A proof of concept study to evaluate putative benefits of montelukast in moderate persistent asthmatics

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Aims Whether chronic dosing with montelukast confers benefit in patients with moderate to severe asthma remains to be fully established. A proof of concept study was performed evaluating putative benefits with montelukast in moderate persistent asthmatics who were taken off inhaled corticosteroids (ICS) and switched to salmeterol. The latter was done to dissociate the effects of montelukast from ICS.

Methods Twenty moderate to severe persistent asthmatics completed a randomized double-blind crossover study. Subjects received montelukast 10 mg daily or placebo for 2 weeks each. This was preceded by a 2-week run-in when ICS were discontinued and salmeterol started, and used on a regular basis throughout the study. Measurements were made after run-in and after both randomized treatments.

Results There were no significant sequence effects for responses as to whether placebo or montelukast were given first or second. Methacholine PD_{20} values after run-in, first and second placebo were 63 μ g, 60 μ g and 64 μ g, respectively (corresponding to 2, 4 and 6 weeks of ICS washout, respectively). Lung function deteriorated pre *vs* post run-in, which was significant ($P < 0.05$) for FEF_{25-75} % predicted. Montelukast conferred significant ($P < 0.05$) improvements as change from post run-in compared with placebo in methacholine PD_{20} , FEV_1 % predicted, FEF_{25-75} % predicted, diurnal peak expiratory flow, symptoms and salbutamol use. For the primary outcome of methacholine PD_{20} , this amounted to a 1.6-fold difference (95% CI 1.1, 2.5).

Conclusions In moderate persistent asthmatics switched from taking ICS to salmeterol alone, adding montelukast conferred significant benefits on all parameters of asthma control. Further studies are indicated to evaluate whether montelukast exhibits additive effects to ICS/long-acting β_2 -adrenoceptor agonist combination inhalers upon clinically important outcomes.

Keywords: asthma therapy, bronchial hyper-responsiveness, leukotriene receptor antagonist, long-acting β_2 -adrenoceptor agonist

Introduction

Inflammation of the bronchial mucosa and bronchial hyper-responsiveness are the hallmark features of asthma of all severities. Inhaled corticosteroids (ICS) are therefore advocated as first-line preventative therapy in

national and international guidelines [1, 2]. Despite their widespread use however, asthma remains a worldwide chronic disabling problem and additional therapeutic options are vital in disease management.

Cysteinyl leukotrienes are mediators of smooth muscle spasm in the airway and possess pro-inflammatory properties. Montelukast, a leukotriene receptor antagonist (LTRA), has both anti-inflammatory and bronchodilatory properties [3], which suggests this class of drug to be a useful additional therapeutic adjunct in the management of persistent asthma. Studies using LTRAs have demonstrated additional clinical benefit in patients incompletely controlled on ICS [4–7], while a meta-analysis has shown a reduction in exacerbations with use

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of LTRAs [8]. Head-to-head comparisons of ICS and LTRAs however, tend to favour the former in terms of most endpoints [4–9].

A previous study has shown that in persistent asthmatics suboptimally controlled on ICS, single doses of both montelukast and a long-acting β_2 -adrenoceptor agonist salmeterol, provided additive effects on both bronchoprotection and bronchodilation [10]. The purpose of the present study was to determine whether chronic dosing with montelukast confers benefit in patients switched from ICS to long-acting β_2 -adrenoceptor agonists. Our rationale for switching from ICS to regular salmeterol was to try and completely dissociate the effects of montelukast from ICS.

Methods

Design

The study was of a double-blind placebo controlled crossover design (Figure 1). Patients attended an initial screening visit to determine suitability and were asked to stop their usual asthma therapy for the duration of the study. For patients taking $>1000 \mu\text{g day}^{-1}$ of beclomethasone (or equivalent fluticasone dose) the dose was first halved for 1 week before stopping their ICS completely; after this tapering phase, such patients then entered the 2-week run-in period.

