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Treatment Options for Initial Maintenance Therapy of Persistent Asthma: a Review of Inhaled Corticosteroids and Leukotriene Receptor Antagonists

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Abstract

Inhaled corticosteroids (ICSs) are recognized as the cornerstone of asthma therapy. They are considered to be the most effective anti-inflammatory medication currently available for the treatment of persistent asthma, regardless of its severity. Leukotriene receptor antagonists (LTRAs) are also used as initial maintenance therapy in patients whose asthma is uncontrolled by bronchodilators alone. There are now sufficient data available to allow a comparison of the relative effectiveness and cost-effectiveness of LTRAs and ICSs as initial maintenance therapy. The consensus from the studies reviewed in this article demonstrates that ICSs are more effective than LTRAs as initial maintenance therapy. In particular, studies on fluticasone propionate have shown that it was more effective than LTRAs in clinical outcomes: producing greater improvements in lung function and asthma control; as measured by either forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF); by a greater reduction in daytime and night-time asthma symptoms; and short-acting β_2-agonist use. This superiority was also seen when patients were switched from an LTRA to fluticasone propionate. Similar findings have been demonstrated with beclomethasone dipropionate (BDP), showing that, in adults, this inhaled steroid also had a greater effect on pulmonary function and symptom scores than did LTRAs.

Quality of life assessments showed that fluticasone propionate achieved improvements that were deemed to be clinically meaningful; these changes were significantly greater than those achieved with LTRAs. However, questionnaire-based patient preference studies comparing BDP with LTRAs showed that children and adolescents generally preferred an LTRA to BDP. A number of comparative analyses showed that inhaled fluticasone propionate is more cost-effective than either montelukast or zafirlukast; these analyses used cost per symptom-free day and cost per successfully treated patient as outcome measures, from the perspective of a third-party payer. In general, these results were supported by resource utilisation studies in real-world settings. Asthma treatment guidelines (e.g. GINA, 2002) recommend combination therapy with ICSs and a long-acting β_2-agonist as initial maintenance therapy if the disease is of sufficient severity. Studies that assessed the effectiveness, cost-effectiveness, and quality of life achieved with a salmeterol–fluticasone propionate combination as initial maintenance therapy also showed it to be superior to LTRAs.

In conclusion, in terms of efficacy and quality of life, fluticasone propionate is more effective than LTRAs as initial maintenance therapy and is associated with significantly lower healthcare costs and less frequent use of healthcare resources than LTRAs. There is also evidence to suggest that initial maintenance therapy with the combination of an inhaled steroid plus a long-acting β-agonist bronchodilator may be a more effective option for the management of persistent asthma than treatment with a single-controller agent alone (ICS or LTRA).

1. Introduction

Asthma is a global problem associated with substantial morbidity and a significant economic burden. It is a chronic disorder characterized most prominently by inflammation and smooth muscle dysfunction of the airways (figure 1);[1] common symptoms include wheezing, breathlessness, chest tightness, and coughing, particularly at night and early in the morning. Asthma symptoms are usually associated with variable airflow obstruction that is reversible either spontaneously or with treatment.[2]

The goal of asthma treatment is to achieve disease control, which is defined as minimal or no chronic symptoms during the day or night, minimal or no exacerbations, no limitations on activities, the maintenance of normal or near-normal pulmonary function, minimal use of inhaled

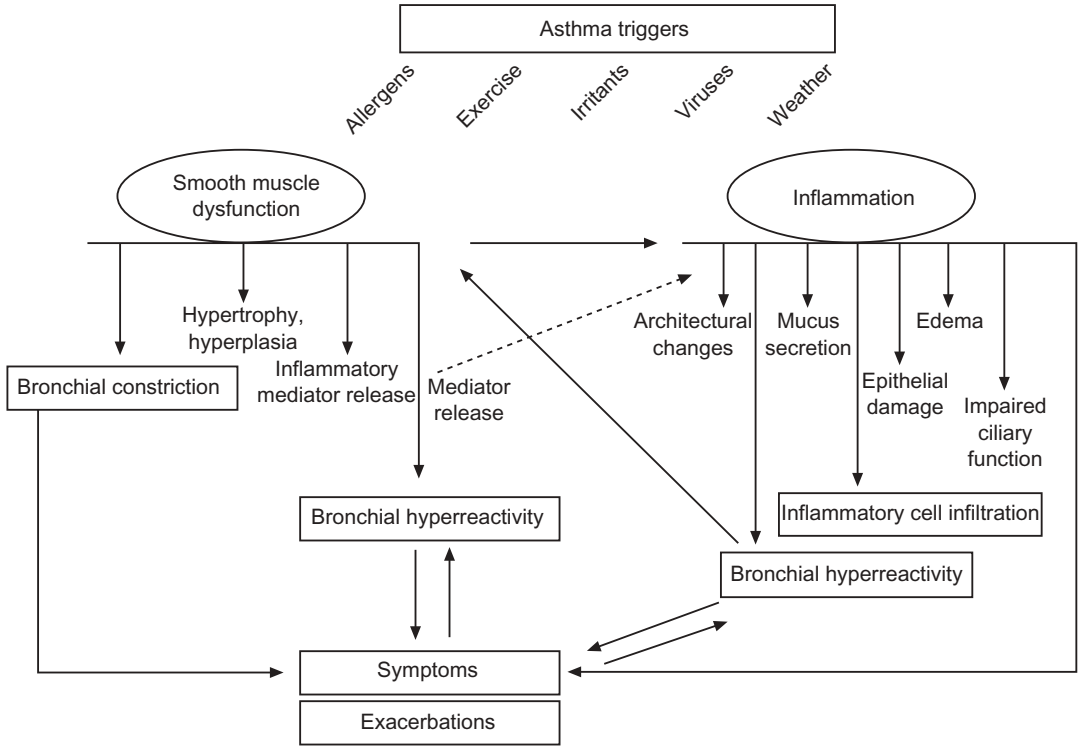

Fig. 1. The relationship between smooth muscle dysfunction, inflammation, and symptoms in asthma. (Reproduced with permission from Creticos PS. The NHLBI guidelines: where do we stand and what is the new direction from the NAEPP? Adv Stud Med 2002; 2: 499-503.[1] © 2002 JHASIM.)

short-acting β_2-agonists, and minimal or no adverse effects from asthma medication.[2,3] If inhaled short-acting β_2-agonists are required more than twice a week, then inhaled corticosteroids (ICSs), leukotriene receptor antagonists (LTRAs), cromolyn sodium or nedocromil may be used as initial maintenance therapy for mild asthma.[2-4]

Inhaled steroids are the preferred first-line choice for the management of mild to moderate persistent asthma.[2-4] In light of this, early intervention with ICS therapy has gained prominence, not only from initial work,[5,6] but most recently by the findings from the Inhaled Steroid Treatment As Regular Therapy in Early Asthma Trial (START).[7] This study of more than 7 000 children and adults treated with an inhaled steroid, budesonide, again demonstrated superior control of asthma symptoms, with (a) a decrease in the frequency of exacerbations, (b) an increase in time to onset of exacerbation, and (c) reduced severity of exacerbations. The study also demonstrated that early intervention with budesonide treatment blunted the expected deterioration in lung function that was otherwise observed in the placebo cohort over the 3-year study time-frame. Even more cognizant of the disease process, national and international asthma guidelines recommend therapy that is appropriate to the severity of the disease, and as such, combination therapy (i.e. ICS and long-acting β_2-agonist [LABA]) may be appropriate as an option for intervention maintenance therapy for certain patients.

Cromolyn sodium and nedocromil have been available for many years, and both drugs have been shown to reduce asthma symptoms, improve morning peak expiratory flow (PEF), and reduce the need for short-acting β_2-agonists.[8,9] However, the clinical response to cromolyn sodium and nedocromil is less predictable than the response to ICSs. Furthermore, both drugs need to be administered up to four times a day, which may reduce compliance. The use of cromolyn sodium and nedocromil as initial maintenance therapy will not be discussed further in this review.

