

Comparative efficacy and anti-inflammatory profile of once-daily therapy with leukotriene antagonist or low-dose inhaled corticosteroid in patients with mild persistent asthma

Owen J. Dempsey, MBChB, Gwen Kennedy, PhD, and Brian J. Lipworth, MD

Dundee, United Kingdom

Background: Current guidelines advocate the use of preventative anti-inflammatory therapy for mild persistent asthma.

Objective: We compared the efficacy and anti-inflammatory profiles of a leukotriene receptor antagonist and a low dose of inhaled corticosteroid in patients with mild persistent asthma.

Methods: Twenty-one adult patients with mild asthma received 4 weeks of either once-daily inhaled hydrofluoroalkane triamcinolone acetonide (450 µg/day ex-actuator dose) or oral montelukast (10 mg/day) in a randomized, placebo-controlled, single-blinded crossover study. Measurements were made before and after 2 and 4 weeks of each treatment.

Results: At the endpoint (after 4 weeks), triamcinolone and montelukast had improved the primary outcome (provocative dose of methacholine required to produce a 20% fall in FEV₁) in comparison with placebo ($P < .05$), there being no difference between the treatments (1.09-fold; 95% CI 0.73 to 1.63). Triamcinolone was better than placebo or montelukast for effects on all other surrogate inflammatory markers ($P < .05$), including exhaled nitric oxide, blood eosinophils, serum eosinophil cationic protein, plasma intracellular circulating adhesion molecule 1, and plasma E-selectin. Both treatments improved ($P < .05$) morning and evening peak flow, nighttime β_2 -agonist use, and symptoms in comparison with placebo, though triamcinolone was better than montelukast ($P < .05$) with regard to peak flow. Triamcinolone produced suppression ($P < .05$) of

overnight urinary cortisol/creatinine and serum osteocalcin.

Conclusion: Once-daily inhaled corticosteroid and leukotriene antagonist improved the primary outcome variable of bronchial hyperresponsiveness to a similar degree. (J Allergy Clin Immunol 2002;109:68-74.)

Key words: Leukotriene antagonist, corticosteroid, asthma, triamcinolone acetonide, montelukast, methacholine, adenosine monophosphate, inflammation

Current definitions of asthma focus on chronic inflammation of the airways as being a key feature.^{1,2} Airway inflammation can be detected early in the course of the disease, often before patients have noted symptoms.^{3,4} Thus, early recognition of airway inflammation might afford the opportunity for therapeutic intervention, possibly preventing airway remodeling.^{5,6}

Inhaled corticosteroids are currently regarded as the gold standard in topical anti-inflammatory therapy, and this is reflected in their positioning in current asthma guidelines for the management of patients with mild, moderate, and severe persistent asthma.^{1,2}

Leukotriene receptor antagonists (LTRAs) have recently been introduced as a novel asthma therapy with bronchodilatory and anti-inflammatory properties.⁷ Current guidelines offer the option of using an LTRA instead of an inhaled corticosteroid in patients with mild persistent asthma.¹ Ideally, however, the decision to choose an LTRA in preference to an inhaled corticosteroid should be evidence-based. There have been studies comparing these therapies in patients with moderate persistent asthma but not in patients with mild persistent asthma.⁸⁻¹¹ The studies have shown superiority of low-dose inhaled corticosteroid (beclomethasone or fluticasone) in comparison with LTRA (montelukast or zafirlukast) for effects on asthma control parameters. In particular, there are no data directly comparing inhaled corticosteroid and LTRA with regard to parameters of asthmatic inflammation.

We compared a low dose of hydrofluoroalkane (HFA) triamcinolone acetonide (450 µg/day ex-actuator dose) with the recommended dose of montelukast (10 mg) in patients with mild persistent asthma. HFA-triamcinolone is like CFC-triamcinolone, a suspension equivalent on a microgram basis. We chose bronchial hyperresponsiveness as our primary outcome variable inasmuch as it is an intrinsic component of the asthmatic disease process.

From the Asthma and Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital and Medical School, University of Dundee.

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Reprint requests: B. J. Lipworth, MD, Professor of Allergy and Pulmonology, Asthma and Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, United Kingdom.

