Increased levels of airway neutrophils reduce the inhibitory effects of inhaled glucocorticosteroids on allergen-induced airway eosinophils

Gail M Gauvreau PhD, Mark D Inman PhD MD, Margaret Kelly MD, Richard M Watson BSc, Sandra C Dorman BSc, Paul M O’Byrne MB FRCPI FRCPC

BACKGROUND: Treatment with inhaled glucocorticosteroids attenuates allergen-induced airway inflammation but is less effective in people with asthma who have noneosinophilic airway inflammation.

OBJECTIVE: Studies in which glucocorticosteroid treatment was used before allergen challenges were re-examined to determine whether the efficacy of steroid treatment could be predicted by baseline levels of sputum inflammatory cells.

PATIENTS AND METHODS: Twenty-eight nonsmoking subjects with atopic asthma controlled by beta2-agonists participated in only one of three studies, each carried out with a double-blind, placebo controlled, randomized, crossover design. Subjects were treated with glucocorticosteroids or placebo for six to eight days and then underwent allergen inhalation challenge. Spirometry was measured for 7 h after allergen challenge, and then sputum inflammatory cells were measured. Sputum inflammatory cells were also measured before and after treatment, and 24 h after allergen challenge. The per cent inhibition of the allergen-induced airway responses by glucocorticosteroids was calculated.

RESULTS: Inhaled glucocorticosteroids significantly attenuated the early and late asthmatic responses, and the number of allergen-induced sputum eosinophils (P<0.05). There was a significant negative relationship between the number of sputum neutrophils at baseline, and the per cent inhibition of allergen-induced sputum eosinophils measured at 7 h (r=–0.61, P<0.001) and 24 h (r=–0.73, P<0.0001) after challenge, suggesting that glucocorticosteroids are less effective in attenuating allergen-induced airway inflammation in subjects with high levels of neutrophils. There was no correlation between the number of sputum eosinophils at baseline and the per cent inhibition of allergen-induced responses.

CONCLUSIONS: Baseline airway neutrophils, not eosinophils, can be used to predict the efficacy of inhaled steroids on allergen-induced sputum eosinophils.

Key Words: Airway inflammation; Allergen inhalation; Eosinophils; Glucocorticosteroids; Neutrophils; Sputum induction
Les taux élevés de polynucléaires neutrophiles dans les voies respiratoires réduisent l’effet inhibiteur des glucocorticoides en aérosol sur les éosinophiles d’origine allergique

CONTEXTE : Les glucocorticoides en aérosol atténuent l’inflammation des voies aériennes d’origine allergique, mais ils sont moins efficaces chez les asthmatiques qui présentent une inflammation non éosinophile des voies respiratoires.

OBJECTIF : Faire en revue les études dans lesquelles le traitement aux glucocorticoides a été administré avant la réalisation des tests de provocation pour vérifier si on peut prévoir l’efficacité des stéroïdes à partir du nombre initial de cellules inflammatoires dans les sécrétions.

PATIENTS ET MÉTHODES : Vingt-huit sujets non fumeurs, souffrant d’asthme atopique maîtrisé par les agonistes bêta2, ont participé à l’une des trois études seulement; toutes ont été menées à double insu, contre placebo, avec répartition aléatoire et permutation. Les sujets ont été traités aux glucocorticoides ou par placebo durant six à huit jours, puis soumis à un test de provocation inhalatoire. On a procédé à des mesures de la spirométrie pendant 7 heures après le test de provocation, puis à celle des cellules inflammatoires dans les expectorations. Il y a également eu mesure de ces cellules avant et après le traitement ainsi que 24 h après le test de provocation. On a aussi calculé le pourcentage d’inhibition des réactions allergiques dans les voies respiratoires, attribuable aux glucocorticoides.

