Effects of Adding Either a Leukotriene Receptor Antagonist or Low-Dose Theophylline to a Low or Medium Dose of Inhaled Corticosteroid in Patients With Persistent Asthma*

Owen J. Dempsey, MBChB; Stephen J. Fowler, MBChB; Andrew Wilson, MD; Gwen Kennedy, PhD; and Brian J. Lipworth, MD

Study objectives: To evaluate the effect of adding zafirlukast or low-dose theophylline to a beclomethasone dipropionate (BDP) extra-fine hydrofluoroalkane aerosol on bronchial hyperresponsiveness as the primary outcome variable.

Methods: Twenty-four patients with mild-to-moderate asthma were studied using a randomized crossover design with the following three treatment blocks: (1) beclomethasone, 100 μg/d, alone for the first 2 weeks followed by 400 μg/d alone for the next 2 weeks; (2) beclomethasone, 100 μg/d, followed by 400 μg/d, with the addition of zafirlukast, 20 mg bid; (3) beclomethasone, 100 μg/d, followed by 400 μg/d, with the addition of theophylline, 200 to 300 mg bid. Measurements were made after 2 and 4 weeks of each treatment and at pretreatment baseline.

Results: The mean trough plasma theophylline concentration was 6.7 mg/L, coinciding with the anti-inflammatory target range (ie, 5 to 10 mg/L). The provocative dose of methacholine causing a 20% fall in FEV₁ (as doubling dose difference from baseline) was significantly (p < 0.05) greater with beclomethasone, 100 μg, plus zafirlukast (1.1 doubling dose) but not with beclomethasone, 100 μg, plus theophylline (0.7 doubling dose) compared to beclomethasone, 100 μg alone (0.4 doubling dose), but not compared to beclomethasone, 400 μg alone (1.1 doubling dose). There were also significant (p < 0.05) differences between beclomethasone, 100 μg, plus zafirlukast (but not BDP, 100 μg, plus theophylline) vs beclomethasone, 100 μg, alone in terms of nitric oxide level, midexpiratory phase of forced expiratory flow, and peak expiratory flow. There were no further significant improvements observed with the addition of zafirlukast or theophylline to beclomethasone, 400 μg.

Conclusions: A leukotriene receptor antagonist, but not low-dose theophylline, conferred significant additive anti-inflammatory effects to therapy with a low-dose inhaled corticosteroid but not to that with a medium dose of an inhaled corticosteroid. Thus, optimizing the dose of inhaled corticosteroid as monotherapy would seem to be the logical first step, which is in keeping with current guidelines.

Key words: airway hyperresponsiveness; asthma; beclomethasone; theophylline; zafirlukast

Abbreviations: BDP = beclomethasone dipropionate; CI = confidence interval; CV = coefficient of variation; HFA = hydrofluoroalkane; ICAM = intercellular adhesion molecule; NO = nitric oxide; PD₂₀ = provocative dose of a substance causing a 20% fall in FEV₁

Asthma is recognized to be a chronic inflammatory disorder of the airways, with many cells and cellular elements playing a role.1 Inflammation occurs throughout the lungs, extending from proximal

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Abnormalities in airway responsiveness, inflammation, and airway hyperresponsiveness occur in asthma, and contribute to the pathogenesis of the disease.2-6 The pathogenesis of asthma is thought to be the consequence of both acute and chronic inflammation in the airways, involving many cells and mediators.7-9 Inflammation occurs throughout the lungs, extending from proximal...
airways through to alveolar tissue.2–4 This airway inflammation can be detected early in the course of the disease, often before patients have noted symptoms.5,6 Consequently, early recognition of airway inflammation may afford the opportunity for therapeutic intervention, thereby preventing irreversible airway remodeling.7,8

Therapeutic strategies are available to target inflammation present in the small airways.9 These may be reached systemically, using tablet therapies such as oral theophyllines or leukotriene receptor antagonists, both of which are believed to have a combination of weak anti-inflammatory and bronchodilatory effects.10,11 Alternatively, with the development of extrafine hydrofluoroalkane (HFA) corticosteroid aerosols, it is now possible to target the small airways more effectively using topical therapy.12

