

Original article

Combined mediator blockade or topical steroid for treating the unified allergic airway

Background: Asthma and allergic rhinitis are manifestations of a single unified allergic airway, for which the best treatment is uncertain.

Objective: To compare the anti-inflammatory efficacy in the unified allergic airway of combined oral mediator antagonism and combined topical steroid.

Methods: Subjects with asthma and perennial allergic rhinitis entered a randomized double blind crossover study comparing montelukast 10 mg and cetirizine 10 mg to extra-fine inhaled beclomethasone 400 mcg/day and intranasal beclomethasone 200 mcg/day, each taken once daily for 2 months, after 2-week placebo washouts. Measurements were made after each washout and randomized treatment, comprising: methacholine PC₂₀, exhaled and nasal nitric oxide, blood eosinophils and eosinophilic cationic protein, symptoms, lung and nasal function tests.

Results: Seventeen patients completed per protocol. For PC₂₀ and exhaled nitric oxide, only combined topical steroid produced improvements ($P < 0.005$) from placebo baseline. Combined steroid was superior by a 0.93 (95% CI 0.14–0.93, $P < 0.05$) doubling dilution difference for PC₂₀ and a 0.99 (95% CI 0.9–15.1, $P < 0.01$) doubling difference for exhaled nitric oxide. Both treatments attenuated eosinophils and eosinophilic cationic protein, and reduced nasal symptoms ($P < 0.05$). Only steroid improved nasal nitric oxide ($P = 0.05$) and asthma symptoms ($P < 0.05$). Neither treatment affected lung or nasal function tests.

Conclusion: Combined topical steroid and combined mediator antagonism both attenuated systemic inflammation in the unified allergic airway, but only the former reduced bronchial and nasal inflammatory markers. The relevance of this to exacerbations and airway remodelling needs to be defined.

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Asthma and allergic rhinitis are clinically overlapping manifestations of a single unified allergic airway disease sharing many pathological and epidemiological characteristics. While estimates of the incidence of allergic rhinitis in patients with asthma vary (1), undoubtedly the two diseases are strongly associated (1, 2). They share a common inflammatory aetiology characterized by infiltration of the respiratory mucosa with activated eosinophils, mast cells and Th2 lymphocytes, and a pattern of

cytokine and immunoglobulin production suggestive of allergic degranulation of these cells within the airway (1, 3, 4). Mediators of this inflammatory process which can also act as surrogates of disease activity such as IL-4, IL-5 and eosinophilic cationic protein (ECP) are found in elevated concentrations in the broncho-alveolar lavage and nasal lavage fluid of patients with asthma and allergic rhinitis (3, 5–7).

Topical steroids have been shown to reduce airway hyper-responsiveness (AHR) and exacerbation rate, suppress inflammatory surrogates in asthma such as fractional exhaled nitric oxide (FE_{NO}), and reduce nasal and asthma symptoms (1, 8–10). In patients with allergic rhinitis and asthma it has further been shown that topical intranasal steroids can have downstream effects on the rest of the airway improving pulmonary function and AHR (1, 11). Leukotriene receptor antagonists are now established as add on treatment for persistent asthma at step 3 of guidelines, blocking the action of potent

Abbreviations: AHR, airway hyper-responsiveness; AS, Asthma Symptoms Score; CMA, combined (histamine and leukotriene) mediator antagonism; CTS, combined (bronchial and nasal) topical steroid; ECP, eosinophilic cationic protein; Eos, eosinophil count; FE_{NO}, fractional exhaled nitric oxide; FEF_{25–75} forced expiratory flow rate from 25 to 75% of vital capacity; FEV₁, forced expiratory volume in 1 s; (HFA)-BDP, (hydrofluoroalkane-134a)-beclomethasone dipropionate; PC₂₀, provocation concentration leading to a 20% fall in FEV₁; PEF, peak expiratory flow rate; PNIF, peak nasal inspiratory flow rate; TNS, total nasal symptoms score.

pro-inflammatory cysteinyl leukotrienes and attenuating influx of eosinophils to the bronchial mucosa with appreciable improvements in pulmonary function and symptoms (12). Their effects are less well documented in perennial allergic rhinitis, but increasingly the evidence indicates potential for their use in this context as well (13, 14). It has also been shown that in mild to moderate asthmatics, combined mediator antagonism (CMA) with leukotriene and H_1 receptor antagonists can have additive effects on bronchial allergen challenge and AHR (15, 16).

