Predictors of loss of asthma control induced by corticosteroid withdrawal

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BACKGROUND: Asthma guidelines recommend reducing the dose of inhaled corticosteroids after establishing control.
OBJECTIVE: To identify predictors of loss of control and the kinetics of symptoms, and inflammatory and physiological measurements when inhaled corticosteroids are reduced in patients with stable asthma.
PATIENTS AND METHODS: In a single-blind study, the daily dose of inhaled corticosteroid was reduced by one-half at intervals of 20±2 days in 17 adults with controlled asthma until loss of asthma control occurred or until the corticosteroid was replaced with placebo for 20 days. The patients recorded symptoms and peak expiratory flow each day, and forced expiratory volume in 1 s (FEV_1), the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}), exhaled nitric oxide, and eosinophils in sputum and blood were measured every 10 days. A loss of asthma control was defined as a worsening of the symptoms score of at least 20%, and either a decrease in FEV_1 of at least 15% or a decrease in PC_{20} of at least fourfold.
RESULTS: Two patients had a respiratory infection and were withdrawn from the study. In eight patients, asthma became uncontrolled after a mean of 33 days (range 13 to 48 days). This was accurately reflected by a worsening of all parameters. The first parameter to change was the sputum eosinophil percentage (20 days before the loss of asthma control). Significant changes in exhaled nitric oxide, FEV_1 and methacholine PC_{20} were observed only when the symptoms became uncontrolled. A high blood eosinophil count at baseline (risk ratio of 2.5, 95% CI 1.0 to 6.5) and an increase in sputum eosinophil count after the reduction of corticosteroids were predictors of loss of asthma control.
CONCLUSION: In patients whose asthma is controlled on inhaled corticosteroid, it is prudent not to reduce the dose further if the blood eosinophils are increased or if the sputum eosinophils increase by as little as 1% after the reduction of corticosteroids.

Key Words: *Asthma exacerbation; Eosinophils; Induced sputum; Inhaled corticosteroid*

Les prédicteurs de perte de contrôle de l'asthme induite par le retrait de la corticothérapie

HISTORIQUE : Les lignes directrices sur l'asthme préconisent de réduire la dose de corticoïdes en aérosol après l'obtention du contrôle.
OBJECTIF : Repérer les prédicteurs de perte de contrôle, la cinétique des symptômes et les mesures inflammatoires et physiologiques lorsque la corticothérapie en aérosol est réduite chez les patients dont l'asthme est stabilisé.
PATIENTS ET MÉTHODOLOGIE : Dans une étude à simple insu, la dose quotidienne de corticoïdes en aérosol a été réduite de moitié à intervalles de 20±2 jours chez 17 adultes dont l'asthme était contrôlé, jusqu'à la perte de contrôle de l'asthme ou au remplacement de la corticothérapie par un placebo pendant 20 jours. Les patients consignaient leurs symptômes et leur débit maximal expiratoire tous les jours, tandis que le volume expiratoire maximal par seconde (VEMS), la concentration de provocation par méthacholine responsable d'une chute de 20 % du VEMS (CP_{20}), le monoxyde d'azote expiré et les éosinophiles dans les expectorations et le sang étaient mesurés tous les 10 jours. La perte de contrôle de l'asthme était définie comme une aggravation de l'indice des symptômes d'au moins 20 %, accompagnée d'une diminution du VEMS d'au moins 15 % ou d'une diminution au moins quadruplée de la CP_{20}.
RÉSULTATS : Deux patients ont souffert d'une infection respiratoire et ont été retirés de l'étude. Chez huit patients, l'asthme est devenu incontrôlé après une moyenne de 33 jours (fourchette de 13 à 48 jours). Ce phénomène était reflété fidèlement par une aggravation de tous les paramètres. Le premier paramètre à changer fut le pourcentage d'éosinophiles dans les expectorations (20 jours avant la perte de contrôle de l'asthme). Des changements importants au monoxyde d'azote expiré, au VEMS et à la CP_{20} par méthacholine ne s'observaient que lorsque les symptômes devenaient incontrôlés. Une numération élevée d'éosinophiles dans le sang en début d'étude (risque relatif de 2,5, 95 % IC 1,0 à 6,5) et une augmentation de la numération d'éosinophiles dans les expectorations après la réduction de la corticothérapie étaient des prédicteurs de perte de contrôle de l'asthme
CONCLUSION : Chez les patients dont l'asthme est contrôlé par corticothérapie en aérosol, il est prudent de ne pas réduire la dose davantage si les éosinophiles sanguins augmentent ou si les éosinophiles dans les expectorations augmentent d'aussi peu que 1 % après la diminution de la corticothérapie.