Inhaled corticosteroids currently remain the “gold standard” in topical anti-inflammatory therapy, and this is reflected in their positioning in UK and US asthma management guidelines, for patients with mild, moderate, and severe persistent asthma.1,13 Nevertheless, it is also recognized that long-term treatment with high doses of inhaled corticosteroids may result in the potential for systemic adverse effects.14

The aim of this study was to evaluate the effects of adding either low-dose oral theophylline or leukotriene receptor antagonist to the treatment of patients with persistent asthma, who already are receiving a low-to-medium dose of an inhaled corticosteroid. We elected to use low-dose theophylline in order to achieve trough plasma levels to coincide with the modern anti-inflammatory target range of 5 to 10 mg/L. Bronchial hyperresponsiveness to methacholine challenge was chosen a priori as the primary outcome variable as it is considered to reflect the underlying inflammatory process in asthma and is more sensitive than conventional lung function variables in patients with mild-to-moderate disease.

**Materials and Methods**

**Patients**

Patients who were recruited were between the ages of 18 and 65 years with an established diagnosis of mild-moderate persistent asthma requiring prior inhaled steroid use of ≤1000 µg budesonide/beclomethasone dipropionate (BDP) or ≤500 µg fluticasone propionate daily. They were required to have an FEV₁ of at least 70% of the predicted normal value at screening and were required to exhibit hyperresponsiveness to methacholine challenge in terms of a provocative dose of a substance (ie, methacholine) causing a 20% fall in FEV₁ (PD20) of <500 µg (which is equivalent to a provocative concentration of methacholine causing a 20% fall in FEV₁ of <5 mg/mL). The Tayside Medical Ethics Committee granted ethical approval to the study, and informed, written consent was obtained from all patients.

**Study Design**

The study had a randomized, placebo-controlled, single-blind, double-dummy, three-way crossover design. Following an initial screening visit, all eligible patients entered a 7 to 10 days placebo run-in. Thereafter, in randomized sequence, each patient received 4 weeks of active treatment, each active treatment being preceded by or separated by either placebo run-in or washout (Fig 1). The three active treatments were as follows:

1. BDP HFA 134a formulation (QVAR Autohaler; 3M Health Care Ltd; Loughborough, UK; 50 µg/100 µg per actuation) at low dose (50 µg bid as 1 puff bid) for the first 2 weeks followed by an increased dose (200 µg bid as 2 puffs bid) for the next 2 weeks, with a placebo tablet given twice daily throughout the 4 weeks.
2. BDP HFA, 50 µg bid for the first 2 weeks followed by 200 µg bid for the next 2 weeks, but in addition zafirlukast (Accolate; AstraZeneca; King’s Langley, UK; 20 mg per tablet), 1 tablet twice daily (ie, 40 mg daily given throughout the 4 weeks).

![Figure 1. Study design. Randomized treatment A = beclomethasone, 100 µg daily for 2 weeks, followed by beclomethasone, 400 µg daily for 2 weeks; randomized treatment B = treatment A + oral low-dose theophylline; randomized treatment C = treatment A + oral zafirlukast.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21980/)
3. BDP HFA, 50 μg bid for the first 2 weeks followed by 200 μg bid for the next 2 weeks, but in addition theophylline (Uniphilin Continuous sustained release 200–mg or 300–mg tablets; Napp Pharmaceuticals; Cambridge, UK), one tablet (ie, 200 or 300 mg twice daily throughout the 4 weeks [the 300–mg dose was only for patients weighing >80 kg, and these patients received 200 mg bid for first week and the higher 300–mg dose bid for the remaining 3 weeks]).

Measurements

Screening Visit: Patients had methacholine PD20 measured on two separate visits to assess the protection afforded 30 min after a 400-μg dose of albuterol (Ventolin Accuhaler [200 μg per actuation]; Glaxo Wellcome UK Ltd; Uxbridge, UK). The inhaler technique was assessed using a placebo inhaler and a checking device (In-check; Clement Clarke International Ltd; Harlow, UK).