These studies indicate that pharmacotherapy with either combined topical corticosteroid (CTS) or CMA should be of benefit in treating either component of the allergic unified airway. A number of investigators have directly compared the impact of both these strategies on upper and lower airway inflammation in isolation (17–20), but uncertainty remains about the efficacy of each approach on the airway as a whole (21).

We have therefore compared treatment with once daily CTS using 400 mcg/day extra fine inhaled HFA-beclomethasone dipropionate (BDP) plus 200 mcg/day intra-nasal BDP against once daily CMA using 10 mg oral montelukast plus 10 mg oral cetirizine, primarily focusing on the effects on both systemic (i.e. blood eosinophils and ECP) and airway specific inflammatory outcome measures (PC_{20} , exhaled and nasal nitric oxide), in patients with persistent asthma and concomitant perennial allergic rhinitis.

Methods

Patients

Male or female patients, aged 16–75 years, with perennial allergic rhinitis and asthma were identified from our database of patients in the Tayside region, Scotland. All participants gave informed consent and the protocol was given a favourable opinion by the Tayside committee on medical research ethics.

Those with methacholine $PC_{20} < 4$ mg/ml, forced expiratory volume in 1 s (FEV_1) 60–90% predicted or forced expiratory flow rate from 25 to 75% of vital capacity (FEF_{25-75}) $< 70\%$ predicted, and skin prick positive responses to one or more perennial allergens were invited to participate. Subjects treated with prednisolone within the preceding 3 months, or with nonallergic conditions affecting nasal airway patency (significant septal deviation or nasal polyps) were excluded.

Figure 1 illustrates the study design.

Interventions

A double blind, double dummy, crossover study was conducted in five visits to the research laboratory. Each randomized treatment (8 weeks of either CTS or CMA) followed a 2-week placebo washout period.

Participants withheld certain medications before each visit; short acting beta agonists for 6 h, caffeine for 8 h. Other drugs were withheld for the duration of the study; long-acting beta agonists from 2 days before screening, and leukotriene antagonists, antihistamines, and theophyllines from 4 days before

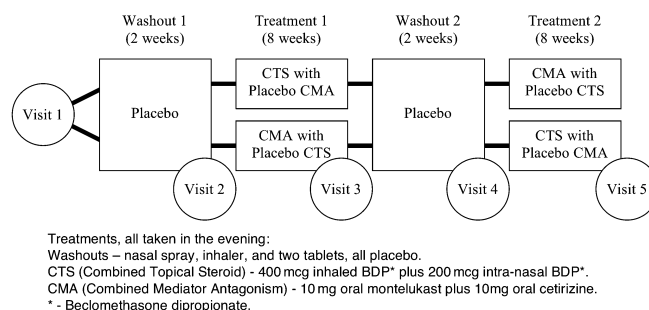


Figure 1. Study design.

screening. For subjects prone to symptoms of allergic conjunctivitis, cromoglicate eye drops were provided to use as required. Inhaled short acting beta agonists were continued as required, but if these were used within the 6 h before a visit, the visit was deferred.

Visit 1 (screening) determined inclusion and exclusion status. Study assessments were made after pretreatment washouts (i.e. at baseline visits 2 and 4) and after each randomized treatment period (i.e. visits 3 and 5).

Measurements

Methacholine challenge. Challenge was conducted to determine the methacholine PC_{20} using a method consistent with American Thoracic Society guidelines (22).

Forced expiratory volume in 1 s. Spirometry was performed according to the ATS best test criteria (23).

Exhaled and nasal nitric oxide. Exhaled FE_{NO} and nasal nitric oxide (nNO) measurements were conducted in accordance with the joint American Thoracic Society and European Respiratory Society guidelines (24).

Domiciliary peak expiratory flow and peak nasal inspiratory flow rates. Best of three peak expiratory flow (PEF) and peak nasal inspiratory flow (PNIF) measurements were recorded each morning in a subject diary using a Mini-WrightTM PEF meter and an In-Check[®] PNIF meter (Clement Clarke International Ltd, Harlow, UK).

Domiciliary asthma symptoms and total nasal symptoms scores. Asthma symptoms (AS) and total nasal symptoms (TNS) scores were recorded in the subject diary. Asthma severity was graded on a single 4 point Likert scale (no symptoms, mild, moderate, or severe symptoms). Assessments were recorded twice daily and summed. The TNS score was the sum of scores for nasal run, blockage, itch and sneeze, each measured daily on the same Likert scale.