RÉSULTATS : Les glucocorticoides en aérosol ont permis d’atténuer sensiblement les réactions asthmatiques précoces et tardives et de réduire significativement le nombre d’éosinophiles d’origine allergique dans les expectorations (P<0.05). On a constaté l’existence d’une relation négative importante entre le nombre de neutrophiles au départ et le pourcentage d’inhibition d’éosinophiles d’origine allergique dans les sécrétions, mesuré 7 h (r=–0.61; P<0.001) et 24 h (r=–0.73; P<0.0001) après le test de provocation, ce qui donne à penser que les glucocorticoides sont moins efficaces pour atténuer l’inflammation d’origine allergique dans les voies respiratoires chez les sujets qui présentent des taux élevés de neutrophiles. Il n’y avait pas de corrélation entre le nombre d’éosinophiles dans les sécrétions au départ et le pourcentage d’inhibition des réactions de nature allergique.

CONCLUSION : Le nombre de neutrophiles, mais pas celui d’éosinophiles, dans les expectorations au départ peut servir à prédire l’efficacité des stéroïdes en aérosol sur les éosinophiles d’origine allergique dans les sécrétions.

Asthma is well recognized as an inflammatory disorder of the airways characterized by increased levels of eosinophils (1,2). Eosinophils have been shown to be sensitive to the effects of glucocorticoids, because treatment with glucocorticoids has been shown to reduce the level of eosinophils in the peripheral blood (3,4) and airways of individuals with asthma (5), and to inhibit the allergen-induced increased levels of eosinophils in the peripheral blood and airways (6-8). The level of sputum eosinophils has been shown to predict the clinical benefit of steroid treatment for people with asthma (9,10).

Although eosinophils are considered to be the hallmark of asthmatic airway inflammation, there is increasing evidence that neutrophils may also play a prominent role. Elevated levels of neutrophils have been measured in the airways of subjects with stable asthma (11), during exacerbations of asthma (12) and in fatal asthma of sudden onset (13). Glucocorticoids are reported to be less effective in people with asthma who have noneosinophilic airway inflammation (14), and we hypothesize that neutrophil levels may also be used to predict the magnitude of benefit as a result of steroid treatment. Thus, the aim of the present study was to re-examine studies in which steroid treatment was used in allergen challenge to determine whether allergic responses or the efficacy of steroid treatment could be predicted by baseline levels of inflammatory cells in induced sputum.

PATIENTS AND METHODS

Patients

Twenty-eight patients with mild atopic asthma each participated in one of three studies (6-8) approved by the Ethics Committee of the McMaster University Health Sciences Centre (Hamilton, Ontario). Each of these studies demonstrated significant inhibition of the allergen-induced late asthmatic response (LAR) and sputum eosinophils after regular glucocorticoid treatment, but did not examine the relationship between the baseline number of sputum neutrophils and efficacy of glucocorticoid treatment.

Nonsmoking subjects between the ages of 18 and 65 years were recruited for the studies (Table 1). All sub-

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<td>Mean (range) characteristics for 28 patients with mild atopic asthma</td>
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<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
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<tbody>
<tr>
<td>200 µg budesonide twice daily for eight days</td>
<td>200 µg budesonide twice daily for seven days</td>
<td>400 µg mometosone twice daily for six days</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.8 (21.37)</td>
<td>21.2 (19.24)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>86.6 (77.9, 97.8)</td>
<td>82.2 (70.6, 96.3)</td>
</tr>
<tr>
<td>MCh PC20 (mg/mL)</td>
<td>1.7 (0.4, 6.3)</td>
<td>1.1 (0.2, 19.9)</td>
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<tr>
<td>LAR placebo (% change)</td>
<td>–23.4 (–3.2, –38.3)</td>
<td>–23.7 (–9.2, –44.3)</td>
</tr>
<tr>
<td>LAR glucocorticoid (% change)</td>
<td>–4.6 (–12.5, 0)</td>
<td>–6.6 (–15.2, –3.4)</td>
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FEV1: Premétrie prédite de la capacité expiratoire forcée en un seconde; MCh PC20: Concentration provoquée de méthacholine causant un 20% de la FEV1; LAR glucocorticoid Maximum per cent change in FEV1 during the late response with glucocorticoid treatment; LAR placebo Maximum per cent change in FEV1 during the late response with placebo treatment
projects had documented allergen-induced early asthmatic response (EAR) and LAR of an at least 15% fall in forced expiratory volume in 1 s (FEV₁), gave signed consent to participate, and were randomly assigned to inhale glucocorticoid and placebo for six to eight days. Subjects did not have asthma exacerbations or respiratory tract infections and were not knowingly exposed to altered levels of sensitizing allergens for at least four weeks before entering the studies. All subjects had stable asthma with a baseline FEV₁ greater than 70% of predicted normal on all of the study days before allergen inhalation. Subjects used no medication other than inhaled beta₂-agonists as required to treat their symptoms, and beta₂-agonists were withheld for at least 8 h before each visit. Subjects were instructed to refrain from vigorous exercise and caffeine in the mornings before visits to the laboratory. Four subjects were excluded—two experienced deterioration of their asthma, one was unable to inhale the same dose of allergen during the two challenges and one was not available to complete the second allergen challenge.

