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Traditional and patient-centred outcomes with three classes of asthma medication

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ABSTRACT: Lung function is commonly used as the primary endpoint in asthma clinical trials, but it may not reflect changes which are important to patients. The present study compared changes in, and relationships between, traditional and patient-centred end-points during treatment with three classes of asthma medication.

Subjects with mild-to-moderate asthma were randomised to double-blind, double-dummy crossover treatment with eformoterol 12 μg *b.i.d.* or montelukast 10 mg *q.d.*, then single-blind treatment with fluticasone 250 μg *b.i.d.*/placebo capsules, with 6-week treatment periods and 1-week washouts. Individual ''traditional'' end-points (symptoms, reliever use, forced expiratory volume in one second per cent predicted, morning peak expiratory flow, airway hyperresponsiveness) and ''patient-centred'' end-points (asthma control questionnaire, quality of life, patient global assessments) were assessed. Principal component analysis and linear modelling were used to explore overall rank orders for treatment, and relationships between outcomes.

A total of 58 subjects were randomised. The rank order of benefit from eformoterol and fluticasone differed for three factors derived from principal component analysis (eformoterol>fluticasone for symptom/reliever use factor, fluticasone>eformoterol for lung function factor, eformoterol=fluticasone for patient-centred factor). Montelukast was ranked third for all three factors. A significant relationship between patient-based variables and lung function was found only for montelukast treatment.

In asthma treatment, traditional end-points do not fully capture patient-centred benefits, and the relationship between end-points differs with medication class.

KEYWORDS: Asthma treatment, lung function, patient-centred outcomes, quality of life

In asthma, the clinical assessment of response to therapeutic interventions has traditionally been based on lung function and symptom control [1, 2]. Likewise, international asthma guidelines primarily base the classification of asthma severity or control on symptom control and lung function, with more severe asthma indicated by poor lung function, frequent symptoms or reliever use, night waking and exacerbations [3–5]. Recommendations for asthma treatment are usually based on the results of clinical trials or meta-analyses, which use such measures as end-points. However, the effectiveness of a medication is not just determined by its reported efficacy, but also by patient adherence, which may be affected by their perception of benefit [6]. Patients perceive some asthma symptoms as more troublesome than others [7] and may report benefits from asthma treatment which cannot be explained on the basis of clinical lung function [8, 9]. The assessment of exacerbations is a crude measure of a protective effect against triggers which would otherwise produce a worsening of asthma. However, patients may be aware of a day-to-day protective benefit which is not reflected in any single functional assessment. Some treatments may be preferred by patients on the basis of such subjective changes, rather than on the conventional clinical and symptom measures which are used in clinical trials.

There is increasing use in clinical trials of patient-centred outcomes, such as quality of life (QoL), and it is recognised that the cross-sectional correlation between QoL and lung function is weak [9]. However, it is not known whether the relationship between patient-centred end-points and more traditional end-points, such as lung function, is the same with different types of asthma medication. It is possible that medication classes which provide important benefits to patients could appear relatively ineffective in clinical trials if the studies assess only traditional end-points, *e.g.* lung function, and omit assessment of patient-centred end-points. Clinicians need to be aware of patients' priorities and values

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in relation to the various benefits and risks of medications [10, 11].

The present study was designed to examine the relationship between clinical and subjective variables in the assessment of response to treatment with three different classes of medication, including a leukotriene receptor antagonist, long-acting β_2-agonist and inhaled corticosteroid (ICS), with a crossover study design, in patients with mild-to-moderate persistent asthma. The current study hypotheses were, first, that some traditional measurements of improvement during asthma treatment may not reflect the estimation of benefit by the patient, and secondly, more specifically, that patients may benefit from these classes of asthma medication in ways which were not captured by the measurement of lung function.

MATERIALS AND METHODS

Subjects

Subjects eligible for the present study were aged 16–75 yrs, and had previously used a short-acting β_2-agonist with/without an ICS $\leqslant$500 μg beclomethasone equivalent. In all subjects, ICS treatment was ceased at entry to the study. During the 2-week run-in period, subjects were screened for the following inclusion criteria: forced expiratory volume in one second (FEV_1) of 50–90% of predicted and/or a ratio of FEV_1/forced vital capacity (FVC) $\leqslant$70%, reversible airway obstruction (FEV_1 increase $\geqslant$15% pred or >200 mL after 200 μg salbutamol) within the previous 6 months, asthma symptoms or short-acting β_2-agonist use $\geqslant$4 days·week^{-1}, and moderate airway hyperresponsiveness (AHR), defined as the provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}) $\leqslant$2 μmol at the end of a run-in period. Exclusion criteria included coexisting lung disease, recent asthma exacerbation or respiratory infection, and current smoking or smoking history $\geqslant$10 pack–yrs.

Study design

After a run-in period, subjects were allocated one of two treatment sequences by a computer-generated randomisation procedure (fig. 1). The first two periods comprised a double-blind, double-dummy crossover comparison of leukotriene receptor antagonist (over-encapsulated montelukast 10 mg tablet *q.d.*) *versus* long-acting β_2-agonist (eformoterol Turbuhaler® 12 μg *b.i.d.*) with matching placebos, and the third treatment period was single-blind ICS (fluticasone propionate Accuhaler/Diskus® 250 μg *b.i.d.*) and placebo capsules. The 6-week treatment periods were separated by 1-week washout periods. Reliever bronchodilator medication (salbutamol) was permitted as required throughout the study. Subjects recorded symptoms, night waking, reliever use, asthma control score and spirometry twice daily throughout the study, using the Asthma Monitor AM2 (Erich Jaeger GmbH, Hoechberg, Germany). Before visits, salbutamol was withheld for 6 h, study inhalers for 24 h and capsules for 48 h. The study was carried out at three sites in Sydney and Melbourne, Australia. The protocol was approved by the institutional review board at each site, and all subjects gave written informed consent prior to enrolment.