Blood Eosinophil Count. Blood eosinophil counts (Eos) were determined using an XE-2100 laser flowcytometer (Sysmex UK Ltd, Milton Keynes, UK).

Serum eosinophilic cationic protein. Serum ECP was quantified using an enzyme immunoassay method (UniCAP; Sweden Diagnostics UK Ltd, Milton Keynes, UK).

Sample size

The study was powered (> 80%) on the primary outcome of PC₂₀ with a sample size of 16 patients completed per protocol to detect a one doubling dilution shift with an overall alpha error of 0.05 (two-tailed). The within subject standard deviation for PC₂₀ is 0.96 doubling dilutions (25).

Blinding

Identical placebos were used for both drug combinations to maintain double blinding of both treatments and washouts. At any point in the study, participants used a nasal spray, a metered dose inhaler and two tablets. During washouts all medications were placebos, during CTS periods both tablets were placebos, and during CMA periods the inhaler and nasal spray were placebos.

Statistical methods

Outcome summaries. Exhaled FE_{NO} and nNO were analysed as the mean of three measurements. PEF, PNIF, AS and TNS were analysed as the means of measurements for the week preceding each visit.

Normality assessments. Each outcome was assessed for normality using Shapiro–Wilk tests and by eye, with consideration of previous data sets and literature.

Outcome analyses. Treatment effects were calculated as change from prior baseline, and differences between these effects calculated for CTS vs. CMA. Paired *t*-tests were applied to determine 95%

confidence intervals and *P*-values for the probabilities of no effect and no difference between treatments, respectively.

Carryover and sequence effect analyses. A carry-over effect analysis was conducted for each outcome by testing for differences in the sums of treatment effects (CTS + CMA) or in the differences between treatment effects (CTS – CMA) for randomization groups using independent sample *t*-tests.

Pollen level effects analysis. For subjects sensitive to grass pollen, a further analysis was conducted to exclude any confounding effect of seasonal exposure during the study. Pollen exposures were estimated from daily pollen counts for three prior years. An independent samples *t*-test was applied to test for differences between randomized treatment groups for change in pollen levels for CTS vs. baseline cf. CMA vs. baseline.

All analyses were performed using SPSS for Mac OS X (v11) © 2005, SPSS Inc., Chicago, IL, USA.

Results

Participant flow

Twenty-three participants were randomized and 17 completed the study. Demographics are presented in Table 1. Ten participants received CMA first, seven received combined steroid treatment first. None deviated from their intended treatments. Two participants withdrew when they left the area, one was withdrawn with uncontrolled asthma, and three further were withdrawn due to potential adverse drug effects; described later.

Table 1. Participant demographics

Patient number	Gender	Age (years)	FEV ₁ *	FEF _{25–75} *	PC ₂₀ (mg/ml)	PNIF (l/min)	GINA severity	SPT†
1	F	20	118	99	0.185	140	Moderate	GP, HDM
2	M	42	81	54	0.428	145	Mild	HDM, C
3	F	23	102	70	1.759	60	Moderate	GP, HDM, D, C
4	F	66	114	71	1.328	120	Mild	HDM
5	F	52	97	55	2.103	60	Severe	GP, HDM, C
6	F	49	104	71	0.145	150	Mild	HDM, C
7	F	37	98	86	2	100	Mild	GP, HDM, C
8	M	49	75	56	2.665	150	Severe	GP, HDM
9	F	55	78	50	0.861	70	Moderate	HDM, D, C
10	M	51	84	47	0.883	100	Mild	GP, HDM
11	F	67	75	65	1	150	Moderate	HDM
12	F	74	71	29	2.919	60	Moderate	GP, HDM, C
13	F	52	70	51	0.574	100	Moderate	GP, WP, HDM, D, C
14	F	22	68	37	0.386	75	Severe	HDM
15	F	16	75	47	1.587	100	Severe	GP, HDM, D, C
16	F	32	92	70	1.414	240	Severe	GP, WP, HDM, D, C
17	F	48	101	60	3.688	60	Severe	GP, HDM
18	M	63	92	65	0.675	160	Mild	GP, WP, HDM, D, C
19	F	38	77	59	0.686	140	Mild	HDM, D
20	M	31	80	74	1.123	130	Mild	GP, HDM, D, C
21	F	38	93	63	0.153	150	Moderate	GP, HDM
22	M	35	76	35	0.052	200	Moderate	GP, TP, HDM, D, C
23	F	32	87	59	0.427	150	Mild	GP, HDM
Mean (SEM)		43.2 (3.2)	88 (2.9)	61 (3.2)	1.2 (0.19)	113 (10.3)		

*FEV₁ and FEF_{25–75} expressed as percentage of predicted value.