Sustained-release theophylline may also be considered as potential initial maintenance therapy for mild asthma. However, international and USA guidelines do not consider theophylline to be the preferred treatment for initial maintenance therapy of persistent asthma.[2-4]

LTRAs are used as initial maintenance therapy in patients whose asthma is uncontrolled by bronchodilators alone, but these drugs are not recommended over ICSs as first-line therapy. The efficacy of LTRAs has been established in placebo-controlled trials.[10-15] However, studies against placebo are of limited value, because clinicians need to compare efficacy with established treatments recommended in asthma guidelines in order to make informed decisions.

The purpose of this review is to compare the published evidence on clinical efficacy, tolerability, health outcomes and pharmacoeconomics for ICSs, used either as monotherapy or in combination with LABAs, and compared with LTRAs, in order to evaluate which treatment option is the most effective initial maintenance therapy for persistent asthma.

2. Scope of Review

The studies reported in this review were identified using a Medline search. The search terms were: 'inhaled cortico$', 'fluticasone', 'beclomethasone', 'budesonide', 'triamcinolone', 'flunisolide', 'leukotri$', 'montelukast', 'zafirlukast' and 'pranlukast'; '$' denotes any character or combination thereof ('wild card' suffix). Results for the individual searches on ICSs and LTRAs were combined so that studies that used an ICS and an LTRA were selected; for example, the searches for fluticasone and montelukast, fluticasone and zafirlukast, fluticasone and pranlukast were combined. These combined searches were repeated for beclomethasone, budesonide, triamcinolone and flunisolide, respectively. All abstracts and citations found from the search were checked and studies that specifically compared any ICS (alone and in combination with an LABA) with LTRAs in patients whose asthma was not controlled by short-acting β_2-agonists alone were retained for review. No studies were identified that compared

LTRAs with budesonide, triamcinolone or flunisolide and matched the search criteria.

Studies were also found by reviewing the reference lists within the articles retained for review, to ensure that no studies were missed in the original search, and by searching abstracts presented at the annual meetings of the American Academy of Asthma, Allergy and Immunology, the American Thoracic Society, and the European Respiratory Society (using the search terms already described, up to September 2002). Only those articles and abstracts with sufficient information on patient characteristics and outcomes were included for review. Individuals with asthma (i.e. a degree of airway reversibility) were included, but individuals with chronic obstructive pulmonary disease were excluded. Studies using unlicensed doses of either ICSs or LTRAs were excluded. No additional statistical analyses were performed.

3. Clinical Efficacy and Health Outcomes

3.1 Fluticasone Propionate Compared With Leukotriene Receptor Antagonists

Five multicenter, randomized, double-blind, parallel-group, comparative studies were found that compared the therapeutic efficacy of fluticasone propionate up to 100μg inhaled twice daily with that of montelukast 10mg orally once daily[16,17] or zafirlukast 20mg orally twice daily[18-20] as initial maintenance therapy. One study also included a placebo group.[19] Patients eligible for these studies were at least 12 years old (at least 15 years old in the studies with montelukast), with a diagnosis of asthma (as defined by the American Thoracic Society) for at least 6 months. They had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of 50–80% of the predicted value, and an increase in FEV_1 of at least 12% (at least 15% in the studies with montelukast) after inhalation of salbutamol 200μg, and required rescue use of salbutamol on at least six occasions in the week before random allocation to study groups (the reversibility of lung function abnormalities greatly enhances the diagnostic confidence for asthma,[2] and an increase in FEV_1 of at least 12% is considered reasonable for a positive bronchodilator response[21]). The duration of active treatment ranged from 4 to 24 weeks (table I). An additional retrospective analysis[22] is also reported, which compared the efficacy of fluticasone propionate and zafirlukast in 1 742 patients younger than 50 years and 243 patients aged at least 50 years, using data from five randomized, double-blind, double-dummy studies of 4–12 weeks duration, including the three studies listed above.[18-20,22,23]

The results from the five studies[16-20] showed that at endpoint (the patient's last assessment), lung function showed consistently greater improvements from baseline in those receiving fluticasone propionate ($n = 1\,006$) than in those receiving either zafirlukast ($n = 492$) or montelukast ($n = 526$) [table I]. In general, mean FEV_1 values were significantly greater in the fluticasone propionate group than in the LTRA group at the first treatment assessment of this parameter (2 or 4 weeks), and the greater improvements were maintained throughout the treatment period. A typical example of the changes in mean FEV_1 with an ICS compared with an LTRA is shown in figure 2.[16] Similar results were observed for changes in mean morning PEF. Data from the pooled analysis[22] demonstrated that treatment with inhaled fluticasone propionate 88μg twice daily resulted in a significantly ($p < 0.001$) greater improvement in FEV_1 at pooled endpoint compared with zafirlukast 20mg twice daily, regardless of the patient's age (figure 3).

The five studies also showed that with fluticasone propionate treatment there were significantly greater decreases from baseline in the frequency of as-needed β_2-agonist usage and the frequency of night-time awakenings because of asthma, compared with LTRA treatment.[16-20] These decreases were accompanied by significantly greater increases from baseline in the percentage of symptom-free days and rescue-free days with fluticasone propionate compared with LTRA treatment (table I). In addition, treatment with fluticasone propionate

Table I. Summary of efficacy outcomes in five studies comparing inhaled fluticasone propionate (FP) with leukotriene receptor antagonists (LTRAs) as initial maintenance therapy. Data are presented (FP vs LTRA) as mean changes from baseline at endpoint[a]

Studies	Patients given FP/LTRA (n)	FEV_1 (L)	Morning PEF (L/min)	Evening PEF (L/min)	Salbutamol use (puffs/day)	Symptom-free days (%)	Rescue-free days (%)	Night-time awakening (no. per night)
FP 100μg inhaled twice daily vs zafirlukast 20mg orally twice daily								
4 weeks of treatment								
Nathan et al.[20]b	144/150	0.39 vs 0.33	29.3 vs 18.3*	18.8 vs 14.5	−1.8 vs −1.1*	19.8 vs 11.6*	NR	NR
12 weeks of treatment								
Bleecker et al.[18]	231/220	0.42 vs 0.20**	49.9 vs 11.7**	38.9 vs 10.5**	−2.4 vs −1.5**	28.5 vs 15.6**	40.4 vs 24.2**	−0.28 vs −0.15**
Busse et al.[19]	113/111	0.59 vs 0.36*	46.7 vs 15.2*	33.3 vs 12.8*	−2.8 vs −1.9*	28.8 vs 18.7*	48.9 vs 37.5*	−0.32 vs −0.23*
FP 100μg inhaled twice daily vs montelukast 10mg orally once daily								
24 weeks of treatment								
Busse et al.[16]	271/262	0.51 vs 0.33**	38.5 vs 34.1**	53.9 vs 28.7**	−3.1 vs −2.3**	32.0 vs 18.4**	45.9 vs 31.2**	−0.64 vs −0.48*
Meltzer et al.[17]	258/264	0.48 vs 0.32**	63.7 vs 37.6**	52.7 vs 27.2**	−3.2 vs −2.3**	34.3 vs 20.2**	45.6 vs 33.4**	−0.68 vs −0.44*

a Defined as patient's last assessment.

b Data shown at endpoint for the double-blind treatment period only.

FEV_1 = forced expiratory volume in 1 second; **NR** = not reported; **PEF** = peak expiratory flow.

*$p < 0.05$; **$p < 0.001$.

