events are included in table XI. Unfortunately, the two zileuton studies by Israel et al.[119,121] did not provide an exhaustive list, but instead the most frequent adverse events were mentioned in the text, and it was stated that no significant difference compared with placebo was found with regard to adverse events.

What appears much more important with respect to zileuton is the possibility of liver enzyme level elevations that have occurred in almost all clinical trials. However, these increases are infrequent and serum liver enzyme levels reverse to normal upon discontinuation of zileuton treatment. In one of the studies by Israel et al.,[121] for instance, five patients in the 600mg four times daily group (3.8%) and three patients in the zileuton 400mg four times daily group (2.2%) had increases of γ-glutamyltransferase (GGT), AST or ALT three times above the normal limit. Time to achieve normalisation once treatment had been stopped ranged from 38–56 days. In a publication of another clinical trial, one single patient in the zileuton 800mg twice daily group (2.2%) is reported to have shown increases in liver function tests.[119] The paper by Liu et al.[120] is very exhaustive in terms of reporting laboratory abnormalities regarding the liver. For instance, as a mean, total bilirubin increased significantly in the zileuton 600mg twice daily group on day 8 compared with baseline; the same was true for alkaline phosphatase. Mean lactic dehydrogenase levels increased and decreased during the course of the trial, and at the end of the treatment period the increase over baseline was statistically significant for both the placebo and the active treatment groups, but the increase was of a moderate magnitude (1–2%). GGT was increased significantly (+22%) at the end of the blinded period in the zileuton 600mg treatment branch. Those elevations returned to normal once treatment was discontinued.

The study by Lazarus et al.[122] provides very valuable information regarding serum liver enzyme levels in a very large group of patients. In the group of patients receiving zileuton (zileuton plus usual treatment), elevations of ALT greater than three times the upper normal limit were found in 4.6, versus 1.1% in the group of patients not on zileuton (usual treatment) [$p < 0.001$]. About 70% of ALT increases occurred during the first 3 months of treatment, and by that time, ALT elevations did not differ between the two groups. Half of the patients who experienced ALT elevations had spontaneous decreases to baseline or below twice the upper normal limit without treatment discontinuation. In patients who stopped treatment ALT levels returned to normal by 4 weeks. ALT elevations were neither accompanied by clinical symptoms nor by increases in bilirubin nor alkaline phosphatase levels.

9. Churg-Strauss Syndrome

9.1 Definition

Churg-Strauss syndrome is a systemic vasculitis that includes – according to the first description by Churg and Strauss – a history of asthma, tissue eosinophilia, extravascular granulomas and fibrinoid necrosis of connective tissue; these pathological changes were described from autopsy material.[161] Clinically (with or without pathological findings) the syndrome was defined by Lanham et al.[162] as a combination of asthma, eosinophilia ($>1.5 \times 10^9$/L) and evidence of vasculitis that involves at least two organs. In 1990, the American College of Rheumatology (ACR) established diagnostic criteria and considers diagnosis very likely when four of the following six signs or symptoms are present: asthma, blood eosinophilia (>10%), neuropathy (mono- or poly-), pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophil infiltration on biopsy.[163] Four years later, in 1994, the Chapel Hill Consensus Conference defined Churg-Strauss

Table XI. Adverse events seen with zileuton (ZL) and placebo (P) in long-term follow-up clinical trials. Only adverse events that occurred in at least 5% of patients are included

	Israel et al.[121]		Liu et al.[120]		Lazarus et al.[122]	
	ZL	P	ZL	P	ZL	No ZL[a]
Demographics						
N	92	46	243	122	2458	489
% female	21	23	56	56	61	61
Age range (y)[b]	18–65		18–62		15–86	
Dose (mg four times daily)	400–600		400–600		600	
Adverse events (% of patients)						
Respiratory system						
rhinitis	NR	NR	4.9	2.5	NR	NR
pharyngitis[c]	NR	NR	11.9	9.8	NR	NR
sinusitis	NR	NR	13.2	13.9	13.5	19.2[d]
bronchitis	NR	NR	4.5	4.9	NR	NR
asthma worsening	NR	NR	29.2	38.5	NR	NR
CNS						
headache	13.0	14.0	30.4	26.2	NR	NR
dizziness	NR	NR	4.1	2.5	NR	NR
Gastrointestinal system						
nausea	NR	NR	7.8	4.1	11.8	5.7[d]
dyspepsia	6.5	0	9.5	4.1	16.6	9.8[d]
diarrhoea	NR	NR	5.7	5.7	NR	NR
General						
infection	NR	NR	29.2	33.6	49	46
flu syndrome	NR	NR	11.1	9.0	NR	NR
back pain	NR	NR	10.3	11.5	NR	NR
pain	NR	NR	12.7	9.8	NR	NR
myalgia	NR	NR	7.9	6.6	NR	NR
asthenia	NR	NR	6.2	4.1	NR	NR
accidental injury	NR	NR	4.1	2.5	NR	NR
Overall % patients with adverse events	**42.3**	**44.9**	**NR**	**NR**	**NR**	**NR**

a This study had two groups: an 'usual treatment' group and an 'usual treatment' plus zileuton group.

b Age range applies to total patient population unless otherwise stated.

c Includes upper respiratory tract infection.

d $p < 0.001$ between treatment groups.