†Positive Skin Prick Test reaction to the following aeroallergens: cats (C), dogs (D), grass pollen (GP), house-dust mite (HDM), tree pollen (TP) and weed pollen (WP).

Baseline data

With the exceptions of PC₂₀, ECP, FE_{NO}, and nNO, all other outcomes were found to be normally distributed, and so were summarized and analysed on their natural (arithmetic) scale. PC₂₀, ECP, FE_{NO}, and nNO were analysed on a logarithmic scale (log₂), so data are presented as geometric means, and doubling changes.

There were no significant differences between pretreatment placebo baselines (i.e. after each washout) for any outcomes, so for the purpose of this summary only, baselines have been pooled in Table 2.

Within and between treatment effects

Measurements for all outcomes and between treatment differences are presented in Table 2. Treatment effects and between treatment differences for the lower airway (PC₂₀, FE_{NO}, and AS), upper airway (nNO and TNS) and systemic inflammatory markers (Eos and ECP) are summarized in Figs 2–4, respectively.

Combined topical steroid treatment led to significant improvements compared with placebo baseline in: PC₂₀ ($P < 0.005$), FE_{NO} ($P < 0.0005$), AS ($P < 0.05$), TNS ($P < 0.05$), Eos ($P < 0.005$) and ECP ($P < 0.01$).

Combined mediator antagonism treatment led to significant improvements compared with placebo baseline in TNS ($P < 0.05$), Eos ($P < 0.05$) and ECP ($P < 0.05$).

Significant superiority was seen for CTS over CMA in PC₂₀ ($P < 0.05$) and FE_{NO} ($P < 0.01$).

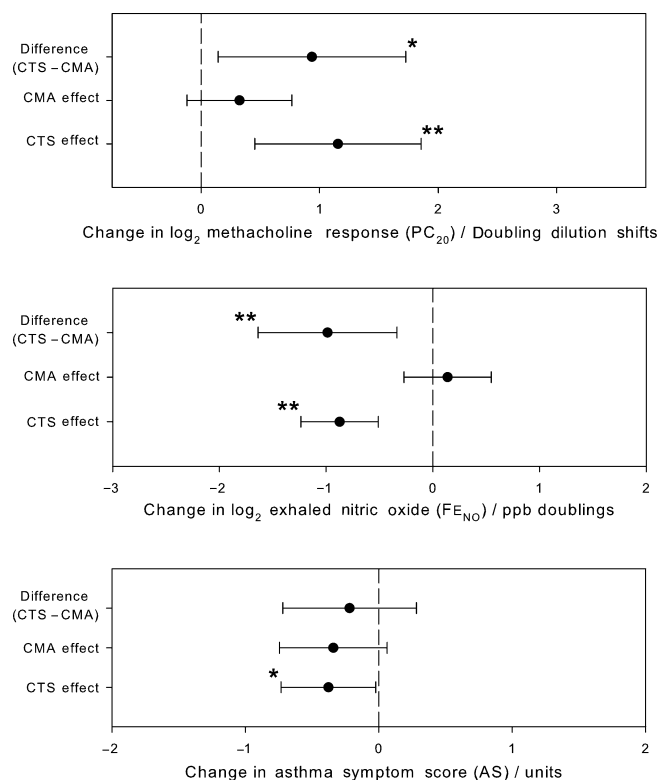


Figure 2. Lower airway outcomes (PC₂₀, FE_{NO} and AS). Means and 95% confidence intervals for the effects of combined topical steroid (CTS), combined mediator antagonism (CMA), and differences (CTS - CMA). Statistical significance is denoted by * $P < 0.05$; ** $P < 0.01$.