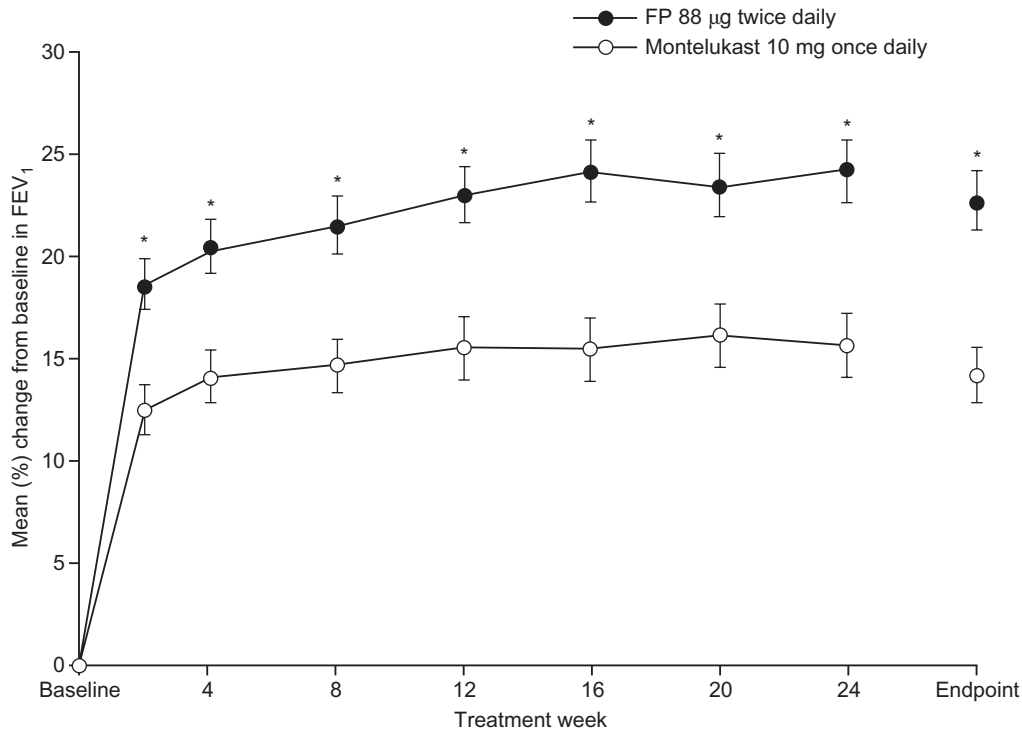

Fig. 2. Mean percentage change from baseline in forced expiratory flow in 1 second (FEV_1) in patients receiving fluticasone propionate (FP) 88μg inhaled twice daily (n = 271) or montelukast 10mg orally once daily (n = 262) during a 24-week double-blind treatment study. *$p < 0.001$, FP compared with montelukast. (Reprinted from Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomised clinical trial. J Allergy Clin Immunol 2001; 107 (Pt 3), 461-8.[16] © 2001, with permission from Elsevier.)

resulted in consistently greater improvements in asthma symptom scores than treatment with LTRAs.

In all five studies,[16-20] fluticasone propionate-treated patients experienced fewer exacerbations than did LTRA-treated patients (table II). Similarly, the pooled analysis [22] showed that treatment with fluticasone propionate resulted in significantly fewer exacerbations than did treatment with zafirlukast. Furthermore, the efficacy of zafirlukast was lower in patients aged 50 years or more, suggesting that the effectiveness of treatment with LTRAs declines in older patients (figure 4).

Both fluticasone propionate and LTRA treatments were well tolerated in the five studies.[16-20] The overall incidences of adverse events in the two treatment groups were not significantly different. Furthermore, the incidences of adverse events potentially related to treatment with fluticasone propionate were similar to or lower than those reported for LTRAs (table II). Rates of withdrawal because of adverse events from the studies were low, and similar in the two treatment groups.

Three of the five identified studies also assessed quality of life using the disease-specific instrument, Asthma Quality of Life Questionnaire (AQLQ).[16,17,19] The differences between fluticasone propionate and LTRAs were not clinically meaningful for any of the AQLQ domain scores in one study,[17] but were clinically meaningful (at least 0.5 points in favour of fluticasone propionate) for two of the four domains (asthma symptoms and emotional function domains) in another study.[16] In the study that included a placebo group, the

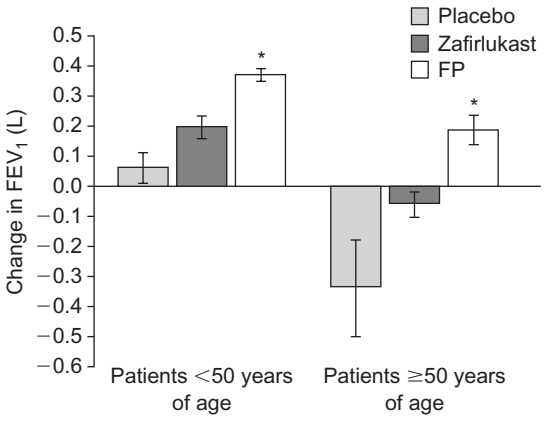

Fig. 3. Mean change in FEV_1 (L) in younger (<50 years of age) and older patients (≥50 years of age) after treatment with either fluticasone propionate (FP) 88μg or zafirlukast 20mg for up to 12 weeks. *$p < 0.05$. (Reproduced with permission from Creticos P, Knobil K, Edwards, LD, et al. Loss of response to treatment with leukotriene receptor antagonists but not inhaled corticosteroids in patients over 50 years of age. Ann Allergy Asthma Immunol 2002; 88: 401-9.[22] © 2002 American College of Allergy, Asthma & Immunology.)

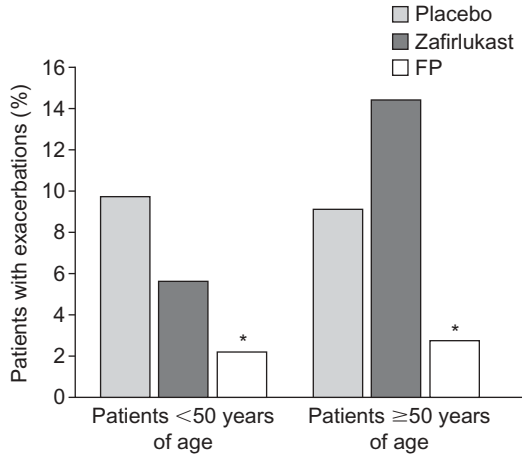

Fig. 4. The percentage of younger (<50 years of age) and older patients (≥50 years of age) who experienced one or more asthma exacerbations after treatment with either fluticasone propionate (FP) 88μg or zafirlukast 20mg for up to 12 weeks. *$p < 0.05$. (Reproduced with permission from Creticos P, Knobil K, Edwards, LD, et al. Loss of response to treatment with leukotriene receptor antagonists but not inhaled corticosteroids in patients over 50 years of age. Ann Allergy Asthma Immunol 2002; 88: 401-9.[22] © 2002 American College of Allergy, Asthma & Immunology.)

treatment differences between fluticasone propionate and placebo for the global scores including the individual domain scores (except for activity limitation) were clinically meaningful; in contrast, the LTRA did not achieve clinically meaningful differences compared with placebo in any AQLQ scores (figure 5).[19]

The physicians' overall assessment of study medication efficacy and the patients' overall satisfaction with study medication both significantly ($p \leq 0.025$) favoured fluticasone propionate over the LTRAs at endpoint in the four studies that assessed these parameters.[16-19] More physicians rated fluticasone propionate as effective compared with ratings for LTRAs (ranges 56–75% and 41–55%, respectively), and more physicians rated LTRAs as ineffective compared with ratings for fluticasone propionate (ranges 22–27% and 10–16%, respectively).[16-19] Likewise, more patients treated with fluticasone propionate were satisfied with their medication than patients treated with LTRAs (ranges 70–85% and 55–66%, respectively).[16,17,19]

In summary, the results of five randomised,

Table II. Summary of the frequency of asthma exacerbations and the incidence of adverse events potentially related to study medication in the five studies comparing inhaled fluticasone propionate (FP) with leukotriene receptor antagonists (LTRAs) as initial maintenance therapy. Data are presented as FP vs LTRA

Study	Asthma exacerbations[a] (%)	Incidence of adverse events (%)
Nathan et al.[20]b	<1 vs 3	4 vs 10
Bleecker et al.[18]	4 vs 6	10 vs 10
Busse et al.[19]	4 vs 12	12 vs 13
Busse et al.[16]	4 vs 8	NR
Meltzer et al.[17]	7 vs 8	NR

a Exacerbations were defined as a worsening of asthma symptoms requiring a change in the patient's asthma therapy (including the use of oral or parenteral corticosteroids), other than an increased use of supplementary salbutamol,[18-20] and/or any event that required a visit to the emergency department, admission to hospital, or unscheduled visit to the doctor.[16, 17]

b Data shown for the double-blind treatment period only.