Outcome measures

The primary outcome variables for calculation of treatment effect were morning peak expiratory flow (PEF; the best from three spirometric manoeuvres), and median daytime and night-time symptom intensity scores (scale: 0–4, where 0=none and 4=severe).

Secondary outcome variables from visits to the clinic included standard spirometric lung function variables, QoL score (as described by MARKS *et al*. [12]), AHR (measured as PD_{20} methacholine) [13] and asthma control questionnaire (ACQ) score (scale: 0–6) [1]. At each visit, patients completed a global assessment of asthma control (GAAC) prior to any staff input, in response to the question ''How well has your asthma been controlled in the last one week?'' (visual analogue score: 0–100, with a low score being ''very poorly controlled'' going up to ''very well controlled'' for a high score). Secondary outcome variables from electronic diary records included symptom-free days, salbutamol as required (inhalations·day^{-1}), percentage salbutamol-free days, percentage waking-free nights, and median daily asthma control score (DACS; text scale: from ''very poor control'' to ''very good control'').

For each treatment, the baseline for electronic monitoring variables comprised the last seven evaluable days of washout, and the end-of-treatment assessment comprised the last 14 evaluable days of treatment (excluding two days' withholding).

Adverse events were recorded, with visual inspection for oral candidiasis at study visits. Asthma exacerbations were recorded as moderate (requiring additional ICS) or severe (emergency hospital treatment and/or oral corticosteroids). Adherence was assessed covertly, using a capsule count for montelukast and Accuhaler counter for fluticasone; however, no measure of eformoterol adherence was available.

Sample size

A target sample size of 60 subjects was calculated for the two-period crossover component, to ensure $\geqslant$80% power to detect a difference between treatments of 20 L·min^{-1} PEF

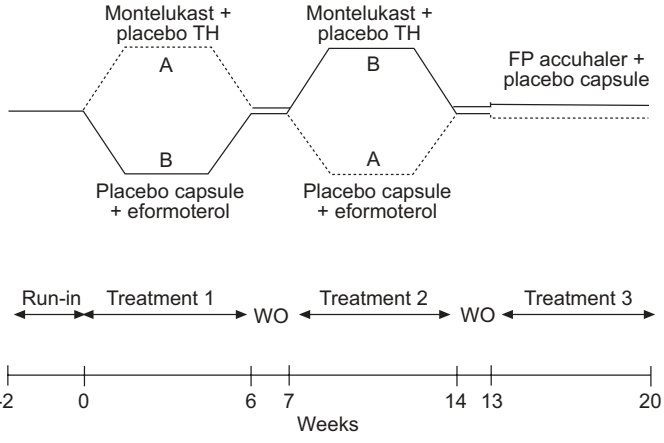

FIGURE 1. Study design: double-blind, double-dummy randomised crossover comparison of encapsulated montelukast 10 mg *nocte* and eformoterol 12 μg *b.i.d.* by Turbuhaler® (TH), followed by single-blind treatment with fluticasone propionate (FP) 250 μg *b.i.d.* by Accuhaler™ and placebo capsule. Sequence A received montelukast then eformoterol; sequence B received eformoterol then montelukast. WO: washout period.

(SD=40 L·min^{-1}). This sample size would also give the study >90% power to detect a mean difference in QoL scores of 0.5, with a SD=0.56.

Analysis

The primary analysis was performed on an intention-to-treat (ITT) basis. All statistical tests were two-sided with a 5% significance level. Statistical comparisons between treatments used end-of-treatment values, with baseline as a covariate. Baseline values for treatment periods 1 and 2 were compared for carry-over effect. The crossover comparison of mean morning PEF for montelukast and eformoterol used the method of JONES and KENWARD [14]. Peak flow comparisons between the final treatment (fluticasone) and each of the crossover treatments (eformoterol and montelukast) were by paired t-tests, ignoring sequence allocation. Symptom scores were analysed as for PEF, using Wilcoxon rank-sum tests. Secondary variables were compared using similar methodology, using unpaired t-tests (PEF) and Wilcoxon rank-sum tests (symptoms) for crossover analysis, and paired t-tests or Wilcoxon signed-rank tests for comparisons with fluticasone. The QoL scores were square root transformed prior to analysis. The ITT populations for each comparison comprised patients who had taken at least one dose of both medications [15].

Exploratory models

Principal component analysis was performed, using the proc factor procedure. The purpose was to reduce the original large number of variables, many of which were expected to be correlated with each other, to a small number of uncorrelated variables. The ''traditional variables'' used in the principal component analysis were spirometry variables, mean morning PEF, PEF per cent predicted, PEF per cent best of the whole study, median daytime/night-time symptom scores, median daytime/night-time salbutamol use, percentage symptom-free days, percentage salbutamol-free days, percentage waking-free nights, and log PD_{20}. The ''patient-centred variables'' were QoL, ACQ, patient GAAC and DACS. The ACQ was included with patient-centred variables because its development focussed on clinical impairment experienced by the patient [1]. All available data for each treatment were used, ignoring sequence of treatment. Values were reversed for parameters of which a higher score indicated worse asthma control. The correlation between each variable and the principal factors derived from the principal component analysis were calculated, and the factor loadings were ''rotated'' to maximise the differences between factors. For each subject, a score was calculated for each principal factor by multiplying the original value for each variable with the relevant rotated factor loading, then summing these products. These derived scores were used in the subsequent analysis of treatment effect and associations.

The first study hypothesis was tested initially by examining the statistical significance and direction of differences between treatments for the multiple individual end-points, and secondly, by summing the derived scores for each principal factor for each treatment. These scores were compared to obtain rank orders for the three treatments, but were not subject to statistical significance testing.