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Abbreviations used

AMP:	Adenosine monophosphate
CV:	Coefficient of variation
ECP:	Eosinophil cationic protein
HFA:	Hydrofluoroalkane
ICAM:	Intracellular circulating adhesion molecule
LTRA:	Leukotriene receptor antagonist
PC20:	Provocative concentration of adenosine monophosphate required to produce a 20% fall in FEV ₁
PD20:	Provocative dose of methacholine required to produce a 20% fall in FEV ₁

METHODS

Patients

Patients aged 18 to 65 years were recruited; each had an established diagnosis of mild persistent asthma at the initial screening visit. Prior use of inhaled corticosteroid was permitted in a daily dose up to 800 µg of budesonide/beclomethasone dipropionate or up to 400 µg of fluticasone propionate. All patients were required to have an FEV₁ of at least 80% of predicted normal and at least 70% of predicted normal after placebo run-in. Patients were required to exhibit bronchial hyperresponsiveness to methacholine challenge in terms of a 20% fall in FEV₁ at a provocative dose of methacholine (PD20) of <500 µg (equivalent to a provocative concentration of methacholine of <5 mg/mL), as well as hyperresponsiveness to AMP challenge in terms of a 20% fall in FEV₁ at a provocative concentration of AMP (PC20) of <100 mg/mL.

Study design

The study had a randomized, placebo-controlled, single-blinded crossover design. After an initial screening visit, the study lasted 12 weeks and consisted of 5 phases.

Step-down (phase 1). This phase was necessary only for those patients deemed to be receiving excessive treatment for their asthma severity, in accord with current guidelines.² In brief, step-down was performed initially by stopping long-acting bronchodilators—eg, long-acting oral or inhaled β-agonists and theophylline—for 1 week; this was followed by tapering of the inhaled corticosteroid dose by 50% every 2 weeks until the patient was stable (ie, FEV₁ > 80% of predicted) on ≤800 µg of budesonide/beclomethasone or ≤400 µg of fluticasone propionate daily.

Placebo run-in (phase 2) and washout (phase 4). After screening, all eligible patients entered a 1- to 2-week placebo run-in, receiving a placebo tablet and a placebo inhaler once daily in the evening. This 1- to 2-week placebo was repeated during the washout period after the first randomized treatment.

Randomized treatment (phases 3 and 5). After placebo run-in or washout, patients received 4 weeks of either 450 µg of triamcinolone acetonide daily (as 2 puffs of Azmacort HFA 225-µg inhalation aerosol (ex-actuator dose; Aventis Pharmaceuticals Inc, Bridgewater, NJ) or 10 mg daily of montelukast sodium (as Singulair tablets, Merck Sharp & Dohme Ltd, United Kingdom), both being taken at bedtime. The placebo inhalers were identical in appearance to Azmacort HFA inhalers. The placebo tablets differed slightly in appearance from Singulair tablets; hence, the study has been described as single-blinded. Nevertheless, because none of the patients had previously received montelukast, we believe that they were not aware of whether they were on active treatment or placebo. All medication was supplied in sealed envelopes by an independent third party.

Measurements

At screening, each patient completed a health questionnaire,

spirometry and skin prick allergy testing were performed, and eosinophils, liver function, exhaled breath nitric oxide, and bronchial hyperresponsiveness to methacholine and AMP were measured. The patient's inhaler technique was also assessed through use of a placebo Azmacort HFA inhaler. At all subsequent study visits, diary cards (pertaining to peak expiratory flow rates, symptoms, and rescue inhaler use and including compliance tick charts) were reviewed and measurements were made of spirometry,² exhaled nitric oxide, bronchial hyperresponsiveness (AMP and methacholine challenges, performed on separate days), overnight urinary cortisol, serum osteocalcin, and eosinophil cationic protein (ECP). At selected visits, measurements were made of the plasma circulating vascular adhesion molecules E-selectin and intracellular circulating adhesion molecule 1 (ICAM-1; visits 1, 3, 4, and 6), liver function (visits 1, 3, and 6 only), and blood eosinophils (visits 1, 3, 4, and 6).