NR = not reported.

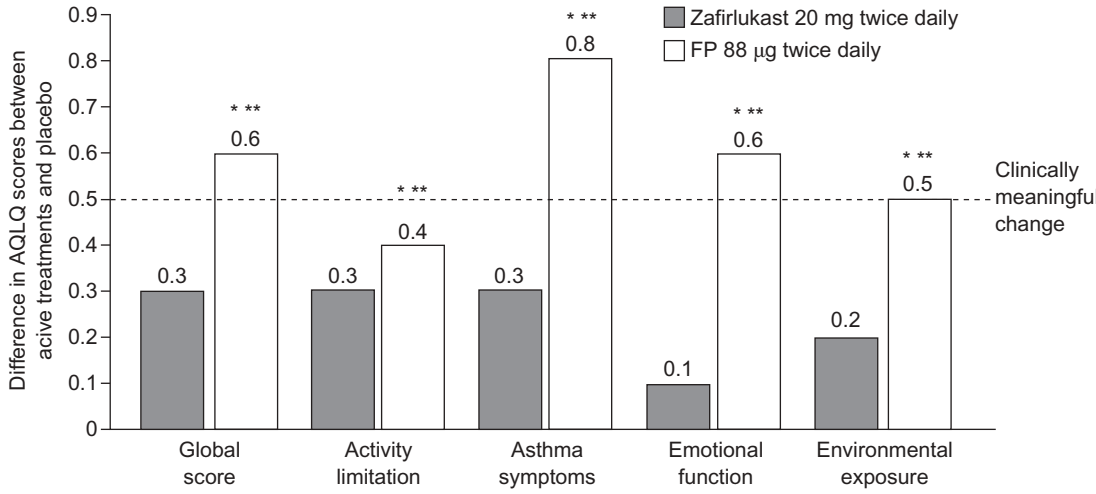

Fig. 5. Differences between twice daily fluticasone propionate (FP) 88μg inhaled (n = 113) and zafirlukast 20mg orally (n = 111) in Asthma Quality of Life Questionnaire (AQLQ) scores. Bars represent the difference between active treatment and placebo. Horizontal line at 0.5 indicates clinically meaningful difference. *p ≤ 0.001, FP compared with placebo; **p ≤ 0.033, FP compared with zafirlukast. (Reproduced with permission from Busse W, Wolfe J, Storms W, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomised double-blind, placebo-controlled trial. J Fam Pract 2001; 50 (Pt 7): 595-602.[19] © Dowden Health Media Inc.)

comparative trials showed that initial maintenance therapy with fluticasone propionate up to 100μg inhaled twice daily provided greater overall control of asthma than was achieved with montelukast 10mg orally once daily or zafirlukast 20mg orally twice daily, in adults and adolescents with persistent asthma; pooled analysis demonstrated that the efficacy of LTRAs (zafirlukast) was generally lower than that of fluticasone propionate in patients older than 50 years. In addition, the incidence of adverse events did not differ significantly between the fluticasone propionate- and LTRA-treated groups. These studies also demonstrated that treatment of asthma with fluticasone propionate was more effective than treatment with LTRAs in terms of improvements in quality of life, and patient and physician satisfaction.

3.2 Studies Comparing Inhaled Corticosteroids (other than Fluticasone Propionate) with Leukotriene Receptor Antagonists

Five published articles were found that met the search criteria for inclusion. Three assessed clinical outcomes,[24-26] and two assessed patient preferences.[27,28]

3.2.1 Clinical Outcomes

The studies assessing clinical outcomes were all randomized, double-blind, double-dummy, placebo-controlled studies that compared beclomethasone dipropionate (BDP) with an LTRA.[24-26] The study by Israel et al.[24] recruited patients of at least 15 years of age with persistent asthma and an FEV_1 of 50–85% of the predicted value, who were receiving short-acting β_2-agonists. Eligible patients were randomized to receive montelukast 10mg daily (n = 339), BDP 200μg twice daily (n = 332), or placebo (n = 111) for 6 weeks. Malmstrom et al.[25] recruited patients 15–85 years old with persistent asthma and an FEV_1 of 50–85% of the predicted value who were receiving short-acting β_2-agonists, theophylline or no treatment. Patients were randomized to receive montelukast 10mg orally once daily (n = 387), BDP 200μg inhaled twice daily (n = 251), or placebo (n = 257) for 12 weeks.

A study by Williams et al.[26] was an extension to that by Malmstrom et al.[25] All patients completing the double-blind primary studies were eligible to enter the extension period, except for those in the placebo group. During the extension period, patients continued with their double-blind treatment for another 37 weeks. The report by Williams et al.[26] also included results of open-label extensions from two other studies, performed by Reiss et al.[11] and Knorr et al.[14] In the first of these studies,[11] patients aged 15–85 years were assigned to open-label BDP 200μg inhaled twice daily (n = 83) or montelukast 10mg orally once daily (n = 291) for 156 weeks. In the second,[14] children aged 6–14 years were assigned to open-label montelukast 5mg orally once daily (n = 207) or BDP 100μg inhaled twice daily (n = 38) for 112 weeks.

The efficacy results from these outcome studies are summarised in table III. The findings of the study by Israel et al.[24] demonstrated that both BDP and montelukast produced significant ($p < 0.001$ compared with placebo) improvements in days of asthma control, which was defined as a day with no more than two puffs of salbutamol, no night-time awakenings, and no asthma attacks; the mean percentages of days of asthma control were 41.4% for montelukast, 41.1% for BDP, and 26.8% for placebo. Compared with the placebo group, both BDP and montelukast also reduced average daily use of short-acting β_2-agonists ($p < 0.001$), and improved FEV_1 (0.14L for montelukast and 0.28L for BDP; $p < 0.001$).

Malmstrom et al.[25] observed that both BDP and montelukast treatment produced improvements from baseline in pulmonary lung function (FEV_1 and PEF) and asthma control as measured by use of salbutamol, daytime symptom scores, and the frequency of night-time awakenings caused by asthma. Furthermore, compared with placebo, both montelukast and BDP significantly reduced asthma attacks (defined as a worsening of asthma requiring oral corticosteroid treatment or unscheduled visit to a physician, emergency department, or hospital); the percentage of patients who had at least one asthma attack during the 12 weeks of treatment

Table III. Summary of clinical outcomes in studies comparing beclomethasone dipropionate (BDP) with montelukast (Mon.). Data are presented as mean changes from baseline over the treatment period using all available measurements (inhaled corticosteroids vs Mon.)

Studies	Study design (duration, weeks)	Patients given BDP/Mon. (n)	FEV_1 (L)	Morning PEF (L/min)	Evening PEF (L/min)	Salbutamol use (puffs/day)	Daytime symptom score	Night-time awakening (nights/week)
BDP 200μg inhaled twice daily vs Mon. 10mg orally once daily (adults/adolescents)								
Israel et al.[24]	DB (6)	332/339	0.38 vs 0.24	NR	NR	−1.9 vs −1.7	NR	NR
Study A[25]	DB (12)	251/387	0.28 vs 0.16	39 vs 24	32 vs 21	−2.2 vs −1.3	−0.6 vs −0.41	−2.4 vs −1.7
Extension study A[26]	DB (37)	167/269	0.3 vs 0.2	46 vs 26	33 vs 20	−2.8 vs −2.2	−0.8 vs −0.6	−2.9 vs −2.8
Extension study B[11, 26]a	OL (156)	83/291	0.4 vs 0.3	38 vs 33	29 vs 22	−2.5 vs −2.2	−0.7 vs −0.7	−3.0 vs −2.4
BDP 100μg inhaled twice daily vs Mon. 5mg orally once daily (children)								
Extension study C[14, 26]b	OL (112)	38/207	0.3 vs 0.3	NR	NR	NR	NR	NR

a FEV_1 measured through to 125 weeks of treatment, other endpoints measured through to 37 weeks of treatment.

b FEV_1 measures through to 64 weeks of treatment.