Study Visits: At all visits, diary cards were reviewed and measurements were made of spirometry, exhaled nitric oxide (NO) concentration, methacholine bronchial challenge, and overnight (ie, 10:00 pm to 8:00 am) urinary cortisol/creatinine levels. At selected visits, blood was taken for measurement of eosinophil levels, liver function, vascular cell adhesion molecule levels, and theophylline concentrations (visits 1, 3, 4, 6, 7, and 9). Patients withheld from taking their study medication on the morning of the laboratory visit, so all measurements were made at trough (ie, approximately 12 h after their preceding evening dose was received). Methacholine challenge was performed according to guidelines using a validated computer-assisted dosimetric method.15,16 The exhaled-breath NO level was measured according to recommended guidelines using an integrated clinical real-time NO gas analyzer (model LR2000; Logan Research; Rochester, Hertsfordshire, UK) with an accuracy of 2 parts per billion NO with a response time of 2 s. Patients filled in a domiciliary diary card daily (ie, morning and evening) throughout the entire study to measure peak flow, asthma symptoms, (scale, 0 to 4) and rescue short-acting β2-agonist requirements.

Blood/Urinary Measurements: The peripheral blood eosinophil counts were measured using a hematology analyzer (model SE-9000; Sysmex UK Ltd; Bucks, UK). Liver function tests (ie, for alanine transaminase, alkaline phosphatase, and bilirubin levels) were measured using an automated biochemistry analyzer (Hitachi 917; Roche Diagnostics Ltd; Sussex, UK). Plasma E-selectin and intercellular adhesion molecule (ICAM)-1 levels were measured by enzyme immunoassays (R&D Systems; UK). The within-assay coefficient of variation for E-selectin and ICAM-1 were 1.0% and 2.7%, respectively. Urinary cortisol was assayed with a commercial radioimmunoassay kit (Incstar Ltd; Berkshire, UK). The coefficient of variation (CV) for analytical imprecision for urinary free cortisol was 5.5% within the assay, and 6.4% between assays. The urinary creatinine level was measured on an autoanalyzer (Cobas-bio; Roche Products Ltd; Hertfordshire, UK). The within-assay CV was 1.0%, and the between-assay CV was 1.0%.

Statistical Analysis

The study was designed with at least 80% power to detect a one doubling-dose difference in methacholine PD20, (the primary end point) between treatments using a crossover design. The logarithmic transformation of the data for methacholine PD20, blood eosinophil level, and overnight urinary cortisol level was required in order to normalize the distribution. Analysis was performed on the 24 patients who completed all visits per protocol, with an initial comparison being made of placebo baseline values prior to each treatment. Multifactorial analysis of variance and Bonferroni multiple-range testing were used to compare within-treatment and between-treatment effects after 2 and 4 weeks of active treatments. Between-treatment comparisons were made in terms of the change from the respective placebo pretreatment baseline value. Within-treatment comparisons were made by comparing values after 2 and 4 weeks with the respective pretreatment baseline.

RESULTS

Patients

Thirty-two patients fulfilled the inclusion criteria at the initial screening visit and entered the placebo run-in prior to randomization. Of these patients, four were unable to tolerate the placebo run-in prior to randomization at visit 1 because of worsening asthma symptoms. Thus, 28 patients were randomized to receive active treatments in crossover fashion. Of these 28 patients, 3 were withdrawn from the study following asthma exacerbation, and 1 was withdrawn from the study following an episode of intolerance to theophylline (ie, nausea). Thus, 24 patients completed the study in total, and their demographic data are summarized in Table 1. At screening, on two separate visits, patients exhibited a 4.4 (95% confidence interval [CI], 3.5 to 5.3) doubling-dose difference in methacholine PD20 comparing reversibility for before vs after albuterol administration, 400 μg.

No significant differences in pretreatment (placebo) baseline values for any end points were seen analyzed according to either treatment (Table 2) or sequence (data not shown). The mean (SE) plasma theophylline concentration at trough was 37 μmol/L (3.1 μmol/L [equivalent to 6.7 mg/L]) after 4 weeks when patients were randomized to receive theophylline.