The specific relationship of lung function with patient-centred outcomes was tested by a general linear modelling approach, using the derived score for patient-based end-points as the dependent variable and individual lung function variables (FEV_1 % pred, FEV_1/FVC, % best PEF and mean morning PEF) as the independent variables.

RESULTS

The present study extended from December 2000 to October 2002. A total of 29 subjects were randomised to each order of treatment (sequence A received montelukast then eformoterol; sequence B received eformoterol then montelukast), and 52 subjects completed the study (fig. 2). Baseline characteristics are shown in table 1. Male:female ratio was, by chance, significantly higher in sequence B than in sequence A. Baseline observations were consistent with suboptimally-controlled asthma (table 1). Comparison of baseline values for the first and second treatment periods revealed no significant carry-over effect, except for clinic FEV_1, which was significantly lower in the first washout period for subjects who received eformoterol first compared with those who received montelukast first (mean difference -0.15 L; p=0.004). Nevertheless, data from the second crossover period were included in the subsequent analyses of treatment effect, as recommended by PATEL [16].

Primary variables

Mean morning PEF was significantly higher with eformoterol (453 L·min^{-1}) and with fluticasone (468 L·min^{-1}) than with montelukast (428 L·min^{-1}; p<0.0001 for each t-test). The difference in PEF between eformoterol and fluticasone was not statistically significant (fig. 3; table 2).

Median night-time symptom score was significantly lower with eformoterol and with fluticasone compared with montelukast (p<0.0001 and p=0.01, respectively, Wilcoxon signed-rank test). For daytime symptom scores, the differences between eformoterol and fluticasone compared with montelukast only approached significance (p=0.054 and 0.06, respectively).

Secondary variables

Results for other end-points are shown in table 2. In contrast with morning PEF, clinic FEV_1 % predicted and PD_{20} FEV_1 did not differ significantly between montelukast and eformoterol, but were significantly better with fluticasone compared with either eformoterol or montelukast. The pattern for ACQ was similar to that for morning PEF, with no significant difference between eformoterol and fluticasone, but significantly lower scores (better control) during both eformoterol and fluticasone treatment than during montelukast treatment. A similar pattern was seen for QoL, but the absolute mean improvement with eformoterol and fluticasone (0.2 points for each) was not clinically important. Patient GAAC showed no significant difference between eformoterol and fluticasone. Compliance with study medications was 98% for montelukast and 95% for fluticasone.

Principal component analysis was performed using all end-of-treatment data to further test the first hypothesis that traditional measures of improvement in asthma may not reflect those of patients. Examination of the rotated factor loadings for the traditional variables (table 3) showed a clear division into two factors. ''Traditional factor 1'' included all of