DB = double-blind; **FEV_1** = forced expiratory volume in 1 second; **NR** = not reported; **OL** = open-label; **PEF** = peak expiratory flow.

was 10% in the BDP group, 16% in the montelukast group, and 27% in the placebo group. The effects of BDP and montelukast treatment on lung function and symptom control were maintained throughout the 37-week extension period, with greater treatment responses in the BDP group than in the montelukast group.

The study by Reiss et al.[11,26] showed that, in both treatment groups, all efficacy endpoints demonstrated mean improvements from baseline during the study. Again, treatment with BDP produced consistently greater improvement than treatment with montelukast. However, in the study by Knorr et al.,[14,26] both BDP and montelukast produced the same improvement in FEV_1. Changes in other clinical parameters were not reported. The paediatric study extension was the only study that assessed quality of life. Both BDP and montelukast produced similar improvements from baseline in quality of life global scores after 24 weeks of treatment.

In terms of safety assessments, Israel et al.[24] showed that both BDP and montelukast were generally well tolerated. The discontinuation rates were similar between the three treatment groups: 4.5% discontinued treatment in the placebo group, compared with 3.2% in the montelukast group and 4.2% in the BDP group. The most frequently reported adverse events (more than 5% of patients) were upper respiratory tract infections, headache, and sinusitis.

In the study by Malmstrom et al.,[25] 2% of patients in the BDP and montelukast groups discontinued treatment because of adverse events, compared with 4% receiving placebo. Rates of withdrawal from the study extension as a result of adverse events were 4% in both treatment groups. Overall withdrawal rates (for any reason) were 12% in the montelukast group and 14% in the BDP group.

In the extension study performed by Reiss et al.,[11,26] rates of withdrawal because of adverse events occurred in 6% of patients in the montelukast group and 5% in the BDP group; however, only 34% of montelukast-treated patients and 33% of BDP-treated patients completed the 156-week study extension. In the paediatric study extension, 4% of those in the montelukast group withdrew because of adverse events (no withdrawals were attributed to adverse events in the ICS group); 44% and 50% of children treated with montelukast and BDP, respectively, completed the 112-week study extension.

In summary, the results of the studies assessing clinical outcomes in adults suggest that BDP was more effective than montelukast. The study by Israel et al.[24] demonstrated that BDP had a greater effect on improvement in FEV_1 than did montelukast, and the study by Malmstrom et al.[25] showed that BDP had a greater effect on daytime symptom scores and FEV_1 improvement than did montelukast. In contrast, the available data in children suggest that both BDP and montelukast may have similar effects on lung function.[14,26] In addition, a recently published systematic review, which compared ICSs and LTRAs as single agents for the treatment of asthma using data from 13 trials, found that ICSs (doses equivalent to 400 μg/day BDP) were more clinically effective than LTRAs in adults, but data were lacking to make any justifiable conclusions in children.[29]

3.2.2 Patient Preferences

Of the two studies assessing patient or parent preferences, satisfaction, and resource utilisation with treatment; one was in children (6–11-year-olds),[27] and the other was in adolescents (12–17-year olds).[28]

The study in children[27,30] was an open-label extension study, which assessed the safety of, satisfaction with, and adherence to montelukast 5mg orally once daily ($n = 83$) or BDP 100μg inhaled twice daily ($n = 41$) for 6 months. Satisfaction was assessed using validated questionnaires concerning symptom relief, ease of use, lifestyle interference, and overall satisfaction; each response was scored on a 4–6-point scale with a high score signifying high satisfaction. Asthma-related resource utilisation was also reported and is described in section 4.1 of this review. The children recruited had FEV_1 values between 60% and 85% of the predicted value, and improvement of at least

12% in FEV_1 after use of a β-agonist. Of the children recruited, 94% and 93% completed the study extension in the montelukast and BDP treatment groups, respectively. At the end of the 6-month study extension, the mean increase from baseline in percentage predicted FEV_1 was 11.8% ($p < 0.001$) in both treatment groups. Children (and their parents) in the montelukast group had a higher mean satisfaction score than those in the BDP group. Furthermore, almost twice as many children in the montelukast group than in the BDP group (82% and 45%, respectively) were compliant to treatment (i.e. fully compliant for more than 95% of days). The two study groups were similar with respect to overall safety and change in FEV_1.

The study in adolescent patients with asthma[28] was an open-label, randomized, crossover trial that assessed patient preference for BDP 100 or 200μg twice daily or zafirlukast 20mg twice daily, after 4 weeks of treatment. The study recruited 132 patients with an FEV_1 at least 75% of that predicted, who were being treated with short-acting β_2-agonists and low-dose ICS (fluticasone propionate up to 125μg, budesonide 200μg, or BDP up to 200μg). All patients completed a questionnaire on preference and ease of use. The questions included whether the patients preferred the tablet or inhaler, which was easier to use, and how easy the treatment was to use (ranging from very easy to very difficult). Of these patients, significantly more preferred zafirlukast than preferred BDP (70% compared with 27%, respectively). Furthermore, significantly more patients treated with zafirlukast found the treatment very easy to use compared with BDP (65% compared with 30%, respectively). Clinical assessments showed no relevant changes in PEF or FEV_1 during either treatment period.

In summary, children or their parents had a greater satisfaction with montelukast than with BDP. Similarly, more adolescents preferred montelukast than BDP. However, the majority of these results have to be interpreted with caution because of their open-label design, which has some major limitations such as the potential of bias attributed to the patients' knowledge of their treatment regimen.

3.3 Inhaled Corticosteroid–Leukotriene Receptor Antagonist Switching Studies

Three studies were found that assessed the effects of switching from one treatment to another. Two were randomized, double-blind, double-dummy studies that compared the effects of switching from ICS therapy (other than fluticasone propionate) to fluticasone propionate 100μg inhaled twice daily ($n = 445$) or zafirlukast 20mg orally twice daily ($n = 432$) for 6 weeks, in patients with stable asthma aged at least 12 years and with an FEV_1 between 60% and 85% of that predicted.[23,31] In these patients, switching to fluticasone propionate resulted in significantly greater improvements in lung function measures than did switching to zafirlukast (table IV). The greater improvements in pulmonary function with fluticasone propionate were apparent within 1 week (at first treatment assessment) and were maintained throughout the duration of the study.[23] Furthermore, switching to inhaled fluticasone propionate was more effective in maintaining or improving symptom control than was switching to zafirlukast. Fewer fluticasone propionate-treated patients experienced exacerbations of their asthma than those treated with zafirlukast: 1% compared with 6% in one study,[31] and 2% compared with 6% in the other.[23] The percentage of patients who withdrew because of lack of efficacy was lower in the fluticasone propionate group than in the zafirlukast group (2% compared with 13%, respectively), in the one study that reported this parameter.[31]

The third study in this group consisted of two study periods: a randomized, double-blind, double-dummy period with fluticasone propionate or zafirlukast (reported in section 3.1) followed by an open-label period in which patients initially assigned to receive zafirlukast ($n = 150$) were switched to fluticasone propionate for 4 weeks while the others continued with their fluticasone propionate ($n = 144$).[20] Those patients who switched to fluticasone propionate during the open-label period experienced additional improvements in lung function (e.g. morning and evening PEF improved by 17.2 L/min and 13.6 L/min,

Table IV. Summary of efficacy outcomes in two studies comparing the effect of switching treatment from inhaled corticosteroid (other than fluticasone propionate [FP]) to FP 100μg twice daily or zafirlukast (Zaf.) 20 mg twice daily for 6 weeks. Data are presented as mean changes (FP vs leukotriene receptor antagonists) from baseline at endpoint[a]

Studies	Patients given FP/Zaf. (n)	FEV_1 (L)	Morning PEF (L/min)	Evening PEF (L/min)	Salbutamol use (puffs/day)	Symptom-free days (%)	Rescue-free days (%)	Nights with no awakening (%)
Brabson et al.[31]	224/216	0.24 vs 0.08†	30.0 vs 6.0†	22.0 vs 5.0†	−0.58 vs 0.1†	22.0 vs 8.0†	23.0 vs 10.0‡	<1% vs −5%**
Kim et al.[23]	221/216	0.22 vs 0.03†	17.8 vs 3.1‡	16.7 vs 2.6‡	−0.66 vs 0.27†	16.2 vs 7.1**	23.4 vs 9.3†	−1.0 vs −9.0†

a Defined as patient's last assessment.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow.