Consensus guidelines recommend inhaled corticosteroids as the preferred anti-inflammatory treatment of asthma (1). However, the optimal dose varies among patients. It is recommended that once control of asthma is achieved, the dose should be reduced to the minimum required to maintain control. This requires causing a mild exacerbation before the minimum dose can be identified and, because of this, many physicians keep patients on a higher dose than is necessary. In keeping with this, when inhaled corticosteroids are reduced in research studies, they can often be discontinued without an exacerbation (2).

The use of measurements of inflammation in sputum has been shown to allow for improved asthma control and reduced exacerbations (3,4). In the present study, we investigated whether these measurements could help to identify risk factors for loss of asthma control when reducing the corticosteroid

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TABLE 1
Characteristics of the patients at baseline

Patient number	Sex (M/F)	Age (years)	Duration of asthma (years)	Atopic status	FEV_1 (% predicted)	PC_{20} (mg/mL)	ICS/LABA therapy (µg/day)	Blood Eo ($\times 10^9$/L)	Sputum Eo (%)	ENO (ppb)
Exacerbated patients										
1	M	56	10	0	87	1.96	400	0.39	8.3	37
2	M	64	50	5	55	2.12	400 S50	0.39	2.0	7
3	M	47	40	8	75	0.94	800	0.01	0.0	56
4	F	37	27	3	86	0.64	800	0.57	1.0	9
5	F	74	9	1	96	1.84	800	0.32	1.0	9
6	F	29	29	4	94	10.72	800	0.15	0.3	17
7	F	52	7	1	92	2.42	800	0.20	0.3	4
8	F	21	21	1	93	0.66	800 S100	0.83	38.5	20
Mean (SD)		48 (18)	24 (16)		85 (14)	1.90 (3.33)		0.36 (0.26)	1.0 (13.2)	20 (18)
Nonexacerbated patients										
9	F	55	45	1	106	0.72	800	0.14	0.8	25
10	F	47	47	5	83	2.58	400	0.28	0.0	9
11	F	43	14	–	98	4.54	400	0.09	0.0	16
12	F	21	19	6	85	2.76	800	0.06	0.0	22
13	M	32	32	4	90	4.37	800	0.08	0.0	16
14	F	42	11	7	92	9.28	800	0.18	2.0	11
15	M	35	32	2	78	2.60	800	0.14	0.0	14
Mean (SD)		39 (11)	29 (14)		90 (9)	2.76 (2.72)		0.14 (0.07)	0.0 (0.8)	16 (6)
Infected patients										
16	M	21	21	4	81	2.70	800	1.35	1.8	22
17	F	64	4	0	82	3.78	800	0.58	25.3	22
Mean (SD)		42 (11)	13 (12)		82 (1)	3.24 (0.8)		0.96 (0.51)	13.6 (16.6)	22 (0)

ENO Exhaled nitric oxide; Eo Eosinophils; F Female; FEV_1 Forced expiratory volume in 1 s; ICS Inhaled corticosteroids; LABA Long-acting beta-agonists; M Male; PC_{20} Provocative concentration of methacholine causing a 20% fall in FEV_1; ppb Parts per billion; S50/S100 Salmeterol (50 µg/100 µg)

dose. Using a single-blind method, we reduced the inhaled corticosteroid dose either to produce a mild loss of asthma control or to discontinue the corticosteroid without losing asthma control, and we compared the kinetics of symptoms, as well as airway function tests and inflammatory markers, between the two groups of patients (ie, those who had an exacerbation versus those who did not). In addition, we compared baseline measurements between both groups to determine which patients were at higher risk of loss of asthma control.