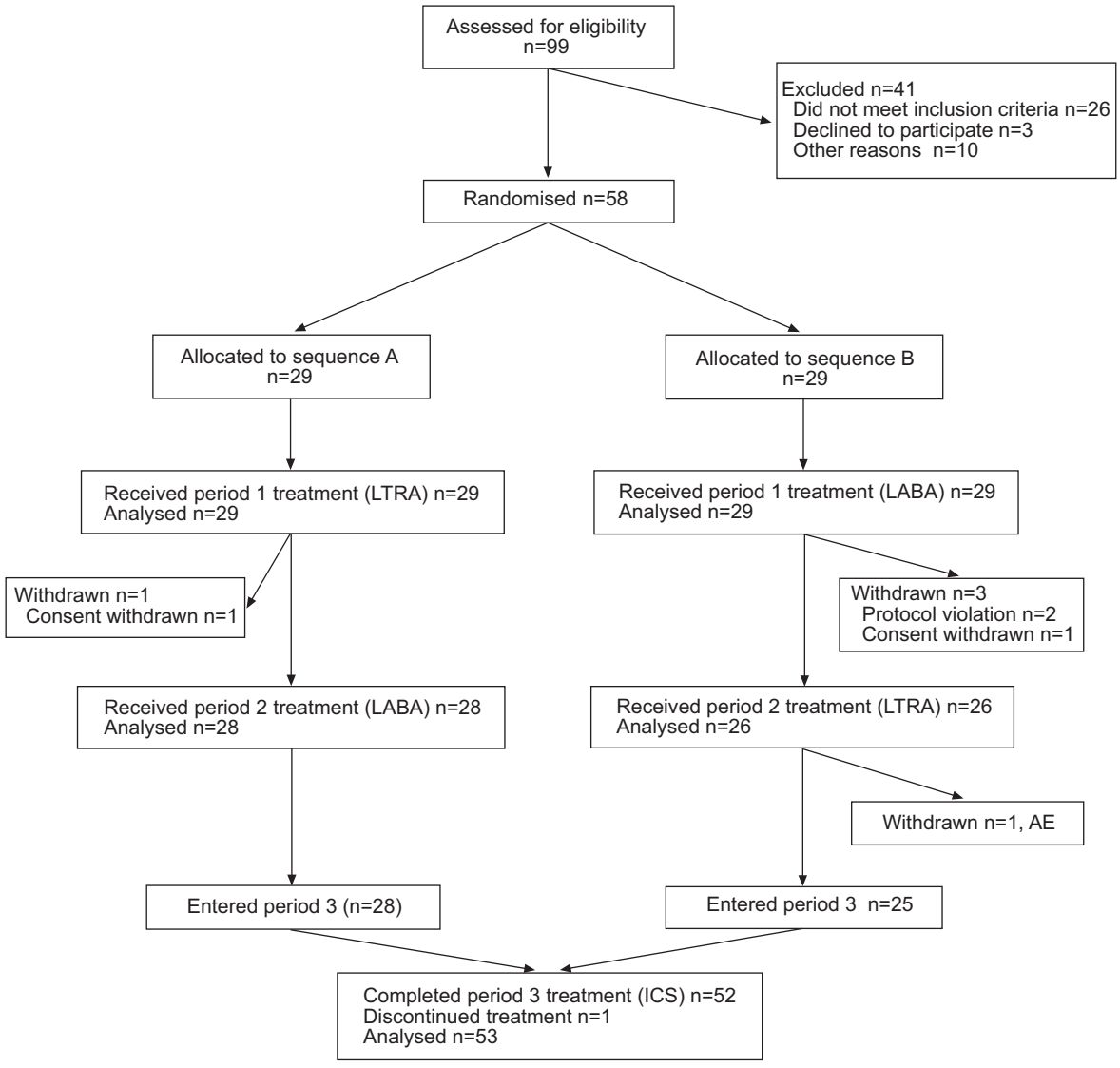

FIGURE 2. Patient disposition. LTRA: leukotriene receptor antagonist (encapsulated montelukast); LABA: long-acting β_2-agonist (eformoterol); AE: adverse event; ICS: inhaled corticosteroid (fluticasone propionate).

the day and night symptom and salbutamol end-points. Clinic and electronic diary lung function end-points loaded together into a second factor called ''traditional factor 2''. For patient-centred variables (table 4), a single factor (''patient factor 1'') containing ACQ, QoL, patient GAAC and DACS explained almost 70% of the variance; therefore, no further factors were explored. An overall score was obtained by summing across subjects the scores obtained during principal component analysis for each of the three factors. The rank order of these summed scores differed for different medications. For traditional variables, the scores for eformoterol treatment were higher compared with those for fluticasone for the symptom/salbutamol factor (16.47 *versus* 2.24), but lower than for fluticasone for the lung function factor (-0.19 *versus* 7.55). However, for the patient-centred factor, eformoterol and fluticasone achieved approximately equal scores (7.78 and 8.02, respectively). Montelukast was ranked third for all three factors (-18.7, -7.36 and -15.8, respectively).

The second hypothesis was that different classes of medications provide benefits to patients which are not captured by the measurement of lung function. Linear modelling using ''patient factor 1'', derived from principal component analysis, identified a statistically significant association between this factor and lung function end-points for montelukast (FEV_1 % pred, $p=0.001$; FEV_1/FVC ratio, $p=0.002$; and PEF % best, $p=0.005$), but not for the other treatments (eformoterol: $p=0.6$, 0.9 and 0.09, respectively; fluticasone: $p=0.15$, 0.2, 0.13, respectively). Further modelling, to test whether different treatments correlated differently with patient-based scores, yielded no consistent findings.

Adverse events

One patient withdrew from the study due to an exacerbation of pre-existing psoriasis. There were five severe asthma exacerbations (montelukast: n=3; eformoterol: n=1; and washout after eformoterol: n=1), and 11 moderate exacerbations

TABLE 1 Baseline demographic and clinical characteristics

	Sequence A[#]	Sequence B[¶]	All
Clinical variables			
Subjects n	29	29	58
Sex M:F	13:16	22:7[+]	35:23
Age yrs[§]	40.7 (16–71)	36.2 (19–60)	38.5 (16–70)
Atopic[ƒ]	27 (93)	27 (93)	54 (93)
Former smokers	3 (10)	8 (28)	11 (19)
Taking ICS prior to enrolment	15 (52)	18 (62)	33 (57)
FEV_1 % pred	75.0±10.7	77.1±13.2	76.1±11.9
FEV_1/FVC ratio	0.73±0.09	0.71±0.10	0.72±0.10
PD_{20} methacholine μmol[##]	0.31 (0.22–0.46)	0.42 (0.32–0.56)	0.37 (0.29–0.46)
Total QoL score[¶¶]	0.69±0.10	0.57±0.08	0.63±0.09
ACQ score	2.09±0.79	1.81±0.69	1.95±0.75
Patient GAAC[++]	51.2±25.6	51.7±25.4	51.4±25.3
Electronic diary variables			
Subjects n	24	25	49
Day symptom score[§§]	1.5 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)
Night symptom score[§§]	1.0 (0.9–2.0)	1.0 (1.0–1.5)	1.0 (1.0–2.0)
Symptom-free days %	0.0 (0.0–3.3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Waking-free nights %	47 (13–84)	57 (29–100)	50 (25–88)
Day salbutamol use puffs·day^{-1}	3.0 (1.0–4.4)	2.0 (1.0–6.0)	3.0 (1.0–5.5)
Night salbutamol use, puffs·day^{-1}	2.0 (0.0–3.1)	2.0 (0.5–2.0)	2.0 (0.0–2.0)
Salbutamol-free days %	0.0 (0.0–13.3)	0.0 (0.0–0.0)	0.0 (0.0–13.0)
Median DACS[ƒƒ]	3.0 (3.0–4.0)	4.0 (3.0–4.0)	3.0 (3.0–4.0)

Data are presented as mean±SD, median (interquartile range) or n (%). M: male; F: female; ICS: inhaled corticosteroids; FEV_1: forced expiratory volume in one second; % pred: per cent predicted; FVC: forced vital capacity; PD_{20}: provocative concentration of methacholine causing a 20% fall in FEV_1; QoL: quality of life; ACQ: asthma control questionnaire; GAAC: global assessment of asthma control; DACS: daily asthma control score. [#]: sequence A: montelukast then eformoterol; [¶]: sequence B: eformoterol then montelukast; [+]: p=0.03 *versus* sequence A, Chi-squared test; [§]: mean (range); [ƒ]: atopy defined as >5 aeroallergens (*Dermatophagoides pteronyssinus*, rye, cat, *Aspergillus*, *Alternaria*) ⩾4×4 mm and >saline control; [##]: geometric mean (95% confidence intervals); [¶¶]: data summarised as square root then back-transformed; [++]: visual analogue score for asthma control over last week, 0–100, very poorly controlled to very well controlled; [§§]: day and night symptom scores, each range 0–4 from pre-set text responses; [ƒƒ]: asthma control score for last 24 h from electronic diary, range 1–5 (very poorly controlled to very well controlled) in text responses.