Table 2. Summary statistics of all outcomes for pooled placebo baselines (i.e. after placebo washouts before each randomized treatment) and after randomized treatments with combined intranasal and inhaled steroid (CTS) or combined mediator antagonism (CMA)

	Placebo baseline, mean (SEM)	CTS mean (SEM)	CMA mean (SEM)	CTS - CMA difference (95% CI)
Log ₂ PC ₂₀ , mg/ml	-0.91 (0.42)	0.00 (0.48) $P = 0.003$	-0.49 (0.41) $P = 0.14$	0.93 (0.1 to 1.7) $P = 0.02$
log ₂ FE _{NO} , ppb	3.3 (0.21)	2.7 (0.19) $P = 0.0001$	3.4 (0.28) $P = 0.48$	-0.99 (-1.6 to -0.3) $P = 0.006$
log ₂ nNO, ppb	9.2 (0.10)	9.0 (0.16) $P = 0.05$	9.1 (0.17) $P = 0.51$	-0.33 (-0.77 to 0.11) $P = 0.12$
FEV ₁ , l	2.5 (0.13)	2.5 (0.15) $P = 0.11$	2.7 (0.16) $P = 0.11$	0.01 (-0.19 to 0.21) $P = 0.92$
PEF, l/min	409 (19)	411 (20) $P = 0.51$	426 (21) $P = 0.09$	-10.3 (-32 to 12) $P = 0.34$
PNIF, l/min	124 (9.6)	131 (13) $P = 0.58$	127 (14) $P = 0.63$	2.9 (-13 to 19) $P = 0.71$
AS, units	0.62 (0.18)	0.29 (0.11) $P = 0.04$	0.40 (0.13) $P = 0.09$	-0.22 (-0.72 to 0.28) $P = 0.36$
TNS, units	2.2 (0.44)	0.89 (0.34) $P = 0.02$	1.12 (0.43) $P = 0.03$	0.18 (-1.0 to 1.4) $P = 0.75$
Eos, $\times 10^9$ /l	0.36 (0.04)	0.25 (0.03) $P = 0.005$	0.26 (0.03) $P = 0.02$	-0.04 (-0.23 to 0.15) $P = 0.62$
log ₂ ECP, mcg/l	4.7 (0.23)	4.25 (0.29) $P = 0.006$	4.13 (0.34) $P = 0.01$	0.03 (-0.63 to 0.69) $P = 0.92$

Data presented are measurement means with standard errors, and mean differences with 95% confidence intervals. PC₂₀, FE_{NO}, nNO and ECP data are shown on the log₂ scale, so the differences represent the number of doubling changes between randomized treatments.

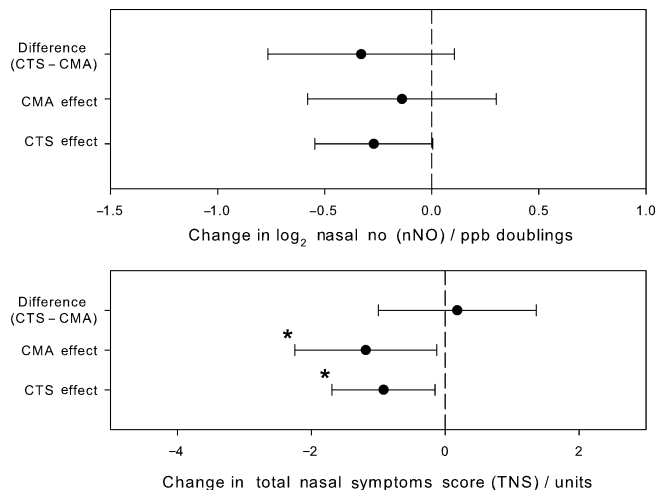


Figure 3. Upper Airway outcomes (nNO and TNS) Means and 95% confidence intervals for the effects of combined topical steroid (CTS), combined mediator antagonism (CMA), and differences (CTS – CMA). Statistical significance is denoted by * $P < 0.05$; ** $P < 0.01$.

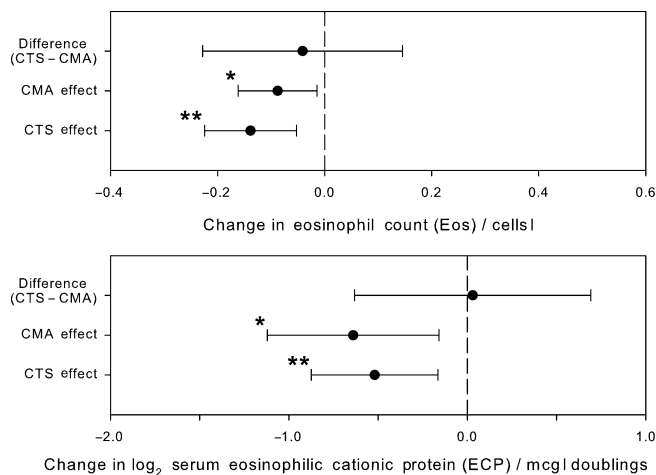


Figure 4. Systemic Inflammatory outcomes (Eos and ECP) Means and 95% confidence intervals for the effects of combined topical steroid (CTS), combined mediator antagonism (CMA), and differences (CTS – CMA). Statistical significance is denoted by * $P < 0.05$; ** $P < 0.01$.