Methacholine bronchial challenge was performed according to current guidelines through use of a standardized computer-assisted dosimetric method.^{13,14} In brief, methacholine was administered in cumulative doubling doses from 3.125 to 1600 µg with a microprocessor-controlled dosimeter at 5-minute intervals until a 20% fall in FEV₁ was recorded. AMP bronchial challenge testing was performed as previously described.¹⁵ In brief, AMP was administered in doubling cumulative doses given at 90-second intervals until a fall in FEV₁ of at least 20% was recorded. Measurement of exhaled breath nitric oxide was performed through use of an integrated LR2000 clinical real-time nitric oxide gas analyzer (Logan Research, Rochester, United Kingdom) with an accuracy of 2 parts per billion nitric oxide and a response time of 2 seconds; the procedure described by Kharitonov et al¹⁶ was used.

Each patient filled in a daily diary card every morning and every evening during the placebo and active-treatment phases of the study. Daytime and nocturnal symptoms of asthma were documented according to a 4-point scale, 0 indicating no symptoms and 3 indicating severe symptoms. Each patient also recorded his or her requirement for rescue bronchodilator (short acting β₂-agonist) therapy.

Serum ECP was measured through use of a radioimmunoassay kit (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden). The within-assay coefficient of variation (CV) for analytical imprecision for ECP was 4.1%; the between-assays CV was 8.2%. E-selectin and ICAM-1 were measured through use of enzyme immunoassays (R&D Systems, Abingdon, United Kingdom); the within-assay CV values for E-selectin and ICAM-1 were 1.0% and 2.7%, respectively. Serum osteocalcin was measured through use of a radioimmunoassay kit (DiaSorin Inc, Stillwater, Minn); the between-assays CV for analytical imprecision for osteocalcin was 7.7%.

Each patient was instructed to empty his or her bladder at 10 PM the night before visiting our laboratory and to discard this urine. Patients were instructed to collect all voided urine thereafter until 8 AM the following morning, completing a 10-hour collection. Urinary cortisol was measured with a commercial radioimmunoassay kit (Incstar Ltd., Berkshire, United Kingdom); the within-assay CV for analytical imprecision for urinary free cortisol was 5.5% and the between-assays CV was 6.4%.

Statistical analysis

The study was designed with at least 80% power, using 20 completed subjects to detect a 2-fold (1 doubling dose) difference in methacholine PD20 (the primary endpoint) between treatments through use of a crossover design. Because this was a crossover design, analysis was performed on the 21 patients who completed all visits according to the protocol. The endpoint was considered to be the effects after 4 weeks of treatment. No significant differences in placebo values having been demonstrated either according to treatment or according to sequence, a pooled placebo value was

TABLE I. Demographic data

Patient no.	Sex	Age (y)	FEV ₁ (L)	FEV ₁ (% predicted)	FEF ₂₅₋₇₅ (L/s)	FEF ₂₅₋₇₅ (% predicted)	MCH-PD20 (μg)	AMP-PC20 (mg/mL)	Steroid	Daily dose (μg)	No. of positive skin tests
1	F	18	3.15	86	2.40	56	45	14	BDP	400	8
2	M	26	4.49	102	4.03	80	80	54	BUD	800	4
3	M	41	3.93	88	3.30	72	10	24	BUD	400	5
4	F	31	3.49	117	3.66	89	17	26	BDP	200	5
5	F	44	2.59	92	2.54	73	52	91	BDP	200	2
6	F	21	3.19	97	2.70	65	18	34	BDP	400	7
7	F	24	2.91	95	2.72	67	20	16	BDP	200	5
8	F	20	3.03	98	3.05	75	51	52	—	—	6
9	F	44	2.43	94	1.75	51	17	57	—	—	8
10	M	39	3.84	126	3.35	83	13	4	BDP	200	3
11	F	22	3.22	108	3.69	91	8	30	BDP	600	5
12	M	28	4.70	105	3.85	77	36	9	—	—	3
13	F	27	2.94	85	2.88	70	25	23	—	—	2
14	F	42	2.43	82	1.55	43	61	34	BDP	500	6
15	F	43	3.26	103	2.30	63	115	33	BDP	400	2
16	F	40	2.73	97	2.21	62	67	69	BDP	400	2
17	F	43	2.12	82	1.72	49	70	100	—	—	6
18	M	52	3.25	91	2.39	61	46	22	BUD	400	4
19	M	36	3.62	81	2.34	49	27	59	BDP	200	5
20	F	45	2.69	91	2.99	89	29	54	—	—	5
21	F	18	3.32	102	3.49	85	13	81	—	—	4
Mean		33.5	3.21	96.3	2.81	69.0	30.4§	32.9§	—	200*	5*
SE			(2.3)(0.14)	(2.5)	(0.16)	(3.13)	(5.0)	(5.8)	—	(0-400)	(3-6)

Data are shown for the 21 patients who completed all visits and were included in the analysis. Means (SEs) are shown for all parameters except those marked with the symbol §, which denotes geometric mean (SE), and those marked with the symbol *, which denotes median (interquartile range).