Eligible subjects (i.e. off all ICS therapy) entered an initial 2-week run-in period during which they used a salmeterol dry powder inhaler (one puff twice daily; Serevent Accuhaler $50 \mu\text{g}$ per actuation; GlaxoSmithKline, Uxbridge, UK) for the duration of the study. Patients were also issued with a salbutamol dry powder inhaler (Ventolin Accuhaler $200 \mu\text{g}$ per actuation, GlaxoSmithKline, Uxbridge, UK) for use as required. Following the run-in, patients were randomized to receive an evening dose (22.00 h) of montelukast 10 mg or identical placebo for 2 weeks each.

Patients

Moderate persistent asthmatics with a provocative dose of methacholine causing a 20% fall (PD_{20}) in forced expiratory volume in 1 s (FEV_1) $< 500 \mu\text{g}$ were enrolled. Within a 3-month period before the screening visit, all patients were maintained on a constant dose of ICS of at least $400 \mu\text{g day}^{-1}$ of beclomethasone equivalent with or without second line nonsteroidal controller therapy, had no history of respiratory tract infection and no oral corticosteroid use. Baseline patient demographics (pre run-in) are shown in Table 1. At the end of the run in, eligible patients required to have an $FEV_1 > 60\%$ predicted and $PD_{20} < 500 \mu\text{g}$. All subjects gave written con-

Figure 1 Study flow diagram.

sent and the Tayside committee on medical research ethics gave approval for the study.

Measurements

Following the initial run-in and after each randomized treatment period (i.e. on 3 mornings within a 2-h window), patients attended the laboratory for spirometry and a methacholine bronchial challenge. Patients withheld their salmeterol on the morning of their visit and short acting β_2 -adrenoceptor agonist 6 h prior to attendance, and took their last dose of montelukast or placebo 12 h previously. A peak flow diary card was completed twice daily throughout the study to record diurnal peak expiratory flow (PEF), symptom score (0–3 scale) and salbutamol use. In terms of domiciliary data, values recorded during the last 5 days of the randomized treatment periods were used to calculate mean values.

Spirometry was performed according to American Thoracic Society criteria [11] using a Morgan Spiroflow bellows spirometer (PK Morgan Ltd, UK) that was calibrated daily. The methacholine bronchial challenges were performed using a standardized computer assisted dosimetric method as previously described [12]. In brief, methacholine was administered in doubling cumulative doses from 3.125 to $3200 \mu\text{g}$ given at 5-min intervals until a 20% fall in FEV_1 was recorded. The PD_{20} was determined by logarithmic interpolation of the log dose–response curve. For safety reasons bronchial challenges were only performed if FEV_1 was $> 60\%$ predicted.

Statistical analysis

The study was powered at 80% to show a between treatment difference of two fold (i.e. one doubling dose)

Table 1 Demographic data pre run-in.

Gender	Age (years)	FEV ₁ %predicted	FEF ₂₅₋₇₅ %predicted	ICS	ICS daily dose	Other asthma treatment
F	40	92	59	BDP	1000	None
F	65	69	42	BDP	800	None
F	25	92	63	BDP	400	Montelukast
M	54	84	68	BDP	800	None
F	46	104	77	BDP	800	None
M	36	85	54	FP	400	Salmeterol
M	25	71	39	BDP	800	None
F	17	95	85	BDP	800	None
M	43	61	32	FP	1000	None
M	26	98	72	BDP	400	None
F	47	68	25	BDP	500	Salmeterol
F	65	86	44	BDP	1200	None
M	45	58	28	BDP	400	None
M	35	60	28	BDP	600	None
M	58	73	45	BUD	800	None
F	42	93	72	BUD	400	None
M	22	74	41	BDP	400	None
F	32	82	56	BDP	400	None
F	45	104	72	FP	1000	None
F	44	73	46	BUD	800	None
9 M, 11 F	41	81	52		685	
	(3)	(3)	(4)		(58)	