Bronchial Hyperresponsiveness to Methacholine

Significant (p < 0.05) bronchoprotection was seen within each active treatment group, compared to the respective placebo pretreatment baseline PD20 value. For patients treated with beclomethasone monotherapy, this improvement in PD20 was significant (p < 0.05) only at the 400-μg dose, whereas with the addition of theophylline or zafirlukast, significant (p < 0.05) bronchoprotection was seen with 100-μg and 400-μg doses of beclomethasone.

For between-treatment comparisons (Fig 2) given as the doubling-dose difference from pretreatment baseline, there was a significantly greater (p < 0.05) improvement in PD20 with beclomethasone, 100 μg, plus zafirlukast (1.1 doubling dose), but not with beclomethasone, 100 μg, plus theophylline (0.7 doubling dose), vs beclomethasone, 100 μg, alone (0.4
doubling dose) but not vs beclomethasone, 400 μg, alone (1.1 doubling dose).

**Inflammatory Surrogates**

Significant (p < 0.05) suppression of exhaled breath NO was seen within each active treatment group, compared to the respective pretreatment placebo baseline (Fig 3). At beclomethasone, 100 μg, significant (p < 0.05) suppression of NO was seen only in those patients treated with additive zafirlukast, whereas with beclomethasone, 400 μg, significant suppression occurred in all three groups.

For between-treatment comparisons given as the percentage change from pretreatment baseline, there was a significantly (p < 0.05) greater fall in NO with beclomethasone, 100 μg, plus zafirlukast (48% fall), but not beclomethasone, 100 μg, plus theophylline (34% fall), vs beclomethasone, 100 μg, alone (32% fall) but not vs beclomethasone, 400 μg, alone (50% fall).

Circulating E-selectin levels (only measured at 4 weeks) were significantly (p < 0.05) suppressed with all three active treatments among patients who received beclomethasone, 400 μg, compared to pretreatment placebo baseline values. Circulating ICAM-1 levels (only measured at 4 weeks) were significantly suppressed vs baseline values only within the group receiving zafirlukast in addition to beclomethasone, 400 μg. Significant (p < 0.05) suppression of blood eosinophils (only measured at 4 weeks) was seen in patients receiving beclomethasone, 400 μg, either as monotherapy or with theophylline vs placebo baseline. There were no significant differences in the change from baseline values among the three treatments for any of the above parameters.

**Spirometry and Peak Flow Measurements**

Significant (p < 0.05) improvements in spirometry and peak flow occurred within all three treatment groups, compared to the pretreatment placebo baseline (Table 3). The effect of beclomethasone monotherapy on spirometry and morning peak flow was significant only for the 400-μg dose, whereas with the addition of zafirlukast there were significant improvements in the 100-μg and 400-μg doses of

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**Table 1—Demographic Data**