(run-in: n=8; eformoterol: n=2; fluticasone: n=1). Oral candidiasis was observed in three subjects (run-in: n=1; montelukast: n=1; fluticasone: n=1). Hoarseness was reported by 15 (26%) subjects (fluticasone: n=8; other periods: n=7).

DISCUSSION

The present study demonstrates that the relative efficacy of asthma medications from different pharmacological classes may depend on the specific end-points which are examined. For the individual end-points which were examined in this study, fluticasone was superior to eformoterol for clinic lung function and AHR. It was equivalent to eformoterol for symptoms, morning PEF, daytime reliever use, QoL, ACQ and patient assessments of asthma control; and inferior to eformoterol for night-time reliever use. For most individual variables, the magnitude of improvement with montelukast was small, with significantly less benefit compared with eformoterol or fluticasone. Planned exploratory modelling, which took into account the correlations between some variables, indicated that, overall, eformoterol gave greater benefit than fluticasone with regards to symptoms and reliever use, fluticasone gave greater benefit than eformoterol for clinic and diary lung function variables, and eformoterol and fluticasone gave similar benefits for patient-centred variables. Montelukast ranked third for all three factors. However, in further modelling, montelukast was the only medication for which overall patient-centred benefit correlated with changes in clinic lung function. This indicates that, at least for ICS and long-acting β_2-agonists, assessment of efficacy should include both traditional and patient-centred end-points, rather than relying on measurement of lung function alone to assess treatment response.

Some aspects of the study design may limit the interpretation of the current findings. A fully-randomised crossover comparison of the three medications was rejected on safety grounds to avoid prolonged fluticasone washout; hence, comparisons of fluticasone with eformoterol and montelukast were exploratory because of complete confounding between period and treatment effects. A significant negative carry-over effect was observed for lung function for subjects receiving eformoterol first, possibly because of 9 weeks without anti-inflammatory medication. For practical reasons, the study hypotheses were tested during monotherapy rather than with multiple combinations of add-on therapy. Monotherapy with a long-acting β_2-agonist is not recommended for maintenance treatment [3–5],