Neither randomized treatment had a significant effect on nNO, FEV₁, PEF, or PNIF, although the CTS effect on nNO approached significance ($P = 0.054$).

There were no significant differences between randomization groups for carryover or sequence effects for any of the outcomes. No significant differential effect was seen for estimated total pollen exposures by treatment group ($P = 0.295$).

Adverse events

During the study, one patient was withdrawn with diarrhoea, which later unblinding showed was after

CTS, but before CMA. Another was withdrawn after developing a severe skin rash during CMA and after CTS. A third withdrew complaining of itchy skin during CMA and before CTS.

One participant developed oral thrush after taking CTS, before CMA. Two participants developed upper respiratory tract infections; one during the initial placebo washout, and another while taking CTS and before CMA. No serious adverse events occurred.

Discussion

The results of the present study showed that for the primary outcome measure of methacholine AHR, treatment for 2 months with CTS but not CMA conferred a significant improvement in PC₂₀ relative to the placebo baseline, while there was also evidence of significant superiority for the effects of CTS over CMA.

We chose not to exclude subjects that were sensitive to pollens, but ensured that all subjects were sensitive to at least one perennial allergen. Although the study continued throughout the year, tests found no significant differences in pollen exposures by treatment period ($P = 0.295$) and randomization should have ensured that seasonal exposure introduced no systematic bias. Thus, no confounding effect is expected.

Airway hyper-responsiveness to methacholine has been shown to be a sensitive measure of bronchial inflammation, and may also be related to airway remodelling (26, 27). The magnitude of difference between the two treatment strategies amounted to approximately a one doubling-dilution shift in methacholine responsiveness, reflecting the superiority of CTS over CMA treatment in suppressing lower airway inflammation. The same pattern of difference between CTS and CMA was observed for exhaled nitric oxide, lending further weight to the supposition that once daily CTS confers superior anti-inflammatory activity than CMA on the lower airway. On the upper airway only CTS produced a reduction ($P = 0.05$) in nasal nitric oxide, again reinforcing the better anti-inflammatory spectrum of CTS on the unified airway.

The study primary outcome was methacholine PC₂₀, for which the study was adequately powered *a priori*. Analysis of the secondary outcomes should be considered potentially underpowered and exploratory, especially where no significant effects were seen. Nonetheless, many interesting effects and trends were noted.

There were no significant changes in PNIF, FEV₁, and PEF with either treatment compared with placebo baseline, but this is perhaps not surprising as these measures are distant from the underlying inflammatory process and are more reflective of airway calibre. Previous studies by Sont et al. and Green et al. demonstrated that inhaled steroid therapy for asthma guided by inflammatory surrogates (i.e. methacholine AHR or sputum eosinophils) rather than lung function (i.e. FEV₁ or

PEF) leads to fewer exacerbations and reduced airway remodelling over time (27, 28). Notably, in the study undertaken by Green et al., there were reductions in all inflammatory surrogates including sputum eosinophils, FE_{NO} , and methacholine AHR, but no difference in PEF, FEV_1 , symptoms, reliever use or quality of life. These studies have underscored the necessity to ensure that pharmacotherapy for asthma is effective at modulating the underlying airway inflammation, and not simply directed at improving lung function. This is an important observation in asthmatics with mild to moderate disease (as in our cohort) in which a demonstrable improvement in these spirometric parameters would be difficult to detect given the mild nasal and asthma symptoms at baseline after the initial placebo washout period.

We observed significant improvements in nasal symptoms with CTS and CMA compared with placebo baseline, while only CTS led to a significant reduction in asthma symptoms, which was mirrored by a reduction in exhaled nitric oxide. Interestingly, the improvement in nasal symptoms with CMA was not associated with any reduction in nNO , in contrast to CTS where there were reductions in both outcome measures.