Study design
Three studies were carried out with a double-blind, placebo controlled, randomized, crossover design. The subjects were randomly assigned to complete two treatment periods inhaling: 200 µg budesonide or placebo twice daily for eight days, with the last dose of drug taken the morning of allergen challenge (study 1, n=8); or for seven days, with the last dose of drug taken 24 h after allergen challenge (study 2, n=7); or 400 µg mometasone furoate or placebo twice daily for six days, with the last dose of drug taken 24 h after allergen challenge (study 3, n=9) (Figure 1). Each treatment period consisted of four visits to the laboratory. Baseline measurements of FEV₁, the provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀), and induced sputum total and differential cell counts were determined before receiving treatment, and again at 24 h before allergen challenge, 7 h after allergen challenge and 24 h after allergen challenge. Allergen inhalation challenges were carried out in the morning, and spirometry was measured for 7 h. Treatment periods were separated by a washout period of at least three weeks.

Interventions
Methacholine inhalation test: The methacholine inhalation challenge was performed as described by Cockcroft (15). Subjects inhaled normal saline and were then administered double the concentrations of methacholine phosphate (ACIC Fine Chemicals Inc, Canada) from a Wright nebulizer (Roxon Medi-Tech Ltd, Canada) via a Hans Rudolph valve (Hans Rudolph Inc, USA) for 2 min. FEV₁ was measured at 30, 90, 180 and 300 s with a Collins water sealed spirometer and kymograph (Warren Collins, USA). The test was terminated when a fall in FEV₁ of 20% of the postsaline value occurred, and the PC₂₀ was calculated.

Allergen inhalation challenge: Allergen challenge was performed as described by O'Byrne and coworkers (16). The starting allergen extract concentration inhaled by each subject was determined from a formula using the results from the skin test and the methacholine PC₂₀ (17). Allergen inhalation challenges were performed using a Wright nebulizer pressurized by air at 50 pounds per square inch, and at a flow rate that gave an output of 0.13 mL/min and an aerodynamic mass median diameter of 1.0 to 1.5 µm. Concentrations of allergen were inhaled by tidal breathing (nose clipped) for 2 min, with the FEV₁ measured 10 min after each inhalation. Subjects inhaled the same concentration of allergen for both challenges, resulting in a greater than 15% EAR and LAR during a previous screening period. FEV₁ was subsequently measured at 20, 30, 45, 60, 90 and 120 min, and at hourly intervals up to 7 h postallergen inhalation using a water-sealed spirometer. The EAR was taken to be the largest fall in FEV₁ within 2 h after allergen inhalation, and the LAR was taken to be the largest fall in FEV₁ between 3 and 7 h after allergen inhalation.