** $p < 0.01$; † $p < 0.001$; ‡ $p < 0.005$.

respectively) and other measures of asthma control (e.g. reduction in symptom score and supplementary use of salbutamol), whereas those who continued with fluticasone propionate showed little additional improvement.

In all three studies, switching to fluticasone propionate or zafirlukast was well tolerated. In two studies, fewer patients who switched to zafirlukast had adverse events potentially related to treatment compared with those who switched to fluticasone propionate (4% and 7%, respectively, in one study,[31] and 7% compared with 14%, respectively, in the other).[23] In the third study, adverse events potentially related to treatment occurred in 5% of patients switched from zafirlukast to fluticasone propionate and 4% of patients who continued with fluticasone propionate during the open-label period.[20] Withdrawal because of adverse events potentially related to treatment were rare and occurred in fewer than 2% of patients in both groups.[20,23,31]

Health-related quality of life was measured using the AQLQ in the study by Kim et al.[23] In the patients who switched to fluticasone propionate treatment, clinically meaningful improvements from baseline at endpoint (⩾0.5 points) were reported in both the global AQLQ score and the individual domain scores (activity limitation, asthma symptoms, emotional function, and environmental domains). In contrast, those switching to zafirlukast did not experience clinically meaningful improvements in global score or any of the individual domain scores. Furthermore, clinically meaningful differences were observed at endpoint between fluticasone propionate and zafirlukast for the global score and for each domain score except for activity limitation; these differences were also statistically significant.

In summary, these results suggest that initial maintenance treatment with fluticasone propionate is more effective than treatment with LTRAs in improving or maintaining control of asthma in patients who switch from low-dose ICSs to fluticasone propionate or LTRAs. Moreover, switching from an LTRA to fluticasone propionate resulted in improved lung function and asthma control.

3.4 Salmeterol–Fluticasone Propionate Combination Compared with Leukotriene Receptor Antagonists

As previously stated, in patients in whom asthma is not adequately controlled by short-acting β_2-agonists alone, current guidelines recommend the initiation of maintenance therapy appropriate to disease severity.[2] As asthma manifests itself principally as a two-component disease, monotherapy with either ICSs or LTRAs may fail to treat it adequately. Therefore, a more effective strategy may be to use a combination of treatments that address both the inflammatory and smooth muscle dysfunction components of the disease.

The clinical efficacy of salmeterol–fluticasone propionate (SFC) 50/100μg inhaled twice daily (n = 429) as initial maintenance therapy has been compared with that of montelukast 10mg orally once daily (n = 429) in two randomized, double-blind, double-dummy, parallel-group trials of 12 weeks duration.[32,33] Patients in these studies were aged at least 15 years, had symptomatic asthma despite treatment with short-acting β_2-agonists, and had an FEV_1 between 50% and 80% of that predicted.

Compared with montelukast treatment, treatment with SFC resulted in significantly greater improvements from baseline in lung function measures (table V). The greater improvements in pulmonary function with SFC were apparent at first treatment assessment (on the first day of treatment for PEF assessments, and at 1 week for FEV_1 assessments) after the start of treatment, and were maintained throughout the study. An example of the greater improvement in lung function with SFC treatment compared with montelukast is shown in figure 6.[33] Consistent with these results, significantly greater decreases from baseline in asthma symptom scores, the frequency of as-needed β_2-agonist usage and night-time awakenings caused by asthma were observed at endpoint with SFC treatment, as compared with montelukast treatment. In both studies, the proportion of symptom-free days and rescue-free days increased significantly from baseline with SFC treatment compared with montelukast treatment at endpoint.

Table V. Summary of efficacy outcomes in two studies comparing salmeterol–fluticasone propionate combination (SFC) with montelukast (Mon.) as initial maintenance therapy. Data are presented as mean changes (SFC vs Mon.) from baseline at endpoint[a]

Studies	Patients given SFC/Mon. (n)	FEV_1 (L)	Morning PEF (L/min)	Evening PEF (L/min)	Salbutamol use (puffs/day)	Symptom-free days (%)	Rescue-free days (%)	Nights with no awakening (%)
SFC 50/100μg inhaled twice daily vs Mon. 10mg orally once daily for 12 weeks								
Pearlman et al.[32]	213/213	0.61 vs 0.32**	81.4 vs 41.9**	64.6 vs 38.8**	−3.6 vs −2.2**	40.3 vs 27.0**	53.4 vs 26.7**	29.8 vs 19.6*
Calhoun et al.[33]	213/213	0.54 vs 0.27**	89.9 vs 34.2**	69.9 vs 31.1**	−3.3 vs −1.9**	48.9 vs 21.7**	53.0 vs 26.2**	
							23.0 vs 15.5**	

a Defined as patient's last assessment.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow.

*$p < 0.05$; **$p < 0.001$.

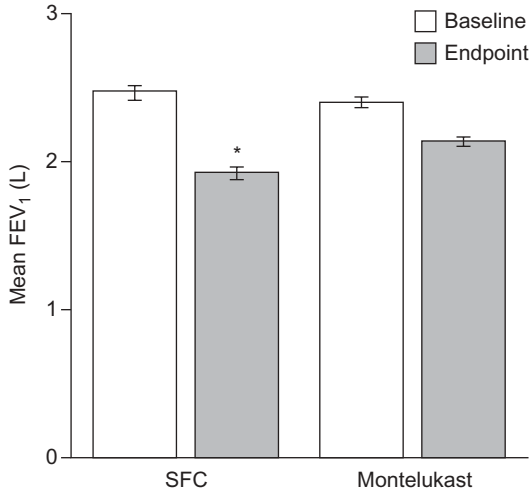

Fig. 6. Mean change from baseline in forced expiratory flow in 1 second (FEV_1) after 12 weeks of treatment with either salmeterol–fluticasone propionate combination (SFC) 50/100μg inhaled twice daily (n = 213) or montelukast 10mg orally once daily (n = 213). *$p < 0.001$, SFC compared with montelukast.[33]

In both studies, the incidences of adverse events were similar between the two groups. However, fewer patients treated with the SFC had an exacerbation (defined as any requirement for additional medication other than those permitted by the protocol) compared with patients treated with montelukast: 3% and 6%, respectively, in one study ($p = 0.109$),[32] and 0% compared with 5%, respectively, in the other study ($p < 0.001$).[33] Furthermore, fewer patients treated with SFC withdrew from the two studies because of adverse events potentially related to study medication, compared with those treated with montelukast: <1% and 2%, respectively, in one study,[32] and 2% compared with 3%, respectively, in the other study.[33]

One of the studies reported an assessment of quality of life.[32] Although both treatments produced clinically meaningful improvements at endpoint in AQLQ scores compared with baseline, treatment with SFC resulted in significantly greater improvements in the global AQLQ score and all the individual domain scores, compared with treatment with montelukast. Furthermore, the differences in global scores, in addition to the difference in asthma symptoms and emotional function scores between SFC and montelukast were clinically meaningful (i.e. ≥0.5 points) (figure 7).