PATIENTS AND METHODS

Patients

Seventeen adults with asthma were recruited from patients attending the Firestone Chest and Allergy Clinic (Hamilton, Ontario) (Table 1). The diagnosis of asthma was based on episodic chest tightness, dyspnea or wheeze, and airway hyperresponsiveness to methacholine (ie, a PC_{20} of less than 16 mg/mL, where PC_{20} is defined as the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s [FEV_1]). The patients had stable asthma for at least one month and they were on regular treatment with inhaled corticosteroids. They were nonsmokers or ex-smokers of at least six months. The study was approved by the research committee of St Joseph's Healthcare (Hamilton, Ontario) and all patients gave written informed consent.

Design

The study consisted of a single-blind reduction of inhaled corticosteroid therapy. An initial screening visit was followed by a run-in period of one week during which all the patients were switched to an equivalent dose of inhaled budesonide. Following this, the dose of budesonide was reduced by one-half every 20 days to 400 µg and then was replaced by placebo for 20 days. The budesonide and placebo were prepared and blinded by the hospital pharmacy; the patients were told that the budesonide would be either reduced or not reduced, and they were to use it in a dose of two inhalations twice daily. The patients were seen in the laboratory after the run-in period and then every 10 days until asthma became uncontrolled or until they had been on placebo for 20 days. At each study visit, daily diaries were evaluated, and exhaled nitric oxide (ENO) measurements, a methacholine inhalation test, venesection and sputum induction were consecutively performed. A loss of asthma control was defined as a worsening of the symptoms score of at least 20%, and either a decrease in FEV_1 of at least 15% or a decrease in methacholine PC_{20} of at least fourfold. Because the study aimed to examine the loss of asthma control caused by inhaled corticosteroid reduction, patients were withdrawn if the exacerbations were considered to be infective, as indicated by their cold symptoms score (5). At the end of the study, asthma control was re-established with additional budesonide, the baseline dose was resumed and the patient returned to the care of the treating physician.

Procedures

Symptoms were scored with a modified Likert scale (one was the worst and nine was the best) once daily (6). A cold symptoms score (zero to three) evaluated the intensity of symptoms due to viral respiratory tract infections. Symptoms included nasal discharge, sneezing, nasal congestion, sore throat, cough, headache, malaise, chills and fever. Rescue beta-2-agonist use was expressed as the cumulative number of inhalations needed. Peak expiratory flow (PEF) was recorded as the best of three measurements twice a day and diurnal variability was calculated as the amplitude

per cent mean. Spirometry was performed according to the specifications of the American Thoracic Society (7) and FEV_1 was expressed as the per cent predicted. Methacholine inhalation tests were carried out as described by Juniper et al (8) and the results were expressed as the PC_{20} in noncumulative units. ENO was measured by a rapid linear-response chemiluminescence analyzer (Sievers 240, GE Analytical Instruments, USA) as described by Silkoff et al (9). Skin tests were performed by the modified prick technique with 11 common inhalant allergen extracts (10). Sputum was induced with hypertonic saline, selected from the expectorate, processed and examined, as described by Pizzichini et al (11), blind to any clinical details. Sputum eosinophils were expressed as the percentage of nonsquamous cells. Total and differential white blood cell counts were performed on an automatic counter and eosinophil counts were expressed as the number of cells per litre. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-5 were measured in peripheral blood and in sputum using an ELISA (Genzyme Diagnostics, USA). These sputum measurements were expressed per volume of the selected sample.

Statistical analysis

Descriptive statistics were used to summarize clinical and demographic characteristics. Measurement results were sorted by treatment and visit. Data are reported as the arithmetic mean (SD), except eosinophils in sputum and PC_{20}, which are expressed as the median (interquartile range) and the geometric mean (SD), respectively. Baseline and last visit data were used for analyses; the last visit occurred at the exacerbation or, if there was no exacerbation, after 20 days of receiving no corticosteroid treatment. Symptom scores and PEF were based on the mean of the last five days before each visit. A repeated measures ANOVA model was used to analyze the differences between the exacerbated and nonexacerbated group and times. The evaluation of risk factors was performed by logistic regression analysis using block entry of variables and removing them by a backward stepwise method based on the likelihood ratio. Significance was accepted at the 95% level. Data were analyzed using the statistical package SPSS (version 10.0, SPSS Inc, USA) on a PC-compatible computer.