<table>
<thead>
<tr>
<th>Subject No./Sex</th>
<th>Age, yr</th>
<th>FEV₁ L, % predicted</th>
<th>FEF₂⁵–₇₅ L/s, % predicted</th>
<th>PD₁₅,₂₀ μg</th>
<th>Daily Dose, μg</th>
<th>Other Treatments</th>
<th>Atopic</th>
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<tbody>
<tr>
<td>1/F</td>
<td>62</td>
<td>2.02 103</td>
<td>2.26 82</td>
<td>412 1,252</td>
<td>BUD 400</td>
<td>β₂</td>
<td>N</td>
</tr>
<tr>
<td>2/M</td>
<td>63</td>
<td>2.11 76</td>
<td>1.49 47</td>
<td>25 891</td>
<td>BDP 200</td>
<td>β₂</td>
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</tr>
<tr>
<td>3/M</td>
<td>36</td>
<td>2.63 74</td>
<td>2.32 53</td>
<td>44 3,200</td>
<td>BDP 400</td>
<td>β₂</td>
<td>Y</td>
</tr>
<tr>
<td>4/M</td>
<td>26</td>
<td>4.28 95</td>
<td>3.91 77</td>
<td>31 570</td>
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<tr>
<td>5/F</td>
<td>55</td>
<td>1.94 108</td>
<td>1.88 65</td>
<td>10 3,436</td>
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<tr>
<td>6/F</td>
<td>44</td>
<td>3.14 110</td>
<td>3.50 100</td>
<td>23 223</td>
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</tr>
<tr>
<td>7/F</td>
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<td>2.27 78</td>
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<td>127 1,017</td>
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<tr>
<td>8/M</td>
<td>46</td>
<td>2.58 88</td>
<td>1.91 51</td>
<td>38 372</td>
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<td>β₂</td>
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<tr>
<td>9/M</td>
<td>20</td>
<td>3.40 74</td>
<td>2.09 41</td>
<td>73 181</td>
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<td>β₂, AH</td>
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<tr>
<td>10/F</td>
<td>8</td>
<td>2.08 90</td>
<td>2.49 77</td>
<td>33 1,833</td>
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<tr>
<td>11/F</td>
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<td>2.05 117</td>
<td>1.84 70</td>
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<td>β₂</td>
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<tr>
<td>12/F</td>
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<td>2.47 80</td>
<td>2.27 59</td>
<td>41 236</td>
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<td>Y</td>
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<td>13/M</td>
<td>33</td>
<td>3.34 74</td>
<td>2.47 51</td>
<td>16 122</td>
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<tr>
<td>14/M</td>
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<tr>
<td>15/F</td>
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<td>234 212</td>
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</tr>
<tr>
<td>16/F</td>
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<td>3.40 82</td>
<td>23 285</td>
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</tr>
<tr>
<td>17/F</td>
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<td>3.30 112</td>
<td>4.00 109</td>
<td>15 1,098</td>
<td>BDP 400</td>
<td>β₂, NC</td>
<td>Y</td>
</tr>
<tr>
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<td>2.05 54</td>
<td>19 1,330</td>
<td>BDP 200</td>
<td>β₂</td>
<td>Y</td>
</tr>
<tr>
<td>19/M</td>
<td>18</td>
<td>3.53 82</td>
<td>2.74 55</td>
<td>8 380</td>
<td>BDP 400</td>
<td>β₂</td>
<td>Y</td>
</tr>
<tr>
<td>20/F</td>
<td>48</td>
<td>2.06 73</td>
<td>1.55 46</td>
<td>23 2,429</td>
<td>BDP 400</td>
<td>β₂</td>
<td>Y</td>
</tr>
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<td>2.42 61</td>
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<td>22/F</td>
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<td>3.75 98</td>
<td>17 1,853</td>
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<td>23/F</td>
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<td>2.73 76</td>
<td>321 2,034</td>
<td>BDP 400</td>
<td>β₂</td>
<td>Y</td>
</tr>
<tr>
<td>24/F</td>
<td>18</td>
<td>3.14 104</td>
<td>3.35 83</td>
<td>35 803</td>
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<tr>
<td>Mean (SE)</td>
<td>39</td>
<td>2.82 92</td>
<td>2.52 66</td>
<td>42† 869†</td>
<td>400†</td>
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</table>

*AH = oral antihistamine; β₂ = short-acting β₂ agonist; BUD = budesonide; FP = fluticasone propionate; NC = nasal corticosteroid; F = female; M = male; N = no; Y = yes; FEF₂⁵–₇₅ = midexpiratory forced expiratory flow.

†Values given as geometric mean (SE).

‡Values given as median (range).
beclomethasone. With the addition of theophylline to beclomethasone, 100 µg, only the midexpiratory forced expiratory flow rate showed a significant (p < 0.05) within-treatment improvement compared to baseline. For between-treatment comparisons, such as the change from baseline, there were significantly (p < 0.05) greater improvements in midexpiratory forced expiratory flow and peak flow (morning and evening) with beclomethasone, 100 µg, plus zafirlukast (but not theophylline) vs beclomethasone, 100 µg, alone.

**Symptoms and β₂-Agonist Use**

Significant (p < 0.05) improvements were seen within each active treatment group, compared to baseline. Although there were no significant differences between treatments as such, it can be seen that the addition of zafirlukast improved more diary card parameters, compared to baseline, in patients receiving beclomethasone, 100 µg.