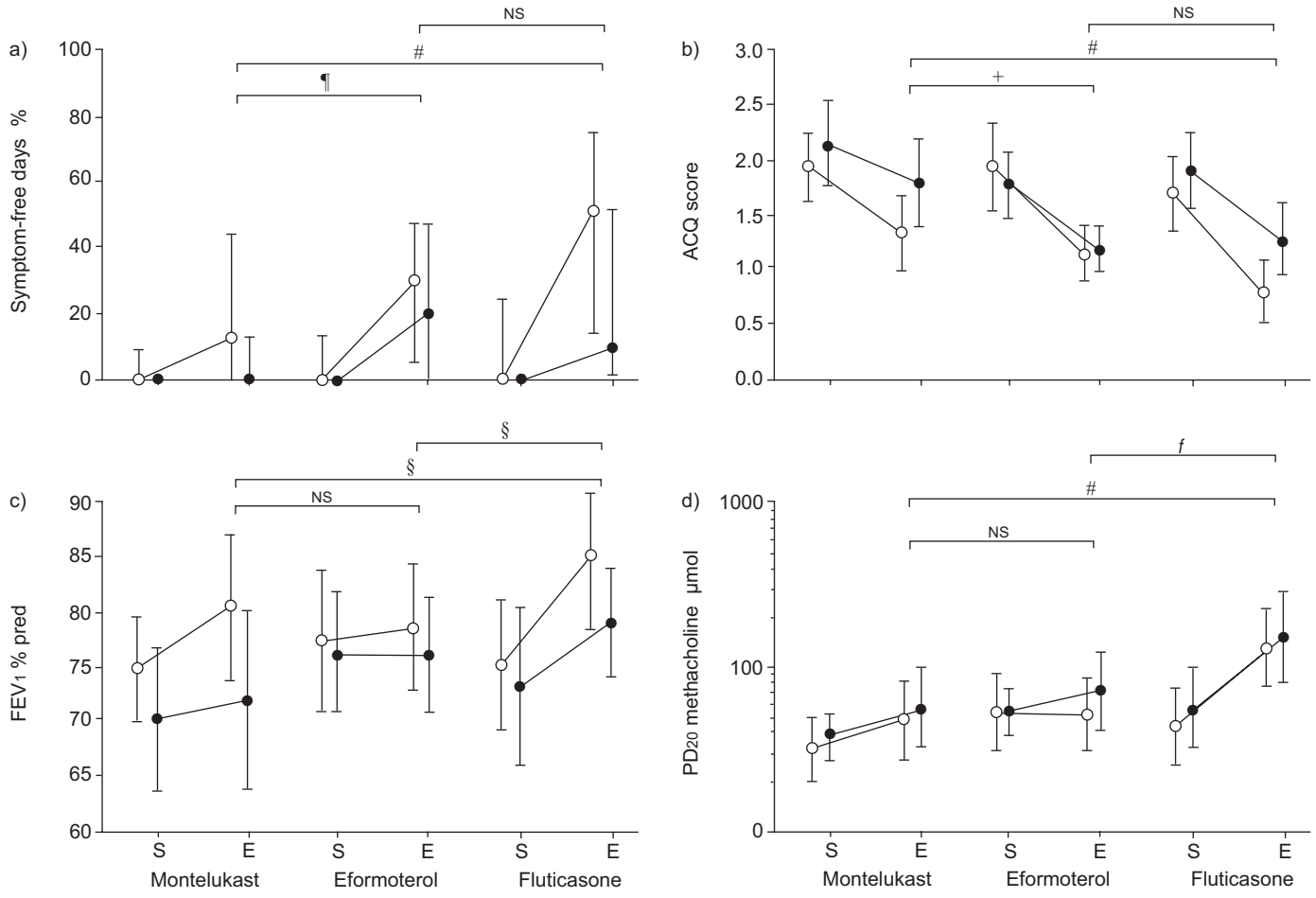

FIGURE 3. Efficacy measurements of encapsulated montelukast 10 mg *q.d.*, eformoterol 6 µg *b.i.d.* and fluticasone 250 µg *b.c.* (each taken for 6 weeks) as assessed by a) Symptom-free 24-h periods (median and IQR); b) asthma control questionnaire (ACQ) score, range 0–6 (mean and 95% confidence intervals (CI)); c) forced expiratory volume in one second (FEV_1) % predicted (mean and 95% CI), using European Community for Steel and Coal predicted values [17]; and d) airway hyperresponsiveness measured as the provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}) (geometric mean and 95% CI). Subjects randomised to group A (○) received montelukast first followed by eformoterol; subjects in group B (●) received eformoterol first followed by montelukast. p-values for montelukast *versus* eformoterol were from randomised crossover analysis; p-values for montelukast *versus* fluticasone and eformoterol *versus* fluticasone used end-of-treatment values for paired t-test or Wilcoxon signed-rank test. $^{\#}$: $p<0.0001$; ¶: $p=0.01$; $^{+}$: $p=0.02$; §: $p=0.0002$; ^{f}: $p=0.0008$; NS: nonsignificant.

although several studies have shown that this does occur in the community [18]. Therefore, the present authors recruited subjects with mild-to-moderate asthma, who might realistically receive monotherapy, although patients needed to be symptomatic enough to show a treatment response. The study was powered to detect clinically important differences in morning PEF and QoL between treatments, and by the end of 6 weeks, the majority of improvement in most end-points, other than AHR, would have been expected to have been observed [19]. At baseline, although lung function, AHR and reliever use indicated suboptimal asthma control and the opportunity for improvement with treatment, QoL was surprisingly well-preserved, suggesting that these subjects were not particularly troubled by their asthma. As a result, there was little room for improvement in QoL, limiting the conclusions which could be drawn about the relationship between changes in QoL and other variables. The study was not powered to detect differences in exacerbation rates between the three treatments. Interpretation of the results needs to take into account the withholding of medications prior to study visits. This is standard practice in clinical trials to reduce acute effects on spirometry and challenges, although the withholding period is often shorter than the medication's duration of action. Clinic lung function measures may, therefore, reflect a different aspect of treatment response from diary end-points, such as reliever use and morning PEF, although it could be argued that the acute protective effects represent benefits which may be just as valuable to patients as the longer-term benefits of maintenance medication. In the present study, shorter periods of withholding treatment would have been expected to favour eformoterol and montelukast in lung function end-points.

The current study was novel in its comparison of three medication classes within the same patients, and in its exploration of differences between traditional and patient-centred measures of efficacy. Several studies have compared

TABLE 2 Efficacy end-points for treatment with montelukast, eformoterol and fluticasone

	Run-in	Washout 1	Washout 2	Montelukast	Eformoterol	Fluticasone	M *versus* EF	M *versus* FP	EF *versus* FP
Clinical variables									
FEV_1 % pred	76.1±11.9	73.6±15.50	73.9±15.3	76.2±18.0	77.0±13.6	81.8±13.9	0.4	0.0002	0.0002
PD_{20} methacholine μmol[#]	0.39 (0.3–0.5)	0.49 (0.33–0.71)	0.43 (0.31–0.59)	0.57 (0.40–0.81)	0.46 (0.32–0.67)	1.26 (0.86–1.86)	0.4	<0.0001	0.0008
QoL score (Marks *et al*. [12]), range 0–4 least to most impaired	0.63±0.09	NA	NA	0.59±0.09	0.400.08	0.41±0.14	0.001	0.005	0.9
ACQ Score [1], range 0–6 best to worst	1.95±0.75	2.05±0.94	1.8±0.82	1.56±0.92	1.17±0.55	1.05±0.75	0.02	<0.0001	0.3
Patient GAAC, range 0–100, worst to best	54.8±24.8	48.0±25.4	51.5±21.9	63.9±23.8	71.1±21.3	71.4±21.7	0.08	0.03	0.8
Diary variables									
Mean a.m. PEF $L \cdot min^{-1}$	424±119	409±121	415±134	428±125	453±121	468±134	<0.0001	<0.0001	0.08
Day symptom intensity score, range 0–4, best to worst	2.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (0.0–1.6)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	0.049	0.6	0.08
Night symptom intensity score, range 0–4, best to worst	1.0 (1.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–1.5)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	<0.0001	0.01	0.08
Symptom-free days %	0 (0–0)	0 (0–13)	0 (0–14)	0 (0–34)	23 (0–47)	26 (0–67)	0.01	<0.0001	0.2
Daytime salbutamol use puffs·day^{-1}	3.0 (1.0–5.5)	2.0 (0.0–4.0)	2.0 (0.0–3.5)	0.0 (0.0–3.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.01	0.05	0.1
Night salbutamol use puffs·day^{-1}	2.0 (0.0–2.0)	1.3 (0.0–2.0)	0.3 (0.0–2.0)	0.3 (0.0–2.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	<0.0001	0.02	0.04
Salbutamol-free days %	0 (0–13)	0 (0–16)	13 (0–20)	30 (0–49)	40 (20–67)	37 (2–73)	0.008	0.03	0.3
DACS, range 1–5, worst to best	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.5 (3.0–4.0)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	0.01	0.4	0.2