FEF₂₅₋₇₅, Forced expiratory flow at 25% to 75% of forced vital capacity; MCH, methacholine; AMP, adenosine monophosphate; BDP, beclomethasone dipropionate; BUD, budesonide; F, female; M, male.

used for comparison with active treatments. Multifactorial ANOVA and Bonferroni multiple range testing were performed; subject, treatment, sequence, and visit were used as factors. Bonferroni multiple range testing was set at 95% confidence limits. The analysis was performed through use of a Statgraphics statistical package (STS Software Publishing Group, Rockville, Md).

RESULTS

Patients

A total of 36 patients fulfilled the inclusion criteria at the initial screening visit and entered the placebo run-in before randomization; of these, 10 patients did not complete the placebo run-in before randomization at visit 1. Thus, 26 patients were randomized to receive active treatments in crossover fashion. Of these, 5 patients were withdrawn; the remaining 21 patients completed the study. Of these 5 withdrawn patients, each of 3 had an asthma exacerbation (one at visit 6, having just had montelukast; one after visit 3 while on placebo; and one at visit 2, having just had montelukast), 1 withdrew for personal reasons (after visit 3, while on placebo), and 1 had an unexpected pregnancy (after visit 1, while on triamcinolone). Demographic data for the 21 patients successfully completing the study are summarized in Table I.

Baseline values for the primary outcome variable—methacholine PD20—were not different (26 μg [95% CI 17 to 42] after the run-in and 26 μg [95% CI 16-41] after the washout; $P = .94$). There were no significant differences for any of the other points in placebo baseline values after run-in or washout (data not shown).

Anti-asthmatic efficacy

After 2 weeks (data not shown), only those treated with triamcinolone were afforded bronchoprotection against methacholine in comparison with placebo ($P < .05$), whereas bronchoprotection against AMP occurred with both treatments ($P < .05$). Only triamcinolone improved evening peak expiratory flow rates at 2 weeks in comparison with placebo ($P < .05$). Furthermore, at 2 weeks triamcinolone exhibited greater suppression of exhaled nitric oxide than montelukast or placebo ($P < .05$).

At the endpoint (after 4 weeks), both treatments afforded bronchoprotection in comparison with placebo ($P < .05$) for methacholine and AMP challenge, no difference being seen between the treatments (Figs 1-3 and Table II). The geometric mean “fold” difference in methacholine PD20 from placebo was 1.5 (95% CI 1.0 to 2.3) for montelukast and 1.7 (95% CI 1.1 to 2.5) for triamcinolone; the between-treatment difference was 1.09-fold (95% CI 0.73 to 1.63). After 4 weeks, the superiority ($P < .05$) of triamcinolone over montelukast or placebo was demonstrated for all other surrogate inflammatory markers, including breath nitric oxide, blood eosinophils, serum ECP, plasma E-selectin, and plasma ICAM-1. Both treatments improved peak flow after 4 weeks in comparison with placebo ($P < .05$), though the effect of triamcinolone was greater ($P < .05$) than that of montelukast for morning peak flow (between-treatments difference, 13.5 L/min [95% CI 2.5 to 24.6]) and evening peak flow (between-treatments difference, 10.5 L/min [95% CI 1.3

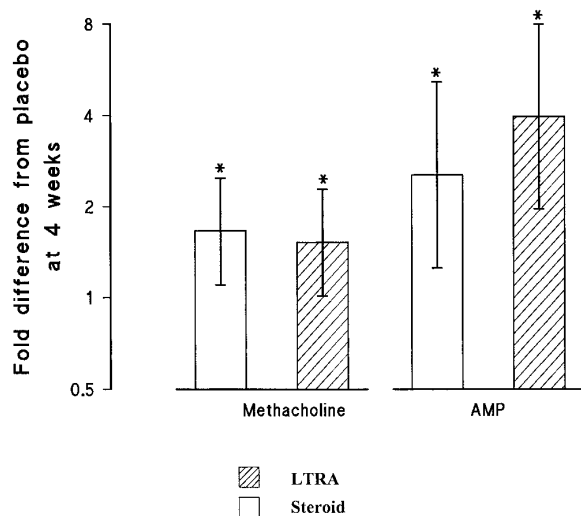


FIG 1. Effects on bronchial hyperresponsiveness: geometric mean "fold" differences (and 95% CIs) from placebo for inhaled corticosteroid and LTRA. * $P < .05$ versus placebo.