The observed improvement in asthma symptoms while statistically significant was of small magnitude and of uncertain clinical relevance. In this regard, it is important to point out that our patients were selected *a priori* according to the presence of AHR (the primary outcome variable) and not on the basis of symptoms. We also included 2-week washout periods before each randomized treatment during which all steroid therapy was withdrawn and replaced by placebo inhalers and nasal sprays to ensure that the potential inflammatory signal was as high as possible before the subsequent randomized active treatment blocks.

Another interesting observation from our study is the apparent disconnect between systemic (i.e. blood eosinophils and serum ECP) and airway specific (i.e. methacholine PC_{20} , FE_{NO} and nNO) markers of inflammation with respect to each treatment strategy. Thus, while CMA and CTS were equally effective in reducing systemic markers, only CTS significantly reduced both systemic and airway specific inflammatory surrogates. Assuming there is no disconnect between the different inflammatory markers chosen – different markers were measured in the serum and the airway – this suggests that topical steroid not only leads to effective attenuation of local airway inflammation, but also has an adjunctive downstream effect on extra-pulmonary eosinophils and eosinophil activation.

It could be argued that the peripheral effects on inflammatory measures observed with CTS may be the result of systemic absorption of BDP from the nose and lung, but in balance we feel this is an unlikely explanation. Although there is some evidence that BDP can lead to growth suppression at comparable doses in children (29, 30), other previous work has shown that neither

400 mcg daily of the same inhaled HFA-BDP formulation (i.e. the same dose as in the present study), nor 400 mcg daily of the same intra-nasal aqueous BDP formulation (i.e. twice the dose used in the present study) exhibit significant systemic bioavailability in terms of adrenal suppression in adults (31, 32). Therefore, the systemic bioavailability of each moiety at these doses is low and unlikely to exert direct suppressive effects on peripheral bone marrow eosinophil progenitors. In our opinion, a more plausible explanation is that effective modulation of the inflammatory process in the airway leads to a reduction in cytokine production reducing in turn bone marrow eosinophil production and degranulation by circulating cells.

We were somewhat surprised that CMA which included montelukast for 2 months duration did not produce a significant change in AHR given the findings of a previous study by Dempsey et al. in mild atopic asthmatics where the same drug produced a significant reduction in methacholine PC_{20} after 2 weeks (33). However, it is also worth noting that in the same study montelukast did not produce any significant reduction in FE_{NO} .

No significant sequence or carryover effects were detected in our study to suggest that the lack of effects of CMA on AHR and FE_{NO} were false negative findings.

In patients with atopic asthma and seasonal allergic rhinitis, we have previously shown that CMA and CTS were equally effective on symptoms and lung function, and that only CTS suppressed FE_{NO} , but the converse applied for effects on adenosine monophosphate challenge (19). There are several important differences between this previous report and the current study. In the previous report, patients received 2 weeks of treatment compared with 8 weeks in the present study, adenosine monophosphate rather than methacholine was used, no systemic inflammatory markers were evaluated, and patients had seasonal rather than perennial allergic rhinitis.

Previous comparative studies in patients with either asthma or allergic rhinitis alone have had conflicting results. In seasonal allergic rhinitis, we have shown comparable efficacy on symptoms and PNIF with both intra-nasal steroid and CMA (18, 20), while others have shown superiority with intra-nasal steroid (34). Equally, there are conflicting data to support additivity on nasal symptoms for CMA compared with anti-histamine alone in seasonal allergic rhinitis (35, 36).

Treatment of the upper airway may be of benefit in asthmatic patients leading to better symptom control, improved pulmonary function, reduced lower airway inflammation and possibly fewer exacerbations (1, 37, 38). Controversy remains over the precise mechanism by which the nose and lungs interact, and exactly how treatment for rhinitis modulates the downstream inflammatory mechanisms (39, 40). While our study has demonstrated that treatment of the unified airway with CTS is superior to CMA on asthmatic inflammation, the relative

contribution of the inhaled and intranasal steroid components remains to be established. A limitation of our study is that it did not contain a comparator arm with inhaled steroid alone at the same dose (i.e. with concomitant intranasal placebo), or an arm containing a lower dose of inhaled steroid (e.g. 100 mcg daily of extra-fine HFA BDP) plus intra-nasal steroid to assess whether the latter confers inhaled steroid sparing effects. Moreover, the effects over time on airway remodelling and disease exacerbation of pharmacotherapy targeted toward modulation of the inflammatory process needs to be examined more closely.

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