NR = not reported.

syndrome as 'eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotising vasculitis affecting small-to medium sized vessels and associated with asthma and eosinophilia'.[164] For epidemiological purposes it is important to know which one of those definitions is used when the results of different incidence studies on Churg-Strauss syndrome are compared.

Since the description of the first suspected case[165] and eight additional cases of Churg-Strauss syndrome in asthma patients taking zafirlukast reported by Wechsler et al.[166] in 1998 there have been more such reports for this CysLT1 antagonist; however, there have also been reports involving pranlukast[167,168] and montelukast.[169,170]

9.2 Epidemiology

One of the problems with very infrequent conditions is to know precisely their real incidence. For

instance, in 1995, Watts et al.[171] estimated the incidence of Churg-Strauss syndrome from 1988–1994 within the Norwich Health Authority (UK) area to be 2.4 cases per million patient-years (MPY) when using the Lanham et al.[162] criteria, but only half that when the ACR definition was applied.[163] The same group reported later that in the time period from 1988–1997 there had been a doubling of Churg-Strauss syndrome incidence in the second 5-year half as compared with the first one (3.7 vs 1.5 cases per MPY).[172] The authors believe that this increase was based on a report bias due to a better recognition of the disease, probably as a result of the introduction of antineutrophil cytoplasmic antibody testing. The overall incidence in this period was 2.7 cases per MPY using the ACR criteria and 3.4 cases per MPY when the 'Lanham definition' was used.

Other estimates of Churg-Strauss syndrome in the general population are those by Reid et al.[173] (Lanham definition: 2.7 cases per MPY; ACR definition: 2 cases per MPY), and by Martin et al.[174] (6.8 cases per MPY; 95% CI 1.8–7.3). The study by Martin et al. includes very interesting data, namely estimates of Churg-Strauss syndrome incidence in the asthma population (64.4 cases per MPY, 95% CI 13.3–188.1) and the non-asthma population (1.8 cases per MPY, 95% CI 0.05–10.2) prior to the introduction of CysLT1 antagonists. The high estimated rate in the asthma population is quite in agreement with the rate estimated by Lilly et al.[175] who, assuming that asthma has a prevalence of 5–8% in the general population, calculate that Churg-Strauss syndrome is 12.5–20 times more frequent among patients with asthma than among those without. This assumption leads to an incidence of 30–74 cases per MPY (using Watts' incidence figures[171,172]) in asthma patients. The incidence estimates offered by Loughlin et al.[176] in a cohort of asthma patients ranges from zero (Lanham criteria) to 67 cases per MPY (Ingenix Epidemiology adaptation of the ACR definition); this huge margin definitely underlines the importance of definition criteria in order to make studies comparable. Applying the 1990 ACR criteria to a population of more than 4 million UK residents with more than 300 000 asthma patients, Wechsler et al.[177] estimate that Churg-Strauss syndrome incidence among asthma patients is 6–18 cases per MPY, much less than the numbers reported above. The incidence of confirmed Churg-Strauss syndrome according to the ACR criteria associated with zafirlukast treatment is 70 cases per MPY, and with montelukast 45 per MPY.[178] Hence, there is some epidemiological – yet inconclusive – evidence for the concept that CysLT1 antagonists are not associated with an increase in the incidence of Churg-Strauss syndrome. Still, there are no studies yet that by using the same methods and definitions could finally rule out such a suspected association.

9.3 The 'Unmasking' Theory

The initial explanation by Wechsler et al.[166] for the first Churg-Strauss syndrome cases related to zafirlukast treatment was that this drug would provoke unmasking of a disease that had been under control while the asthma patient was treated with oral corticosteroids; i.e. the tapering of corticosteroids allowed by the introduction of CysLT1 antagonist was the suspected cause of revealing a disease that was totally unrelated to any drug. In fact, there are some reports of newly-diagnosed Churg-Strauss syndrome in patients whose oral corticosteroids were diminished in dose or completely discontinued without the introduction of any other drug.[179] If the unmasking mechanism was true in all cases, then the incidence of Churg-Strauss syndrome should have been the same in such asthma patients whether they are or are not taking the suspected drugs. Epidemiological data indeed support this.