In both studies, significantly more patients treated with SFC were satisfied with their medication compared with montelukast.[32,33] Likewise, compared with montelukast, more patients treated with SFC were satisfied with how well their medication worked. The aggregate results of the two studies reviewed demonstrate that treatment with SFC was superior to treatment with the recommended dosage of montelukast as initial maintenance therapy in patients with asthma.

In a pooled analysis of four studies,[34] initial maintenance therapy with SFC 50/100μg inhaled twice daily (n = 427) was superior to that achieved with either fluticasone propionate 100μg inhaled twice daily (n = 529) or montelukast 10mg once daily (n = 954). Improvements in FEV_1 and mean morning PEF from baseline to endpoint were significantly greater in the SFC group than in the fluticasone propionate group ($p \leq 0.03$) or the montelukast group ($p < 0.001$). The frequency of salbutamol use with SFC decreased from baseline to endpoint by 3.5 puffs/day, compared with a change of 3.1 puffs/day with fluticasone propionate ($p \leq 0.03$ compared with SFC), and one of 2.1 puffs/day with montelukast ($p < 0.001$ compared with SFC). The proportion of rescue-free days in the SFC group increased by 55%, compared with a change of 43% with fluticasone propionate ($p \leq 0.03$ compared with SFC), and one of 29% with montelukast ($p < 0.001$ compared with SFC). These data suggest that SFC, which treats both the inflammatory and smooth muscle dysfunction components of asthma, is more effective as initial maintenance therapy than either fluticasone propionate or montelukast alone.

4. Pharmacoeconomic Analyses

4.1 Cost-Effectiveness Analyses

Four studies were found that assessed the cost-effectiveness of fluticasone propionate and SFC

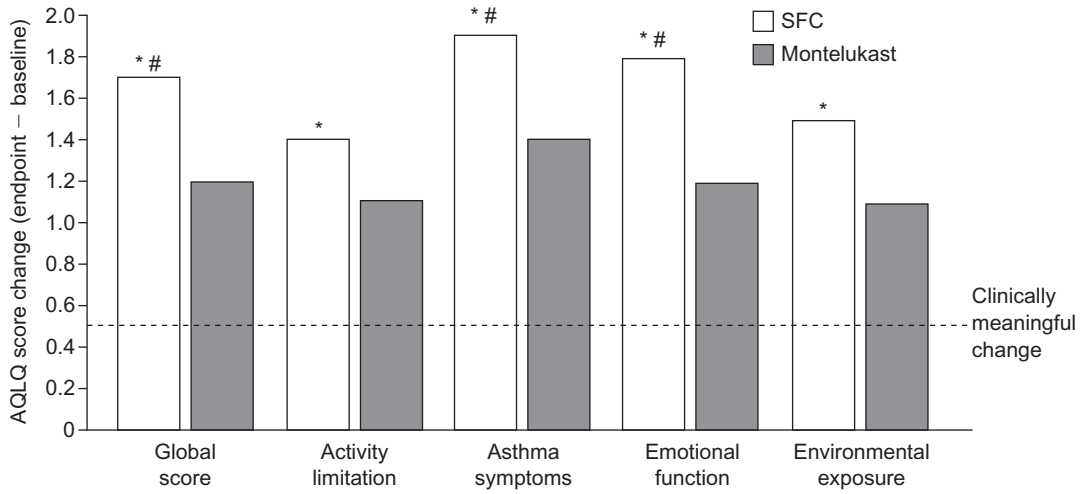

Fig. 7. Change in Asthma Quality of Life Questionnaire (AQLQ) scores from baseline to study endpoint in patients treated with either salmeterol–fluticasone propionate combination (SFC) 50/100μg inhaled twice daily (n = 213) or montelukast 10mg orally once daily (n = 213). Horizontal line at 0.5 indicates clinically meaningful differences. *$p \leq 0.001$, SFC compared with montelukast at endpoint (i.e. patient's last assessment); #clinically meaningful difference between treatment groups. (Reproduced with permission from Pearlman DS, White MV, Lieberman AK, et al. Fluticasone propionate/salmeterol combination compared with montelukast for the treatment of persistent asthma. Ann Allergy Asthma Immunol 2002; 88 (Pt 2): 227-35.[32] © 2002 American College of Allergy, Asthma & Immunology.)

with LTRAs from the perspective of a third-party payer. The first two studies assessed the cost-effectiveness of fluticasone propionate 100μg inhaled twice daily (n = 342) with that of zafirlukast 20mg orally twice daily (n = 327) as initial maintenance therapy in adults and adolescents.[35,36] The endpoints used for comparing treatment effectiveness were: the proportion of patients in each group achieving an increase in FEV_1 of at least 12% from baseline,[35] or achieving an improvement from baseline of more than 0.5 in the AQLQ score,[36] and the proportion of symptom-free days achieved over the 12-week trial period.[35,36]

The second pair of studies compared the cost-effectiveness of SFC 50/100μg inhaled twice daily (n = 427) with montelukast 10mg orally once daily (n = 428) as initial maintenance treatment in adults and adolescents with asthma.[37,38] The endpoints used for comparing treatment effectiveness were the proportion of patients in each group achieving an increase in FEV_1 of at least 12% from baseline and the proportion of symptom-free days achieved over 12 weeks of treatment.

In the two comparisons of fluticasone propionate and zafirlukast, the former was found to be the more cost-effective treatment on the basis of analysis using direct costs (table VI).[35,36] Results from the study by Menendez et al.[35] indicated that fluticasone propionate achieved a symptom-free day at approximately one-third the cost compared with zafirlukast and an improvement in FEV_1 of at least 12% from baseline at approximately half the cost. The authors showed these results to be robust as, even using the lowest cost for an asthma-related admission to hospital, the cost of zafirlukast would need to have been discounted by 50% for the incremental ratios to equal zero for improvements in both lung function and proportion of symptom-free days. Similarly, in a preliminary report by Carranza-Rosenzweig et al.,[36] fluticasone propionate was found to achieve a symptom-free day at

about half the cost and a score of more than 0.5 for improvement in quality of life at about three-quarters of the cost compared with zafirlukast. Similar results were obtained on the basis of both direct and indirect costs (such as lost wages and benefits associated with missed work days and school days). These cost-effectiveness ratios were in favour of fluticasone propionate for both effectiveness parameters, even after rigorous sensitivity analyses were performed.

In the two comparisons of SFC and montelukast, SFC was more cost-effective than montelukast (table VI); SFC achieved a greater than 12% improvement in FEV_1 from baseline at 61–65% of the cost compared with montelukast.[37,38] SFC was also more cost-effective than montelukast when symptom-free day was the outcome measure, and achieved a symptom-free day at 51–61% of the cost for montelukast, based on direct costs. Additional benefits were achieved with SFC at minimal extra cost: the incremental costs of achieving a symptom-free day with SFC compared with montelukast were US$1.69 in the first study,[37] and US$0.73 in the second study;[38] the corresponding costs for one additional patient to achieve at least 12% improvement in FEV_1 were US$1.33 and US$0.46, respectively.

The four cost-effectiveness studies reviewed suggest that fluticasone propionate and SFC were more cost-effective than LTRAs from a third-party payer perspective. In addition, fluticasone propionate was also more cost-effective than LTRAs in the study that considered indirect costs such as lost wages and benefits associated with missed work days and school days.

Asthma-related utilization of medical resources, school absenteeism and parental work loss with BDP 100μg inhaled twice daily (n = 41) or montelukast 5mg orally once daily (n = 83) treatment were also assessed in the 6-month open-label study extension in children by Maspero et al.[27] Resource utilization was similar between treatment groups; for example, 23% and 24% of patients receiving montelukast and BDP, respectively, had at least one asthma-related emergency event. Furthermore, there was no significant difference between the treatment groups in the number of visits or phone calls to the doctor, visits to the hospital emergency room, hospital admissions, school absenteeism, or parents losing work time.