ICS, inhaled corticosteroid; BDP, beclomethasone dipropionate; FP, fluticasone propionate; BUD, budesonide. Summary statistics are shown as mean (SE).

in methacholine PD₂₀ (the primary endpoint) with a sample size of 16 completed patients. Analysis of variance was performed followed by multiple-range testing with Bonferroni correction set at 95% confidence intervals (two tailed, $P < 0.05$). The methacholine PD₂₀ was logarithmically transformed prior to analysis to normalize its distribution. Data for PD₂₀ were expressed as geometric mean fold differences (i.e. the antilog of the PD₂₀ log₁₀ difference). The doubling dose difference was calculated by dividing the PD₂₀ log₁₀ difference by log₁₀ 2. Comparisons for the multiple range testing are denoted as being significant at $P < 0.05$ in order not to confound the overall alpha error. The sequence effect was evaluated by comparing responses for montelukast or placebo given first or second in order. All data were analysed using a 'Statgraphics' software package (STSC Software Publishing Group, Rockville, MD, USA).

Results

Thirty-seven patients were screened and 20 completed the study (Table 1). During the initial ICS free run-in, 15 subjects were withdrawn and two were withdrawn after randomization (Figure 2). After randomized placebo

Table 2 Values for methacholine PD₂₀ and FEV₁ according to whether given first or second in sequence.

	Montelukast first vs montelukast second		Placebo first vs placebo second	
Methacholine PD ₂₀ (µg)	135 (68)	72 (23)	60 (16)	64 (50)
FEV ₁ (% predicted)	75 (7)	80 (4)	74 (4)	66 (7)

Values are shown as means (SE) while for methacholine PD₂₀ values are geometric means (geometric SE). There were no significant differences when comparing first vs second sequence values for either montelukast or placebo.

treatment, four patients did not have a methacholine challenge test since their FEV₁ fell below 60% of predicted, while one patient did not have a challenge after randomized montelukast treatment for the same reason. For all other variables data were complete for $n = 20$ patients.

There were no significant differences according to whether montelukast or placebo were given first or second in sequence for the primary outcome of methacholine PD₂₀ or secondary outcome of FEV₁ (Table 2). The

Figure 2 Drop out flow diagram.

differences between values for montelukast when given as first or second sequence for methacholine PD_{20} and FEV_1 were 1.9 fold (95% CI 0.6, 6.0) and 5% predicted (95% CI -11, 20), respectively. Corresponding differences for placebo were 1.1 fold (95% CI 0.3, 3.7) and 8% predicted (95% CI -8, 23), respectively.

Spirometry was measured pre and post run-in, while PD_{20} was only measured at post run-in. Spirometry values fell comparing pre *vs* post run-in for FEV_1 % predicted and FEF_{25-75} % predicted, which was significant for the latter ($P < 0.05$). Subsequently, absolute FEV_1 % predicted and FEF_{25-75} % predicted fell significantly ($P < 0.05$) with placebo *vs* pre run-in values, and then improved significantly ($P < 0.05$) with montelukast *vs* placebo (Table 3, Figure 3). While there was a significant ($P < 0.05$) improvement in PD_{20} for montelukast *vs* post run-in value, there was no significant difference in FEV_1 for the same comparison (Table 3).

Randomized montelukast treatment led to significant ($P < 0.05$) improvements in methacholine PD_{20} , FEV_1 % predicted, FEF_{25-75} % predicted, diurnal PEF, symptom scores and salbutamol rescue compared with placebo values (Table 3). The individual data for methacholine PD_{20} fold shift from baseline are illustrated in Figure 4.