**Overnight Urinary Cortisol/Creatinine**

No significant differences were noted in overnight urinary cortisol corrected for creatinine excretion. Geometric mean pooled values (n = 72) were as follows: placebo, 3.9 nmol/mmol (95% CI, 3.4 to 4.5); beclomethasone (100 µg), 4.1 nmol/mmol (95% CI, 3.5 to 4.7); beclomethasone (400 µg), 3.3 nmol/mmol (2.9 to 3.8).

**DISCUSSION**

Our study showed that adding a leukotriene receptor antagonist to a low dose of an inhaled corticosteroid resulted in improvements in different parameters of antiasthma activity. The combination of a leukotriene receptor antagonist, but not low-dose theophylline, with a low dose of inhaled corticosteroid conferred greater effects on inflammatory surrogates (such as methacholine PD20 and exhaled NO levels) compared to a low dose of inhaled corticosteroid (beclomethasone, 100 µg/d) alone but not compared to a medium dose of inhaled corticosteroid (beclomethasone, 400 µg/d) alone. For example, there was the same 1.1 doubling-dose shift in methacholine PD20 with beclomethasone, 100 µg, plus zafirlukast or beclomethasone, 400 µg, alone. Adding a leukotriene receptor antagonist or theophylline to treatment conferred no additional benefit to a
medium dose of an inhaled corticosteroid used as monotherapy. A 1.0 doubling-dose shift in bronchial hyperresponsiveness would normally be considered a clinically relevant improvement. The 400-μg dose of beclomethasone was not associated with significant systemic suppression of overnight urinary cortisol excretion corrected for creatinine. These findings emphasize the importance of first optimizing the dose of inhaled corticosteroid before considering adding a second-line therapy with a leukotriene receptor antagonist or theophylline. Furthermore, the UK drug costs (£9.64) for 28 days of monotherapy with HFA BDP, 400 μg/d, is considerably less than the combination of HFA beclomethasone, 100 μg/d (£2.20) and zafirlukast, 40 mg/d, (£25.69). There is also the issue of compliance with multiple therapies, which might assume relevance in the long term.

Since inhaled or oral corticosteroids have not been shown to attenuate leukotriene production in

![Figure 2](image)

**Figure 2.** Effects on methacholine hyperresponsiveness. Values are shown as the doubling-dose difference in PD$_{20}$ from pretreatment baseline. $+ = p < 0.05$ vs baseline; $* = p < 0.05$ vs BDP, 100 μg, alone.

![Figure 3](image)

**Figure 3.** Effects on exhaled NO. Values are shown as percentage fall from pretreatment baseline. $* = p < 0.05$ vs baseline; $+ = p < 0.05$ vs BDP 100 μg alone.
Table 3—Treatment Effects*