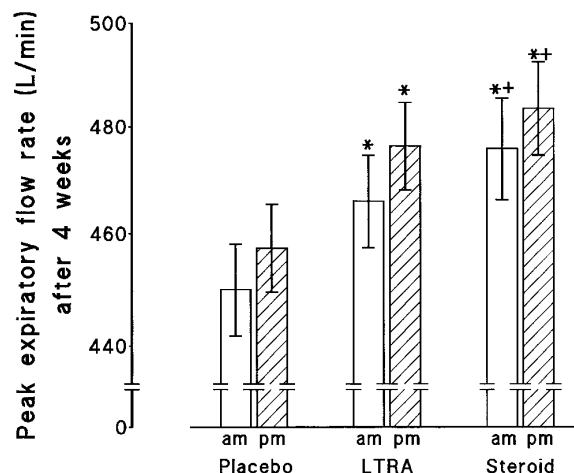


FIG 2. Effects on peak expiratory flow: means (and 95% CIs) for effects of placebo, LTRA, and inhaled corticosteroid on domiciliary peak flow. * $P < .05$ versus placebo. ** $P < .05$ steroid versus LTRA.

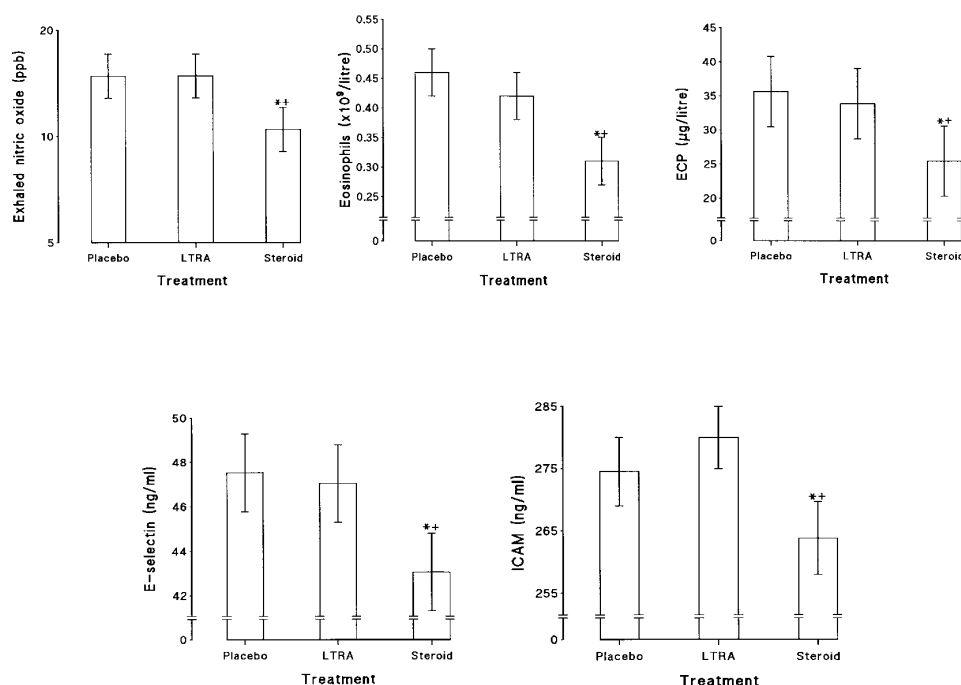


FIG 3. Effects on surrogate inflammatory markers. Arithmetic means (and 95% CIs) are shown for all results except nitric oxide, for which geometric means are shown. * $P < .05$ versus placebo. ** $P < .05$ steroid versus LTRA.

to 19.7]). There were no significant effects on spirometry. Significant improvements ($P < .05$) were seen with triamcinolone with respect to β_2 -agonist use (day and night) and symptoms (night) and with montelukast with respect to night-time β_2 -agonist use and symptoms.