Discussion

LTRAs possess both anti-inflammatory and bronchodilator properties. However, whether these beneficial effects are evident in patients using long-acting β_2 -adrenoceptor agonists remains to be fully established. This study has shown that treatment with montelukast conferred additive effects in moderate persistent asthmatics who had been switched from ICS to salmeterol. Our data dem-

onstrated significant improvements in terms of the primary outcome variable, i.e. methacholine bronchial hyper-responsiveness, plus improvements in spirometry and diurnal asthma control. We acknowledge that montelukast should not be used in combination with salmeterol in patients who are not taking concomitant ICS according to current guidelines [1, 2]. However, we felt that it was important to discontinue ICS to fully evaluate the effects of montelukast, with salmeterol being given to try to prevent exacerbation in such a group of patients.

We included an initial 2-week ICS washout period prior to randomization. In this respect it is important to state that there were no differences in PD_{20} or FEV_1 values for placebo given first or second in sequence. Thus, there were no carryover effects comparing 2, 4 and 6 weeks of ICS washout (corresponding methacholine PD_{20} values after run-in, first placebo and second placebo were 63 μ g, 60 μ g and 64 μ g, respectively).

We elected to use bronchial hyper-responsiveness as our primary endpoint, as this surrogate marker of inflammation is a fundamental component of the asthmatic disease process. We found that additive treatment with montelukast and salmeterol in patients without ICS, provided a significant ($P < 0.05$) 1.6-fold (i.e. 0.7 doubling dose shift in PD_{20}) improvement in bronchial hyper-responsiveness compared with placebo, suggesting anti-inflammatory activity. In addition to bronchoprotective effects, treatment with montelukast maintained airway calibre for FEV_1 and morning PEF when compared with placebo. When patients were treated with placebo these parameters fell by 5% predicted and 18 l min⁻¹ predicted, respectively.

LTRAs are currently indicated for use in mild persistent asthma as monotherapy or as add on to low dose

Figure 3 Values for (a) FEV₁ and (b) FEF₂₅₋₇₅ at pre run-in and following post run-in and randomized treatments. *Denotes significant ($P < 0.05$) difference from pre run-in; †denotes significant ($P < 0.05$) difference from placebo.

ICS [1, 2]. In a large randomized multicentre study [5] it was demonstrated that montelukast provided additional benefits to patients inadequately controlled on inhaled beclomethasone compared with baseline. However, this study failed to determine its effects compared with placebo. In two further studies [4, 9] in which comparisons were made with placebo, montelukast was shown to be better than placebo but less effective than beclomethasone 400 $\mu\text{g day}^{-1}$.

Figure 4 Individual data for PD₂₀ fold shift from post run-in for placebo and montelukast illustrated on a log₂ scale to depict doubling dose shifts. A fold shift < 1 denotes worsening and > 1 denotes improvement as compared with post run-in values. O and Δ denote placebo and montelukast, respectively, with solid lines showing individual change for $n = 16$ patients who underwent challenges on both randomized treatments. Geometric mean fold shifts (geometric SE) are shown.

Measures of airway calibre tend to be downstream markers whereas inflammatory surrogates including bronchial hyper-responsiveness are measures of the components of the asthmatic process, which ultimately are the driving force behind asthma disability and airway remodelling. In a study evaluating 72 moderate-to-severe asthmatics maintained on ICS and mostly taking long-acting β_2 -adrenoceptor agonists, the addition of montelukast 10 mg daily for 14 days conferred no significant improvement in terms of PEF and symptom scores [13]. However, a limitation of this study was failure to evaluate bronchial hyper-responsiveness or other surrogate anti-inflammatory markers [14]. In a further study evaluating mild-to-moderate persistent asthmatics taking fluticasone/salmeterol combination or the same dose of fluticasone alone (500 $\mu\text{g day}^{-1}$), adding montelukast conferred complementary activity on surrogate inflammatory markers, which was dissociated from effects on airway calibre [15]. Thus, monitoring lung function alone may miss potentially beneficial effects of adding in a LTRA. In terms of exacerbations, a meta-analysis showed a significant overall reduction in patients requiring systemic steroids (a 48% reduction) by adding

Table 3 Results after run-in, placebo and montelukast, and difference between randomized treatments.