<table>
<thead>
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<th>Effects</th>
<th>B&lt;sub&gt;100&lt;/sub&gt;</th>
<th>B&lt;sub&gt;100&lt;/sub&gt; + THE</th>
<th>B&lt;sub&gt;100&lt;/sub&gt; + ZAF</th>
<th>B&lt;sub&gt;400&lt;/sub&gt;</th>
<th>B&lt;sub&gt;400&lt;/sub&gt; + THE</th>
<th>B&lt;sub&gt;400&lt;/sub&gt; + ZAF</th>
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<td>Bronchial hyperresponsiveness</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methacholine PD&lt;sub&gt;20&lt;/sub&gt;, μg</td>
<td>60 (45–80)</td>
<td>72 (57–91)†</td>
<td>71 (56–91)‡</td>
<td>97 (73–129)‡</td>
<td>88 (70–112)‡</td>
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<td>Inflammatory surrogates</td>
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<tr>
<td>NO, ppb</td>
<td>8.9 (6.4–11.5)</td>
<td>9.5 (6.6–12.5)</td>
<td>7.7 (4.6–10.8)‡</td>
<td>6.5 (4.0–9.1)‡</td>
<td>6.3 (3.4–9.2)‡</td>
<td>8.0 (4.9–11.1)‡</td>
</tr>
<tr>
<td>Serum eosinophils, × 10&lt;sup&gt;6&lt;/sup&gt;/L</td>
<td></td>
<td></td>
<td>–</td>
<td>0.24 (0.20–0.28)</td>
<td>0.25 (0.22–0.28)†</td>
<td>0.24 (0.20–0.29)</td>
</tr>
<tr>
<td>Plasma E-selectin, ng/mL</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>41 (40–43)</td>
<td>42 (41–44)‡</td>
<td>42 (41–44)§</td>
</tr>
<tr>
<td>Plasma ICAM, ng/mL</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>278 (269–286)</td>
<td>278 (271–285)</td>
<td>277 (268–285)</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, L</td>
<td>2.75 (2.67–2.83)</td>
<td>2.81 (2.71–2.91)</td>
<td>2.78 (2.71–2.86)‡</td>
<td>2.84 (2.76–2.92)‡</td>
<td>2.83 (2.74–2.93)¶</td>
<td>2.81 (2.73–2.89)¶</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25–75&lt;/sub&gt;, L/s</td>
<td>2.26 (2.15–2.37)</td>
<td>2.48 (2.32–2.63)¶</td>
<td>2.35 (2.23–2.48)¶</td>
<td>2.47 (2.36–2.58)‡</td>
<td>2.44 (2.29–2.60)¶</td>
<td>2.45 (2.32–2.57)¶</td>
</tr>
<tr>
<td>Diary card data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day β&lt;sub&gt;2&lt;/sub&gt; use, puffs/12 h</td>
<td>0.6 (0.3–0.8)†</td>
<td>0.7 (0.5–0.9)</td>
<td>0.5 (0.3–0.7)‡</td>
<td>0.6 (0.4–0.9)†</td>
<td>0.7 (0.5–0.9)</td>
<td>0.6 (0.4–0.8)†</td>
</tr>
<tr>
<td>Night β&lt;sub&gt;2&lt;/sub&gt; use, puffs/12 h</td>
<td>0.6 (0.3–0.9)†</td>
<td>0.5 (0.4–0.7)</td>
<td>0.5 (0.3–0.7)‡</td>
<td>0.5 (0.2–0.8)‡</td>
<td>0.5 (0.3–0.7)</td>
<td>0.3 (0.1–0.5)†</td>
</tr>
<tr>
<td>Day symptoms, units/12 h</td>
<td>0.3 (0.2–0.5)†</td>
<td>0.4 (0.3–0.5)</td>
<td>0.3 (0.1–0.4)‡</td>
<td>0.4 (0.2–0.5)‡</td>
<td>0.4 (0.2–0.5)</td>
<td>0.3 (0.2–0.5)‡</td>
</tr>
<tr>
<td>Night symptoms, units/12 h</td>
<td>0.4 (0.3–0.6)†</td>
<td>0.4 (0.3–0.5)</td>
<td>0.3 (0.1–0.4)‡</td>
<td>0.3 (0.2–0.5)‡</td>
<td>0.3 (0.2–0.4)</td>
<td>0.2 (0.1–0.4)†</td>
</tr>
</tbody>
</table>

*Values given as mean (95% CI). B<sub>100</sub> = beclomethasone, 100-μg dose; B<sub>400</sub> = beclomethasone, 400-μg dose; PEF = peak expiratory flow. See Table 2 for other abbreviations not used in the text.

†Values given as geometric mean (SE).

‡Denotes significant (p < 0.05) within-treatment difference compared to baseline.

§Denotes significant (p < 0.05) between-treatment difference as cleavage from pretreatment baseline for B<sub>100</sub> + ZAF vs B<sub>100</sub> alone.
it is perhaps not surprising that using a leukotriene receptor antagonist in patients already receiving low-dose inhaled corticosteroids may confer additional benefits. This is supported by studies comparing the additive effects either of zafirlukast or montelukast compared to placebo in patients already receiving inhaled corticosteroids. In particular, in one of these studies in patients with mild-to-moderate persistent asthma, zafirlukast was found to significantly reduce bronchial hyperresponsiveness to methacholine and exhaled NO when given in addition to a low-to-moderate dose of an inhaled corticosteroid, as was the case in our study. Other studies also have suggested indirectly that leukotriene receptor antagonists provide complementary benefits to inhaled corticosteroid therapy and may even facilitate dose reduction of the latter.