Sputum induction: Sputum was induced and processed using the method described by Pizzichini and coworkers (18). Sputum cell plugs were mixed with a bench rocker in 0.1% dithiothreitol (Sputolysin; Calbiochem Corporation, USA) and Dulbecco’s phosphate buffered saline (Life Technologies [Gibco BRL], USA), filtered through a 52 µm pore nylon gauze (BNSH Thompson, Canada) and then centrifuged at 1571 rad/s for 10 min. Cells were resuspended in Dulbecco’s phosphate buffered saline at 0.75 to 1.0×10⁶/mL, and cytopsins were prepared on glass slides using a Shandon 3 cytocentrifuge (Shandon Southern Instruments, USA). Differential cell counts were obtained from the mean of two slides, with 400 cells counted per slide stained with Diff Quik staining solution (American Scientific Products, USA). The sputum cell measurements are presented as absolute numbers to eliminate the possibility that observed changes in a cell population are a result of increases or decreases in another cell population.
was calculated using the equation: 

\[ \text{% inhibition} = \frac{\text{placebo} - \text{steroid}}{\text{placebo}} \times 100 \]

The relationship between baseline sputum inflammatory cells and per cent inhibition of allergen-induced responses was examined by the Pearson correlation coefficient; baseline cell counts were calculated as the mean values of the preplacebo and proactive drug measurements.

**RESULTS**

The efficacy of inhaled budesonide and mometasone furoate on allergen-induced EAR, LAR, methacholine airway responsiveness and sputum eosinophils has been presented separately elsewhere (6-8), and these data are pooled and summarized below.

The maximum early fall in FEV\textsubscript{1} was \(-33.7\%\pm2.0\%\) with placebo and \(-18.9\%\pm2.7\%\) (P<0.001) with active treatment, corresponding to a mean inhibition of 44.4\%\pm6.9\%. Similarly, the early area under the curve was inhibited by 45.8\%\pm7.8\% (P<0.001). The maximum late fall in FEV\textsubscript{1} was \(-25.4\%\pm2.4\%\) with placebo and \(-5.9\%\pm1.1\%\) with active treatment (P<0.001), a 70.0\%\pm6.8\% inhibition of the late response. The late area under the curve was inhibited by 77.4\%\pm10.0\% (P<0.001).

The methacholine PC\textsubscript{20} increased from 1.5 mg/mL (1.3 mg/mL GSEM) to 2.6 mg/mL (1.5 mg/mL GSEM) after active treatment (P=0.002), but did not change after placebo treatment, being 1.3 mg/mL (1.3 mg/mL GSEM) before and 1.8 mg/mL (1.4 mg/mL GSEM) after (P=0.11). There was a decrease in methacholine PC\textsubscript{20} 24 h after allergen inhalation with placebo treatment, at which time the PC\textsubscript{20} was 0.7 mg/mL (1.4 mg/mL GSEM) (P=0.002 compared with preallergen, post-treatment value), but this effect of allergen was not apparent with active treatment, with the PC\textsubscript{20} being 1.9 mg/mL (1.3 mg/mL GSEM) (P=0.06).

Inhalation of glucocorticoids for four (mometasone furoate), seven and eight days (budesonide) significantly reduced the number of sputum eosinophils from \(15.8\pm4.6\times10^4/mL\) to \(4.9\pm1.8\times10^4/mL\) (P=0.004) compared with the placebo group in which there was no change, from \(9.3\pm2.9\times10^4/mL\) before to \(9.0\pm1.8\times10^4/mL\) after (P=0.76) (Figure 2). There was no significant effect of glucocorticoids on the number of sputum neutrophils, of which there were \(179.5\pm54.9\times10^4/mL\) before and \(135.9\pm26.8\times10^4/mL\) after active treatment compared with \(102.8\pm22.4\times10^4/mL\) before and \(117.2\pm20.5\times10^4/mL\) after placebo (P=0.23) (Figure 2).

Sputum eosinophils increased from \(9.0\pm1.8\times10^4/mL\) to \(60.3\pm9.0\times10^4/mL\) at 7 h and \(99.2\pm18.0\times10^4/mL\) at 24 h after allergen inhalation in the placebo group (P<0.0002). The allergen-induced increase in sputum eosinophil numbers was significantly inhibited with active treatment (P<0.0003); there were \(13.2\pm3.8\times10^4/mL\) at 7 h and \(31.9\pm9.2\times10^4/mL\) at 24 h after allergen inhalation, corresponding to a 71% and 47% inhibition of allergen-induced eosinophils at 7 and 24 h, respectively (Figure 2). There was no effect of allergen inhalation on sputum neutrophils – \(117.2\pm20.5\times10^4/mL\) before, \(208.4\pm40.4\times10^4/mL\) at 7 h and \(154.8\pm34.8\times10^4/mL\) at 24 h after allergen inhalation (P=0.30) (Figure 2).