4.2 Real-World Economic Analyses

In order for a new treatment to become widely accepted, the results obtained under well-controlled clinical trials must be supported by those obtained in a real-world setting. In addition to therapeutic efficacy, the costs associated with asthma must be considered.

Four retrospective analyses of medical and pharmacy claims for patients with asthma were identified. A fifth study was found that assessed resource utilization only. The first four studies quantified resource use and direct medical costs before and after initiating treatment with either inhaled fluticasone propionate (n = 1 923) or an LTRA (n = 1 488) in the USA.[38-41] Resource use was assessed for either 6 or 9 months before the index event (i.e. the first prescription of fluticasone propionate or LTRA), and 9 or 12 months after it. A summary of the results of these studies is shown in table VII.

In three studies, the introduction of fluticasone propionate was associated with decreases ranging from 44% to 71% in the rates of admission to hospital and decreases ranging from 9% to 58% in the number of emergency room visits, compared with the pre-index period.[39-41] However, changes in resource use after the introduction of an LTRA were much less consistent in direction: the post-index changes ranged from −26% to +77% for rates of admission to hospital, and from −32% to +57% for emergency room visits. Two of the four studies showed that fluticasone propionate was associated with reductions in asthma-related costs of 17% and 22%,[40,41] but these costs increased by 29% and 122% in the other two studies.[39,42] All four studies showed that the introduction of an LTRA was associated with an increase in asthma-related costs, ranging from 21% to 239% (table VII).

The fifth study also used medical and pharmacy

Table VI. Cost-effectiveness comparisons[a] of treatment with inhaled fluticasone propionate (FP) or salmeterol–fluticasone propionate combination (SFC) with leukotriene receptor antagonists (LTRAs) in adults and adolescents with asthma. The analyses were based on effectiveness outcomes and direct costs prospectively collected from randomized, double-blind, double-dummy, 12-week trials

Studies	Patients FP or SFC/LTRA (n)	Successful treatment (% of patients)[b]	Symptom-free days (%)	Cost-effectiveness ratio (US$/day)	
				Per successfully treated patient[b]	Per symptom-free day
FP 100μg inhaled twice daily vs zafirlukast 20mg orally twice daily					
Menendez et al.[35]d	231/220	53 vs 37**	33.4 vs 19.3**	3.47 vs 7.81	5.51 vs 14.98
Carranza-Rosenzweig et al.[36]d	111/107	NR	NR	1.90 vs 2.61 (2.54 vs 3.06)[c]	6.62 vs 12.08 (8.86 vs 14.15)[c]
SFC 50/100μg inhaled twice daily vs montelukast 10mg orally once daily					
Sheth et al.[37]e	211/212	71 vs 39**	46.8 vs 21.5**	5.03 vs 8.25	7.63 vs 14.89
Stanford et al.[38]e	216/216	74 vs 46*	43.7 vs 25.9*	4.74 vs 7.35	8.03 vs $13.05

a Costs included: study drugs, emergency room visits, unscheduled physician's visits related to asthma exacerbations, treatment costs for drug-related adverse events, and use of rescue medication.

b Defined as an increase of at least 12% in FEV_1 (over the study period), except for the study by Carranza-Rosenzweig et al.,[36] in which successful treatment was defined as an improvement in quality of life score of more than 0.5 from baseline.

c Includes direct and indirect cost such as lost wages and benefits associated with missed work days and school days.

d USA 1999.

e USA 2002.

NR = not reported.

*$p < 0.05$; **$p < 0.001$.

claims data in the USA to assess resource utilization associated with switching asthma treatment. In this retrospective study, Stempel et al.[43] compared asthma-related admissions to hospital over a 2-year period between a cohort of patients who switched from an ICS in year 1 to an LTRA in year 2 ($n = 285$) and a matched cohort continuously treated with ICS ($n = 570$). During the first year (i.e. when all patients were receiving an ICS), the proportion of patients who had at least one or more asthma-related admission to hospital were similar between the LTRA cohort (1.1%) and the matched cohort (1.4%). During the second year, 2.5% of patients who switched to an LTRA had an asthma-related admission to hospital compared with the cohort continuously receiving ICSs (0.6%). Patients who switched to an LTRA were seven ($p < 0.05$) times more likely to have an asthma-related admission to hospital compared with those who continued to receive an ICS.

These real-world studies obtained from a broad population, with less strict inclusion criteria, including real-world confounders of compliance (such as improper use of medication and lack of adherence to regimen), nonetheless support the superiority of ICSs over LTRAs observed in clinical trials. Furthermore, these data are consistent with LTRAs being associated with a deterioration in control of asthma relative to ICSs in clinical practice.

5. Conclusion

As initial maintenance treatment, fluticasone propionate provides greater improvements in pulmonary function and overall control of asthma than an LTRA, as measured by FEV_1, PEF, use of rescue medication, number of exacerbations, and the number of symptom-free days and nights. In concert with these benefits, patients treated

Table VII. Summary of four retrospective analyses of changes in healthcare utilization and costs after commencement of treatment with inhaled fluticasone propionate (FP) or a leukotriene receptor antagonist (LTRA) in patients with asthma. Data were collected from pharmacy and medical claims. Data are presented as mean percentage change compared with pre-index period (FP vs LTRA)

Studies	Patients given FP/LTRA (n)	Durations of pre- and post-index period (months)	Outcome (mean % change in post-index period compared with pre-index period)			
			Admissions to hospital	Emergency room visits	Asthma-related costs[a]	Total healthcare costs[b]
FP compared with zafirlukast						
Stempel et al.[40]	725/309	9 and 12	−71 vs 0	−56 vs −11	−17 vs +28	−9 vs +20
Brondum et al.[41]	857/392	9 and 12	−64 vs −26	−58 vs −32	−22 vs +21	NR[c]
FP compared with montelukast and zafirlukast						
Pathak et al.[39][d]	284/302/195	9 and 9	−44 vs +77 and +8[f]	−9 vs +30 and +57[f]	+29 vs +154 and +69	NR
FP compared with LTRAs[e]						
Armstrong et al.[42]	57/290	6 and 12	NR	NR	+122 vs +239[g]	NR

a Includes pharmacy and medical costs.

b Includes asthma-related and non-asthma-related pharmacy and medical costs.

c Although the percentage change from the pre-index period was not reported, treatment with FP resulted in a decline of US$324 in total annual healthcare costs, compared with an increase of US$888 for zafirlukast.

d All charges were significantly lower for FP compared with montelukast or zafirlukast ($p < 0.0001$).

e LTRAs included were montelukast, zafirlukast and zileutron.

f Represents percentage of patients with at least one admission to hospital or emergency room visit.

g Adjusted costs.

NR = not reported.

with fluticasone propionate had clinically significant improvements in health-related quality of life compared with those given LTRA treatment, which produced only modest improvements. Furthermore, there is evidence to suggest that switching therapy from an ICS to an LTRA may result in a deterioration of asthma control. Treatment with fluticasone propionate was associated with significantly lower healthcare costs and less use of healthcare resources than was LTRAs. Both treatments were well tolerated, and the incidence of adverse events was similar with both treatments. Studies with other ICSs have shown only modest improvements in pulmonary function and overall symptom control compared with the outcome with LTRAs.

Asthma guidelines recommend treatment that is appropriate to the severity of the disease.[2] In this respect, combination therapy (ICS and LABA) may also be considered as initial maintenance therapy for some patients. The studies reviewed demonstrate that SFC as initial maintenance therapy provides superior improvements in pulmonary function, overall control of asthma and health outcomes than either fluticasone propionate or montelukast alone.

Therefore, combination treatment with an inhaled steroid plus a long-acting β-agonist is not only considered as the preferred treatment choice for initial maintenance therapy of patients who present with moderate persistent asthma, but may likewise be a logical extension in milder persistent asthma, in which the disease entity manifests with apparent smooth muscle abnormalities in conjunction with the underpinning of airway inflammation.

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