The question is: if those drugs really unmask Churg-Strauss syndrome when corticosteroids are tapered, then an increase of Churg-Strauss syndrome incidence should have become apparent not only when CysLT1 antagonists appeared on the market, but also when other oral corticosteroid-sparing anti-asthma medication such as inhaled corticosteroids, salmeterol or maybe even sodium cromoglycate were introduced.[180,181] The fact that

reports in the medical literature associating Churg-Strauss syndrome with inhaled corticosteroids or sodium cromoglycate (independently of the statements on their label warnings) are extremely rare, is therefore intriguing. One might argue, though, that inhaled corticosteroids are absorbed systemically in amounts high enough to control Churg-Strauss syndrome;[182] and that CysLT1 antagonists allow a more substantial reduction of oral corticosteroids than sodium cromoglycate – substantial enough to unmask Churg-Strauss syndrome in contrast to sodium cromoglycate.

However, the 'unmasking' theory is challenged further when some patients with Churg-Strauss syndrome related to zafirlukast or montelukast had not been taking oral corticosteroids, or if taking inhaled corticosteroids, the dose had not been reduced,[183-186] or, most importantly, had not been treated with any kind of corticosteroids before, neither oral nor inhaled.[187] A recent case report[188] of a patient with known Churg-Strauss syndrome that had been controlled well with prednisone and cyclophosphamide, who experienced a relapse of his disease after the additional introduction of montelukast adds evidence to the hypothesis that the unmasking theory is not valid for all cases.

9.4 The 'Worsening' Theory

Some authors hypothesise that the reduction of corticosteroids is not necessarily the only possible mechanism that facilitates the occurrence of Churg-Strauss syndrome. Asthma is one of the symptoms that constitutes the syndrome and it is usually a severe form of asthma. It is quite possible that asthma worsening could be the initial manifestation of incipient Churg-Strauss syndrome. Some time ago such asthma worsening would have been treated with inhaled corticosteroids, but now, corticosteroids might be left for a second step after initial treatment with CysLT1 antagonists. Either montelukast, zafirlukast or pranlukast might be used primarily in order to control asthma worsening, but they will not be able to stop the expression of Churg-Strauss syndrome.[175]

Still this theory assumes that many doctors use CysLT1 antagonists for treating worsening of asthma. Also, if this theory holds true, it seems reasonable to assume that there should be more Churg-Strauss syndrome cases reported in association with long-acting β_2-agonist treatment, as long-acting β_2-agonists can also reasonably be added to inhaled corticosteroids in order to control asthma worsening, instead of increasing inhaled corticosteroids dose or starting oral corticosteroids. In any case, it is fact that most cases of Churg-Strauss syndrome related to CysLT1 antagonists have been described in patients with problematic asthma treated with several drugs.

9.5 The 'Causative' Theory

Of course, it might be the case that CysLT1 antagonists do provoke Churg-Strauss syndrome as an adverse effect. The mechanisms of adverse effects of drugs are: pharmacological, allergic, idiosyncratic, pseudoallergic, or drug interactions. For most drugs, there is a part of the structural component that is responsible for its pharmacological action and also for the extension of this action producing adverse effects (pharmacological mechanism), and this structural component is called 'pharmacophore'. Such a pharmacophore is, for instance, the common part of the molecular structure shared by penicillins and cephalosporins and this explains the cross reactions to these drugs (allergic mechanism). The chemical structures of zafirlukast, montelukast and pranlukast are very different and do not have an identifiable common pharmacophore, and hence a shared allergic reaction through the same pathway seems quite improbable. But the fact that at least in one case zafirlukast was reported to induce a lupus in a child with mild asthma[189] supports the concept that intolerance reactions (probably not hypersensitivity, but autoimmune) are still a feasible mechanism. However, the long time usually observed to have elapsed from the introduction of the drug to the onset of the symptoms (usually 3 months or more[190]) may be used as an argument against the 'intolerance' hypothesis.

Individual autoimmune reactions to individual CysLT1 antagonists cannot be ruled out. Idiosyncratic reactions occur rarely in a subpopulation of predisposed (sometimes genetically predisposed) patients. This kind of reaction can be expected to occur in association with a limited number of agents in the same group of drugs. The fact that Churg-Strauss syndrome has been related not only to antileukotrienes but also to other types of drugs such as fluticasone,[191] erythromycin,[192] carbamazepine[193] or cocaine[194] indicates to some authors[175] that this is not an idiosyncratic reaction; still, it must be underlined that reports of Churg-Strauss syndrome cases related to drugs other than CysLt1 antagonists are very sparse as compared with the 'clusters' of cases reported in association with montelukast or zafirlukast. As for pranlukast, it is difficult to say whether the sparsity of such reports (four cases[167,168,195,196]) depends on pharmacological safety of the drug itself, on the lesser number of patients exposed (Japan and Korea), or on the genetic background of those exposed to it. Altogether, the reasoning against the theory of an idiosyncratic reaction is not very strong when clusters of cases are seen versus one or two individual cases with drugs that have been on the market for much longer periods of time than CysLT1 antagonists and have most probably been administered to many more individuals.