Analogous to leukotriene receptor antagonist therapy, theophylline also is recognized as possessing both bronchodilatory and anti-inflammatory properties. Beneficial immunomodulatory effects may be seen at serum theophylline concentrations below those traditionally regarded as therapeutically useful in terms of achieving bronchodilatation (ie, 10 to 20 mg/L). Our mean trough theophylline level was 6.7 mg/L, which would coincide with the more modern anti-inflammatory target range of 5 to 10 mg/L. We elected to use low-dose theophylline in order to assess whether it exhibited additive effects to an inhaled corticosteroid in terms of surrogate inflammatory markers. In this respect, our patients had only mildly impaired lung function, and so significant bronchodilator responses would not be expected with low-dose theophylline therapy. The addition of theophylline to therapy with an inhaled steroid in patients with more severe asthma has been shown to be beneficial in several studies.

Our choice of primary end point, bronchial hyperresponsiveness to methacholine challenge, is of clinical relevance. While the link between airways inflammation and bronchial hyperresponsiveness is not a simple one, one study has demonstrated that reducing bronchial hyperresponsiveness to methacholine, in conjunction with optimizing symptoms and lung function for > 2 years, leads to more effective control of asthma and to a reduced number of exacerbations, reducing airway remodeling as assessed in bronchial biopsy specimens. Other data also have suggested that methacholine PD_{20} may be a good surrogate for airway inflammation and disease severity. Furthermore, the dose response to inhaled steroids in patients with mild-to-moderate asthma is much steeper for bronchial hyperresponsiveness than for lung function.

Exhaled breath NO is recognized to be a sensitive marker of cytokine-driven airway inflammation. Significantly greater suppression of NO was seen with zafirlukast, but not theophylline, in conjunction with low-dose beclomethasone, in comparison to low-dose beclomethasone alone. This effect was not seen with zafirlukast when given in combination with the medium dose of beclomethasone. This is not surprising given that we know that near-maximal suppression of exhaled breath NO occurs with modest doses of inhaled corticosteroids. We also observed significant suppression of circulating E-selectin following all treatments compared to placebo. E-selectin is a vascular cell adhesion molecule that is involved in the endothelial transmigration of inflammatory cells into the lungs. Of note, it is found only on activated endothelium, in contrast to other adhesion molecules. Elevated levels previously have been reported in patients with acute asthma and may reflect the extensive inflammatory response occurring in the airways during acute exacerbations.

In a previous study using the same extra-fine particle HFA formulation of BDP, the effects of 100 μg/d on spirometry were near maximal after 1 week compared to 6 weeks. However, much longer periods may be needed to achieve peak effects on bronchial hyperresponsiveness. Hence, the greater response to beclomethasone, 400 μg, than to beclomethasone, 100 μg, in terms of methacholine PD_{20} in our study may not merely be a function of dose, but also may be due to duration of therapy (ie, 4 weeks compared to 2 weeks). It is also possible that our results may only apply to the extra-fine HFA formulation of BDP in terms of being able to target the inflammatory process in the small airways. It is therefore conceivable that with a coarser particle formulation, the additive effects of zafirlukast or theophylline might be seen at low or medium doses of the inhaled corticosteroid. In this respect, with conventional chlorofluorocarbon beclomethasone, 400 μg/d, improvements in asthma control were seen with the addition of montelukast.

In summary, a leukotriene receptor antagonist, but not low-dose theophylline, conferred significant additive anti-inflammatory effects to low-dose inhaled corticosteroid therapy, but not to medium-dose inhaled corticosteroid therapy. Our results reinforce the view that inhaled corticosteroids should be used as first-line anti-inflammatory therapy in the management of patients with persistent asthma. Second-line nonsteroidal agents, particularly leukotriene receptor antagonists, may still be useful as add-on therapy, however, although optimizing the dose of inhaled corticosteroid as monotherapy would seem to be the logical first step, in keeping with current asthma management guidelines.

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