Individual baseline sputum neutrophils values were within a wide range from \(10.1\times10^4/mL\) to \(705.4\times10^4/mL\). Baseline sputum neutrophil numbers were taken to be the average between predrug and preplacebo values. Baseline sputum neutrophil numbers negatively correlated with per cent inhibition of allergen-induced sputum eosinophils by glucocorticoids at 7 h (r=-0.61, P<0.001) and 24 h (r=-0.73, P<0.0001) (Figure 3), indicating that glucocorticoids are less effective in reducing allergen-induced airway eosinophils in patients with asthma with higher levels of airway neutrophils. There was no relationship between baseline sputum eosinophils and per cent inhibition of allergen-induced sputum eosinophils by glucocorticoids with the placebo group in which there was no change, from \(9.3\pm2.9\times10^4/mL\) before to \(9.0\pm1.8\times10^4/mL\) after (P=0.76) (Figure 2). There was no effect of allergen inhalation on sputum neutrophils – \(117.2\pm20.5\times10^4/mL\) before, \(208.4\pm40.4\times10^4/mL\) at 7 h and \(154.8\pm34.8\times10^4/mL\) at 24 h after allergen inhalation (P=0.30) (Figure 2).

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of the EAR or LAR (P>0.05). No significant correlations between inhibition of airway responses and baseline neutrophil levels were observed when cell populations were expressed as percentages.

**DISCUSSION**

It has been reported that sputum eosinophilia may be a predictor of clinical benefit to steroid treatment (9,19); however, the association between sputum neutrophilia and reduced protection by glucocorticoids has not yet been reported. Allergen inhalation challenge in dual responding patients with atopic asthma results in EARs and LARs, and airway eosinophilia (20), which are significantly attenuated by treatment with inhaled glucocorticoids (6-8). The magnitude of allergen-induced airway responses and per cent inhibition by glucocorticoids, however, varies considerably between individuals. We hypothesized that this variability may be due to the underlying level of specific inflammatory cells in the airway. These data examine the relationship between the number of inflammatory cells in the unchallenged airway compared with the magnitude of allergen-induced airway inflammation and inhibition of this inflammation by glucocorticoids.

The data presented here are from three separate and already published studies (6-8). Different subjects and designs were used in each study. For this reason, comparisons between the efficacy of the different treatment types and doses were not made and should not be inferred. The sole purpose of pooling these data in the present study is to examine the hypothesis that treatment efficacy (regardless of steroid type or dose) is predicted by baseline inflammatory markers in sputum.

We have demonstrated that allergen-induced airway eosinophilia is not related to baseline levels of eosinophils or neutrophils in the airway, suggesting that when subjects are delivered inhaled allergen, resulting in similar EARs and LARs, the underlying airway inflammation does not have an effect on the magnitude of allergen-induced airway inflammation. On the other hand, inhibition of allergen-induced airway eosinophilia by glucocorticoids is negatively related to the baseline levels of neutrophils in the airway. This suggests that glucocorticoid therapy in patients with asthma who have higher numbers of airway neutrophils is less effective for the treatment of allergen-induced airway eosinophilia than in patients with asthma who have lower numbers of airway neutrophils. In addition, these data demonstrate that airway neutrophilia, but not eosinophilia, in subjects with mild asthma may predict efficacy of glucocorticoids in the inhibition of allergen-induced sputum eosinophilia.

The role of the neutrophil in the pathophysiology of allergic asthma is not well understood. Neutrophils can synthesize eosinophil cationic protein (21), which implies that they may also impart some role in tissue damage in the asthmatic airway. Airway neutrophilia is present in acute asthma exacerbations (12,13). Neutrophils have been shown to increase in bronchialveolar lavage fluid after allergen challenge in some studies (22,23), but not in others (24,25).