Safety

Triamcinolone but not montelukast reduced overnight

urinary cortisol/creatinine and serum osteocalcin at 2 and 4 weeks in comparison with placebo ($P < .05$; Table II). However, there were no significant differences among triamcinolone, montelukast, and placebo in the number of individual low values for overnight urinary cortisol (10 nmol/10 hours). There were no significant changes in biochemical liver function tests, including alanine transaminase, alkaline phosphate, and bilirubin (data not shown).

TABLE II. Effects at 4 weeks (endpoint)

Bronchial hyperresponsiveness		Methacholine PD ₂₀ [§] (μg)		AMP-PC20 [§] (mg/mL)	
Placebo		26 (21-33)		19 (13-29)	
LTRA		40 (32-50)*		76 (51-114)*	
Steroid		43 (34-55)*		49 (33-73)*	
ANOVA <i>P</i> value (steroid/LTRA vs placebo)		.0074		.0001	
ANOVA <i>P</i> value (steroid vs LTRA)		.62		.20	

Spirometry data		FEV ₁ (L)	FEV ₁ (% predicted)	FEF ₂₅₋₇₅ (L/s)	FEF ₂₅₋₇₅ (% predicted)
Placebo		3.03 (2.93-3.12)	90 (87-93)	2.66 (2.52-2.81)	65 (62-69)
LTRA		3.02 (2.93-3.11)	91 (88-94)	2.58 (2.43-2.72)	63 (60-67)
Steroid		3.10 (3.01-3.19)	92 (90-95)	2.77 (2.62-2.91)	68 (64-71)
ANOVA <i>P</i> value (steroid/LTRA vs placebo)		.34	.53	.18	.16
ANOVA <i>P</i> value (steroid vs LTRA)		.18	.45	.087	.083

Diary card	Morning PEF (L/min)	Evening PEF (L/min)	Day β ₂ use (puffs/12 h)	Night β ₂ use (puffs/12 h)	Day symptoms (units/12 h)	Night symptoms (units/12 h)
Placebo	450 (442-458)	457 (449-465)	1.6 (1.2-1.9)	0.7 (0.5-0.8)	0.7 (0.5-0.9)	0.5 (0.4-0.6)
LTRA	466 (457-475)*	476 (468-485)*	1.2 (0.8-1.5)	0.3 (0.1-0.5)*	0.6 (0.4-0.8)	0.3 (0.2-0.4)*
Steroid	476 (466-485)*†	484 (475-493)*†	0.9 (0.5-1.3)*	0.3 (0.1-0.5)*	0.4 (0.3-0.6)	0.3 (0.2-0.4)*
ANOVA <i>P</i> value (steroid/LTRA vs placebo)	.0006	.0002	.037	.0037	.090	.016
ANOVA <i>P</i> value (steroid vs LTRA)	.020	.028	0.17	0.75	0.21	0.69

Inflammatory markers	Nitric oxide [§] (parts per billion)	Blood eosinophils (× 10 ⁹ /L)	Plasma ICAM (ng/mL)	Plasma E-selectin (ng/mL)	Serum ECP (μg/L)
Placebo	14.8 (12.8-17.1)	0.46 (0.42-0.50)	275 (269-280)	48 (46-49)	36 (30-41)
LTRA	14.9 (12.9-17.2)	0.42 (0.38-0.46)	280 (274-286)	47 (45-49)	34 (29-39)
Steroid	10.5 (9.1-12.1)*†	0.31 (0.27-0.35)*†	264 (258-270)*†	43 (41-45)*†	25 (20-31)*†
ANOVA <i>P</i> value (steroid/LTRA vs placebo)	.0012	.0000	.0012	.0012	.017
ANOVA <i>P</i> value (steroid vs LTRA)	.0054	.0002	.0019	.016	.022