Data are presented as mean±SD or median (interquartile range), unless otherwise indicated. FEV_1: forced expiratory volume in one second; % pred: per cent predicted; PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1; QoL: quality of life; ACQ: asthma control questionnaire; GAAC: global assessment of asthma control; PEF: peak expiratory flow; DACS: daily asthma control score. [#]: geometric mean (95% confidence interval). p-values for montelukast *versus* eformoterol were from randomised crossover analysis; p-values for montelukast *versus* fluticasone and eformoterol *versus* fluticasone used end-of-treatment values for paired t-test (parametric variables) or Wilcoxon signed-rank test (nonparametric variables).

drugs from two of these medication classes, and the results are consistent with the present individual pairwise comparisons. Anti-leukotrienes, although still recommended in several guidelines as second-line monotherapy for mild asthma [3–5], have been shown to give less benefit than ICS, even at low doses, in lung function, symptom control, exacerbations and QoL [20]. There are few studies comparing ICS with long-acting β_2-agonists alone, but long-acting β_2-agonists appear to be effective in improving symptoms, reliever use and lung function. An 8-week study of budesonide 400 μg and eformoterol 24 μg *b.i.d.* in mild asthma showed no significant differences for total symptoms and reliever use, but better morning PEF and daytime symptoms for eformoterol compared with budesonide [21]. Another 4-week comparison of salmeterol alone 100 $\mu g \cdot day^{-1}$ with fluticasone at 200 and 500 $\mu g \cdot day^{-1}$ demonstrated a trend for a better outcome for salmeterol for symptoms, waking-free nights and morning PEF [22]. In the present study, use of a moderate dose of potent ICS, which is now not recommended as part of the first-line treatment for asthma, may have favoured the ICS arm over montelukast, but makes the equivalence of eformoterol and fluticasone for several outcomes more striking. However, longer-term studies have demonstrated significant advantages in exacerbation rates for ICS over long-acting β_2-agonists [23, 24].

Few publications have addressed the issue of the relationships between different types of end-points in clinical trials, and none have previously examined these relationships across different pharmacological classes within the same patients. A dissociation between symptoms, lung function and airway inflammation has been identified in several cross-sectional studies [25, 26], and in longitudinal ICS studies [27, 28]. One retrospective analysis of pooled fluticasone, salmeterol and zafirlukast studies concluded that symptoms were a good surrogate for lung function in the assessment of therapeutic response, but this statement was based on correlation coefficients of only approximately -0.20 to -0.40 [29]. Overall, patient-centred measures, such as QoL, tend to be impaired in patients with more symptoms and reliever use [1, 30], and appear to improve with improvements in these measures [31]. However, from factor analysis of three salmeterol studies, JUNIPER *et al*. [9] concluded that QoL was a distinct component of asthma health status, which could not be assessed from symptoms or lung function. In the present study, the results for individual end-points and with exploratory modelling

TABLE 3 Rotated factor loadings for traditional[#] measures

Variable	Traditional factor 1	Traditional factor 2
FEV_1	0.155	0.932[¶]
FVC	0.051	0.924[¶]
Mean morning PEF	-0.032	0.842[¶]
Daytime salbutamol use (reversed[+])	0.768[¶]	0.001
Per cent nights no waking	0.701[¶]	-0.047
Night-time symptom score (reversed)	0.820[¶]	-0.046
Daytime symptom score (reversed)	0.792[¶]	-0.093
Night-time salbutamol use (reversed)	0.795[¶]	0.129
Per cent salbutamol-free 24 h	0.767[¶]	-0.160

Table shows the rotated factor loading between each individual variable and the factors derived from principal component analysis. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow. [#]: FEV_1/FVC, log provocative dose of methacholine causing a 20% fall in FEV_1, FEV_1 % predicted, PEF % best, PEF % predicted and symptom-free days contributed little and were omitted from the final factor analysis for traditional variables; [¶]: Significant loadings, indicating the variables that clustered together, *i.e.* were strongly correlated with each other; [+]: values were reversed for parameters for which a higher raw score indicated worse asthma control.

supported the authors' hypothesis that asthma medications would provide benefits which were not captured by traditional measurements, such as lung function or symptom scores. Principal component analysis was utilised in order to be able to rank the overall benefit of the three medications. The variables of QoL, ACQ and the patient assessments of asthma control all loaded strongly together in the analysis of patient-centred variables. Somewhat surprisingly, clinic spirometry and morning PEF loaded together into a single factor, despite pre-visit medication withholding, but this may not have been observed with a shorter period of treatment. When scores for the three factors were summed for each medication, the overall ranking of benefit from the medications favoured eformoterol for symptoms and reliever use, and favoured fluticasone for lung function outcomes, although montelukast ranked third for each of the three factors. Given the exploratory nature of these analyses, the overall rankings were not subject to statistical testing, although the direction of difference was consistent with the findings for individual variables. The specific relationship between patient-centred outcomes and lung function for each treatment was also examined. Interestingly, the only treatment where a relationship was observed between lung function improvement and a patient-centred factor was montelukast, the drug which showed the least group effect on lung function, symptom control and QoL.

TABLE 4 Rotated factor loadings for patient-centred measures

Variable	Patient Factor 1
Quality-of-life score (reversed)	0.842[¶]
Asthma control questionnaire (reversed)	0.870[¶]
Median daily control score	0.753[¶]
Patient global control assessment	0.855[¶]

Table shows the rotated factor loading between each individual variable and the factors derived from principal component analysis for patient-centred variables. [¶]: Significant loadings, indicating the variables that clustered together, *i.e.* were strongly correlated with each other.