Airway eosinophils and neutrophils appear to respond differently to glucocorticoid treatment. Neutrophil levels are found to increase (26,27) or not change (28) after steroid therapy. It is unclear whether airway neutrophils are increased in asthma but are insensitive to the effects of steroids, or whether they are present at elevated levels in some patients with asthma simply as a consequence of long term treatment with steroids and steroid-induced inhibition of neutrophil apoptosis (29). Despite evidence that airway neutrophilia is associated with increased asthma severity (30,31), these earlier studies do not rule out the possibility that neutrophils are present in higher levels in the airways of individuals with more severe asthma, as a direct response to high dose glucocorticoid therapy. In the present study of steroid-naive patients with asthma, neutrophils were not sensitive to the effects of short term treatment (six to eight days) with glucocorticoids, because there was no change in the number of sputum neutrophils after glucocorticoid treatment (6-8). In contrast, there was a significant reduction in the number of sputum eosinophils after glucocorticoid treatment. Thus, it is evident that glucocorticoids can reduce the eosinophil-driven process, while having no effect on the neutrophil-driven process.

In some instances, glucocorticoids have been proposed to enhance neutrophil function (32,33). Neutrophils may actually contribute to the recruitment of eosinophils into the airways through synthesis of various mediators, such as leukotriene B4, cysteinyl leukotrienes, platelet activating factor and elastase, all of which have been shown to have effects that may enhance eosinophilia. Moreover, priming of neutrophils with proinflammatory agents such as granulocyte macrophage colony stimulating factor and tumour necrosis factor-alpha, cytokines known to be generated after allergen inhalation challenge, leads to a significant enhancement of the capacity of neutrophils to produce 5-lipoxygenase prod-
The neutrophil has a high capacity for synthesis of leukotriene B\textsubscript{4}, shown to chemotact eosinophils when they are primed by interleukin-5 (35). Cysteiny1 leukotrienes, which may come from airway neutrophils, are capable of inducing airway inflammation (36,37). The lipid-derived mediator, platelet activating factor, which is released from airway inflammatory cells, including neutrophils, may contribute to several biological actions relevant to the pathology of airway inflammation, including recruitment and activation of eosinophils (38), and release of mediators such as the cysteiny1 leukotrienes from eosinophils (39). The degranulation of eosinophils can be induced by a variety of physiological stimuli, including platelet activating factor (40) and neutrophil elastase (41). The release of neutrophil-derived mediators supports a mechanism by which neutrophils enhance airway eosinophilic inflammation. With airway neutrophils present in elevated numbers and possible activation of neutrophils by glucocorticoids, there lies a mechanism whereby glucocorticoid-insensitive airway neutrophils may participate in accumulating eosinophils in the airways after allergen challenge, despite glucocorticoid intervention.

A surprising finding was that airway neutrophil levels correlated with the per cent inhibition of allergen-induced increases in sputum eosinophils, but not with the per cent inhibition of the LAR. Early studies have described an inverse relationship between airway eosinophils with airway reactivity and bronchoconstriction during asthma exacerbations (42,43), suggesting a causal relationship. More recent studies, however, have provided evidence that the LAR is not necessarily eosinophil-driven. The LAR has been shown to persist despite significant attenuation of sputum eosinophils with an interleukin-5 blocking antibody (44), and the LAR provoked by intradermal injection of peptides is not accompanied by eosinophils in bronchial biopsy specimens (45).

We have shown that airway neutrophil levels, but not eosinophil levels, in individuals with mild asthma may be used to predict the efficacy of inhaled steroids on allergen-induced eosinophilia, and these individuals may benefit from additional anti-inflammatory treatment such as anti-leukotrienes during exposure to known allergens. We hypothesize that the neutrophil may play an active role in the development of allergen-induced airway eosinophilia due to their insensitivity to the anti-inflammatory effects of steroids, and through their ability to synthesize mediators known to activate and attract eosinophils to the airway. To further test this hypothesis, a formal study is required to confirm that airway neutrophils reduce the benefits of steroids in patients with atopic asthma.

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REFERENCES


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