Nevertheless, despite all the above-mentioned discussions, the concept of an idiosyncratic reaction is nowadays rejected based on the low probability that very different drugs can use the same pathway to produce the same adverse effect.

There is still another type of pharmacological adverse reaction that deserves some commentary, and that is the antagonism of a physiological effect. Some authors[197] have suggested that LTB4, not blocked by CysLT1 antagonists and known to be not only a neutrophil, but also an eosinophil attractant[198] could be in part responsible for eosinophilia and maybe even the full symptomatology of Churg-Strauss syndrome in some cases. Those who reject this reasoning argue that zileuton, which blocks 5-LO and consequently also interferes with LTB4 synthesis, has also been related to one case of Churg-Strauss syndrome. However, this is just one single known incident, the report of which cannot be found in the current medical literature, but in the files of the US FDA (quoted by Wechsler[177]). However, this paucity of reports might also be the result of too few patients exposed to the drug yet in relation to montelukast or zafirlukast.

10. Conclusions

Antileukotrienes are effective bronchoprotective agents blocking the bronchoconstrictive response to a variety of specific or non-specific bronchial challenges. In allergen challenge tests, antileukotrienes are more effective in blunting the early phase than the late phase of the bronchial response to inhaled allergen in asthma patients.

Indices of anti-inflammatory effects of antileukotrienes, as measured by reduced eosinophil counts, are demonstrable in terms of blood, sputum or bronchoalveolar lavage fluid. A possible role of antileukotrienes in preventing airway remodelling is a field that must yet be explored.

In the prevention of exercise-induced asthma montelukast is as efficacious as a long-acting β_2-agonist like salmeterol on a short-term basis. Here, zafirlukast shows a relatively lower efficacy. Zileuton is as effective as zafirlukast within the first 4 hours of administration. On a long-term basis, montelukast does not seem to induce tolerance to its protective effect, which is favourable as opposed to salmeterol.

The effects of all antileukotrienes on long-term asthma control, the main test criterion for an anti-inflammatory asthma drug, are in general significantly better than placebo, but the magnitude of effects is quite modest when compared with low doses of inhaled corticosteroids. From the clinical trials data, antileukotrienes apparently have a greater impact on subjective measurements of asthma control such as symptom scores or QOL measurements than on pulmonary function test results.

As add-on therapy to inhaled corticosteroids, salmeterol has been shown to be of greater benefit than zafirlukast or montelukast with respect to most

study endpoints, but especially with regard to pulmonary function test results. However, in the long term, antileukotrienes might theoretically offer better asthma control, as this therapy is not associated with tolerance induction.

There is some evidence that antileukotrienes could provide greater benefit in certain subgroups of asthma patients, and in certain individuals with specific genetic polymorphisms. This is a field that deserves more research. The safety profile of all antileukotrienes is very good. The only adverse effects as compared with placebo that have been detected so far in clinical trials are elevations of hepatic enzyme levels in patients treated with zileuton that have not been associated with clinical symptoms and that returned to normal in a short period of time after discontinuing treatment. The only serious concern related to antileukotrienes (in particular to the CysLT1 antagonists) is their possible role in the pathogenesis of Churg-Strauss syndrome. In light of current information and considering that most cases of Churg-Strauss syndrome related to CysLT1 antagonists have appeared in the context of corticosteroid reduction, it can be concluded that in patients with moderate to severe asthma this corticosteroid reduction together with the introduction of the leukotriene antagonist is the main risk factor for Churg-Strauss syndrome. However, other possible mechanisms cannot be excluded until more conclusive information, especially from the field of pharmacoepidemiology, is being offered.

The greatest value of antileukotrienes is their benefit-risk ratio. Although inhaled corticosteroids perform significantly better as anti-inflammatory agents in asthma, their adverse effects are more frequent and more severe, especially at high doses. The only important disease related to antileukotrienes is the very rare Churg-Strauss syndrome, whose causal relationship is doubtful. Also, oral administration and – in the case of montelukast – the once daily schedule, make these drugs very convenient in certain circumstances, for example, in young children and in the elderly. Also, they are probably the best choice in exercise-induced asthma. In the treatment of asthma patients on a regular basis with a single drug, a trial with an antileukotriene should be taken into account: it appears preferable to control the disease with an antileukotriene than with an inhaled corticosteroid. Montelukast is an interesting option for use in infants and young children; compared with inhaled corticosteroids, its benefit-risk ratio seems more favourable in children than in adults.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest directly relevant to the content of this manuscript.

We acknowledge Antonela Martinez Torres for her help in writing the manuscript.

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