The results of the current study indicate that different therapeutic effects may be seen between medication classes in asthma according to which outcome variables are examined, despite some shared improvements in symptoms and lung function. Hence, when the results of clinical trials or meta-analyses are being summarised, it is important to specify the relevant endpoint(s), for example, it should not be stated that ''(medication) X is better than Y for moderate asthma'' but that ''X is better than Y for clinic lung function in moderate asthma''. A simple summary of superiority of one medication over another cannot necessarily be given, as in the present study eformoterol led to the greatest improvement in symptom score and reliever use, fluticasone led to the greatest improvement in lung function, and both medications led to equal improvements in patient-based assessments. The study also confirms the importance of including both traditional and patient-centred measurements in clinical asthma trials, in order to fully assess the impact of treatment. The patient-centred measurements which were utilised in the present study take only a few minutes to complete, and can be readily incorporated into either clinical trials or clinical practice, to add to the information obtained from traditional measures. It cannot be assumed that lung function measurements either fully capture the benefit of a treatment, nor that improvement in lung function implies improvements across the board in outcomes that matter to patients.

In conclusion, by understanding this relationship more clearly there will be greater potential to develop interventions that meet patients' needs and, hence, assist choice of, and adherence with, appropriate treatment regimens.

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REFERENCES

1 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14: 902–907.
2 Demoly P, Crestani B, Leroyer C, Magnan A, Mounedji N, Humbert M. Control and exacerbation of asthma: a survey of more than 3000 French physicians. *Allergy* 2004; 59: 920–926.

3 Global Initiative for Asthma. Workshop Report. Global strategy for asthma management and prevention. 2002 Revision. National Institutes of Health, National Heart, Lung, and Blood Institute. NIH Publication No. 02-3659.
4 National Asthma Council Australia. Asthma Management Handbook. Melbourne, Australia, National Asthma Council Australia Ltd, 2002.
5 National Asthma Education and Prevention Program Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. Bethesda, MD, USA, National Institutes of Health 1997; pp. 97–4051.
6 Rubin BK. What does it mean when a patient says ''My asthma medication is not working?''. *Chest* 2004; 126: 972–981.
7 Osman LM, McKenzie L, Cairns J, *et al.* Patient weighting of importance of asthma symptoms. *Thorax* 2001; 56: 138–142.
8 Strunk RC, Korenblat PE. Choice of a medication to treat asthma: is an improvement in symptoms sufficient for deciding? *J Allergy Clin Immunol* 2002; 110: 832–833.
9 Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J* 2004; 23: 287–291.
10 Clark NM, Gong M. Management of chronic disease by practitioners and patients: are we teaching the wrong things? *BMJ* 2000; 320: 572–575.
11 Steven K, Morrison J, Drummond N. Lay *versus* professional motivation for asthma treatment: a cross–sectional, qualitative study in a single Glasgow general practice. *Family Practice* 2002; 19: 172–177.
12 Marks GB, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. *J Clin Epidemiol* 1992; 45: 461–472.
13 Yan K, Salome CM, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983; 38: 760–765.
14 Jones B, Kenward MG. Design and Analysis of Crossover Trials. London, UK, Chapman and Hall, 1989.
15 Gillings DB, Koch GG. The application of the principle of intention-to-treat to the analysis of clinical trials. *Drug Information Journal* 1991; 25: 411–424.
16 Patel HI. Use of baseline measurements in two-period crossover design in clinical trials. *Commun Statis Theor Meth* 1983; 112: 2693–2712.
17 Quanjer PH, Dalhuijsen A, Van Zomeren B. Summary equations of reference values. *Bull Europ Physiopathol Respir* 1983; 19: Suppl. 5, 45–51.
18 Food and Drug Administration. MedWatch: The FDA safety information and adverse event reporting program. 2003 Safety Alert - Serevent (salmeterol xinafoate). www.fda.gov/medwatch/SAFETY/2003/serevent.htm. Date last updated: January 23 2003; Date last accessed: October 10 2004.
19 Reddel HK, Jenkins CR, Marks GB, *et al.* Optimal asthma control, starting with high doses of inhaled budesonide. *Eur Respir J* 2000; 16: 226–235 (published erratum appears in Eur Respir J 2000; 16: 579).
20 Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2002; 3: CD002314.
21 Wallin A, Sandstrom T, Soderberg M, *et al.* The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Resp Crit Care Med* 1999; 159: 79–86.
22 Pearlman DS, Stricker W, Weinstein S, *et al.* Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. *Ann Allergy Asthma Immunol* 1999; 82: 257–265.
23 Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The dutch paediatric asthma study group. *Am J Resp Crit Care Med* 1997; 156: 688–695.
24 Lazarus SC, Boushey HA, Fahy JV, *et al.* Long-acting beta2-agonist monotherapy *versus* continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001; 285: 2583–2593.
25 Bailey WC, Higgins DM, Richards BM, Richards JM, Jr. Asthma severity: a factor analytic investigation. *Am J Med* 1992; 93: 263–269.
26 Rosi E, Ronchi MC, Grazzini M, Duranti R, Scano G. Sputum analysis, bronchial hyperresponsiveness, and airway function in asthma: results of a factor analysis. *J Allergy Clin Immunol* 1999; 103: 232–237.
27 Lim S, Jatakanon A, John M, *et al.* Effect of inhaled budesonide on lung function and airway inflammation. Assessment by various inflammatory markers in mild asthma. *Am J Respir Crit Care Med* 1999; 159: 22–30.
28 Brand PL, Duiverman EJ, Waalkens HJ, van Essen-Zandvliet EE, Kerrebijn KF. Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long term treatment with inhaled corticosteroids. *Thorax* 1999; 54: 103–107.
29 Dorinsky PM, Edwards LD, Yancey SW, Rickard KA. Use of changes in symptoms to predict changes in lung function in assessing the response to asthma therapy. *Clin Ther* 2001; 23: 701–714.
30 Vollmer WM, Markson LE, O'Connor E, *et al.* Association of asthma control with health care utilization and quality of life. *Am J Resp Crit Care Med* 1999; 160: 1647–1652.
31 Bateman ED, Frith LF, Braunstein GL. Achieving guideline-based asthma control: does the patient benefit? *Eur Respir J* 2002; 20: 588–595.