Systemic markers	Overnight urinary cortisol [§] (nmol/10 h)	Overnight urinary cortisol/creatinine [§] (nmol/mmol)	Individual cortisol values [§] <10nmol/10 h	Serum osteocalcin [§] (ng/mL)
Placebo	16.2 (13.1-20.1)	5.3 (4.2-6.5)	4/21 patients (19%)	3.9 (3.5-4.2)
LTRA	16.1 (13.0-20.0)	5.3 (4.2-6.5)	6/21 patients (29%)	3.9 (3.6-4.3)
Steroid	11.3 (9.1-14.1)*†	3.4 (2.7-4.2)*†	7/21 patients (33%)*†	3.2 (2.9-3.5)*†
ANOVA <i>P</i> value (steroid/LTRA vs placebo)	.034	.0088	.29 (steroid vs placebo)	.0028
ANOVA <i>P</i> value (steroid vs LTRA)	.036	.011	.74	.0046

Means (within-treatment 95% CIs) are shown for all values except those marked with the symbol §, which denotes geometric mean.

**P* < .05: steroid/LTRA vs pooled placebo.

†*P* < .05: steroid vs LTRA.

DISCUSSION

For the primary outcome variable of bronchial hyperresponsiveness to methacholine, once-daily treatment with low-dose inhaled corticosteroid or leukotriene antagonist produced similar improvements, though it was noticeable that only the inhaled corticosteroid suppressed other surrogate airway inflammatory markers, including exhaled nitric oxide, circulating eosinophils and ECP,

and circulating vascular cell adhesion molecules. Both treatments significantly improved peak flow, symptoms, and rescue medication, whereas neither treatment had significant effects on spirometry.

Bronchial hyperresponsiveness is associated with airway inflammation and has been used in studies as a non-invasive surrogate.¹⁷⁻¹⁹ Our results are different from those of Westbrook and Pasma,²⁰ who reported that in subjects with mild to moderate asthma, 2 weeks of fluti-

casone propionate 200 µg daily protected against histamine-induced bronchoconstriction to a significantly greater extent than zafirlukast 40 mg daily, the difference being 1.7-fold. Perhaps the findings of Westbroek and Pasma²⁰ reflect (1) the greater potency of fluticasone in comparison with triamcinolone, (2) the twice-daily dosing with fluticasone, and (3) the use of histamine as opposed to methacholine.

Treatment with triamcinolone but not montelukast resulted in significant suppression of blood eosinophils and their activation product ECP. However, other data have shown montelukast to produce a fall in blood eosinophils²; this is relevant, given that the eosinophil is recognized as being an important effector cell in asthmatic airway inflammation. Furthermore, the concentration of serum ECP has been shown to correlate well with activated eosinophils in asthmatic bronchial mucosa and risk of exacerbations.^{22,23} We were rather surprised to observe no fall in exhaled nitric oxide with montelukast in view of reports to the contrary from other investigators.²⁴ Our data nonetheless revealed considerable uniformity in the way that exhaled nitric oxide fell with triamcinolone but not with montelukast.

Our results showed a significant difference between triamcinolone and montelukast with regard to circulating surrogate inflammatory markers but not with regard to bronchial hyperresponsiveness. This might suggest that inhaled corticosteroids have a systemic as well as a topical effect, which would be consistent with the reductions in urinary cortisol and osteocalcin seen with triamcinolone. One might expect a systemically administered drug such as montelukast to influence circulating inflammatory markers. However, it is unclear whether these circulating markers reflect airway inflammation.

Previous studies in moderate persistent asthma have shown a significant but numerically small superiority of inhaled steroid in comparison with leukotriene antagonists.⁸⁻¹¹ Our patients had near normal values for percent of predicted FEV₁, so it was no surprise that this outcome variable showed no significant improvement. It is debatable whether the small difference of 13 L/min in peak flow between triamcinolone and montelukast would be clinically meaningful in patients with mild asthma. Likewise, effects on symptoms and β_2 -agonist use, though statistically significant, were numerically small.

Once-daily triamcinolone produced significant suppression of overnight urinary cortisol and early-morning serum osteocalcin, though the long-term clinical relevance of these changes are uncertain. Administration of the whole daily dose in the evening might have improved its anti-asthmatic efficacy, but at the same time there might have been a trade-off in terms of greater systemic adverse effects. A longer comparison of once-daily and twice-daily dosing schedules would be required to properly evaluate the therapeutic ratio for triamcinolone.

In conclusion, our study showed that there was no difference in effects of inhaled triamcinolone and oral montelukast on the primary outcome variable of bronchial hyperresponsiveness.

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