	Post run-in	Placebo	Montelukast	Difference between montelukast and placebo (95% CI)
Methacholine PD ₂₀ (µg)	63 (15)	61 (16)	94 (25)*†	1.6 fold (1.1, 2.5)
FEV ₁ % predicted	76 (3)	71 (3)	78 (3)*	7 (3, 12)
FEF ₂₅₋₇₅ % predicted	42 (3)	39 (3)	47 (4)*	8 (4, 12)
Morning PEF (l min ⁻¹)	437 (22)	419 (22)†	436 (21)*	17 (6, 28)
Evening PEF (l min ⁻¹)	442 (23)	426 (22)†	443 (22)*	17 (8, 26)
Daytime reliever use (puffs)	1.4 (0.4)	1.8 (0.4)	1.0 (0.4)*	0.8 (0.1, 1.4)
Night time reliever use (puffs)	1.0 (0.6)	1.6 (0.4)	0.6 (0.2)*	0.9 (0.1, 1.8)
Daytime symptoms (units)	0.6 (0.1)	0.6 (0.1)	0.3 (0.1)*†	0.3 (0.1, 0.5)
Night time symptoms (units)	0.5 (0.1)	0.7 (0.1)	0.3 (0.1)*	0.3 (0.1, 0.6)

Values are shown as means (SE) and mean differences (95% CI) except for methacholine PD₂₀ which is expressed as geometric mean dose (µg) and geometric mean fold difference. *Denotes significant ($P < 0.05$) difference between montelukast *vs* placebo; †denotes significant ($P < 0.05$) difference from post run-in value.

in a LTRA, although the data were limited by a small number of studies and a relatively short period of follow up [16].

It is important to be aware that airway hyper-responsiveness to methacholine can be related to changes in airway calibre, or in other words bronchial hyper-responsiveness to methacholine can be attributed to reduced airway calibre [17]. However, our results have demonstrated that the change in the primary endpoint of methacholine PD₂₀ was dissociated from effects on FEV₁ (Table 3), i.e. the improvement in methacholine PD₂₀ with montelukast from post run-in was significant, while the change in FEV₁ was nonsignificant. In this respect, the use of indirect bronchoconstrictor stimuli such as adenosine monophosphate, which principally act via degranulation of primed mast cells, are considered to be of greater value in assessing the anti-inflammatory response [18–20].

There are some methodological points to discuss about our study. It could be argued that our study did not reflect real life situations since long-acting β_2 -adrenoceptor agonists are not indicated for sole use in the management of asthma of any severity. It has to be pointed out however, that our primary aim was to examine the effects of montelukast when used in conjunction with long β_2 -adrenoceptor acting agonists in terms of methacholine bronchial hyper-responsiveness in absence of other anti-inflammatory therapy. Moreover, salmeterol itself demonstrates no meaningful *in vivo* anti-inflammatory activity [21–23]. Despite patients attending for measurement 12 h after the last dose of salmeterol, beneficial effects in terms of bronchodilation and airway hyper-responsiveness would still have been present. For example, in the study by Rabe [24], salmeterol significantly improved FEV₁ and significantly protected

against methacholine-induced bronchoconstriction compared with placebo for up to 24 h after dosing. Current guidelines suggest that salmeterol should only be used on a regular basis in patients receiving ICS. In view of our findings, it may be more relevant to consider whether adding montelukast to a corticosteroid/long-acting β_2 -adrenoceptor agonist combination inhaler provides additional beneficial effects. Further randomized studies are therefore indicated to assess these effects looking particularly at effects upon exacerbations and airway remodelling.

In conclusion, in moderate persistent asthmatics who have been switched from ICS to salmeterol, add on treatment with montelukast showed significant improvements compared with placebo in bronchial hyper-responsiveness, lung function and diurnal asthma control.

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