RESULTS

Asthma control

Two patients developed a loss of asthma control associated with infection (one with sinusitis and the other with pharyngitis) and were withdrawn from the study. The results from the remaining 15 patients were analyzed (Table 1). Asthma became uncontrolled in eight patients at an average of 33 days (range 13 to 48 days) after the onset of corticosteroid reduction. Asthma remained controlled in the other seven patients who were followed for an average of 43 days (21 to 69 days). All but one of the 15 patients (whose asthma became uncontrolled on 400 µg/day) were off budesonide at the time that asthma became uncontrolled or at the last visit.

Baseline differences between groups

At baseline, patients whose asthma became uncontrolled showed higher eosinophil counts in blood (P=0.021) compared with the other group (Table 1). Also at baseline, the exacerbated group compared with the nonexacerbated group differed in sputum IL-5 levels (55.1 [45.8] pg/mL versus 12.9 [8.9] pg/mL, respectively; P=0.04) and blood IL-5 levels (25.1 [35.9] pg/mL versus 2.9 [5.9] pg/mL, respectively; P=0.02). Morning PEF, FEV_1, PC_{20}, ENO and eosinophil counts in sputum also tended to be worse in the exacerbated group, but the difference was not significant. There was also a trend for a difference in blood GM-CSF levels (24.1 [31.0] pg/mL in the exacerbated group versus 5.1 [8.0] pg/mL in the nonexacerbated group; P=0.068). Logistic regression identified raised blood eosinophil counts as a strong risk factor for loss of asthma control (risk ratio of 2.5, 95% CI 1.5 to 6.5). Raised ENO levels also tended to predict loss of asthma control (risk ratio of 1.1, 95% CI 0.94 to 1.2).

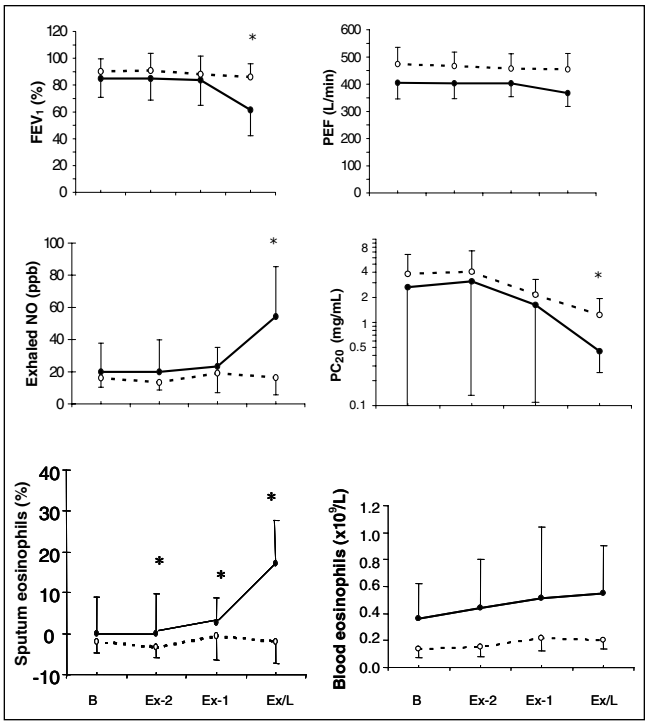

Figure 1) *Changes in forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}), exhaled nitric oxide (NO), blood eosinophil count and sputum eosinophil percentage during corticosteroid reduction. Sputum eosinophil percentage increased at the two visits before exacerbation (Ex-1 and Ex-2), whereas the other variables only showed significant changes at the exacerbation/last visit (Ex/L). The solid line represents the group that had an exacerbation and the dotted line represents the group that did not have an exacerbation. *P<0.05 compared with baseline (B). ppb Parts per billion*

Comparative kinetics of clinical, airway function and inflammatory markers

The reduction in corticosteroid treatment resulted in an increased sputum and blood eosinophil count and ENO level, and decreased FEV_1 and PEF. However, only eosinophil counts in sputum showed a progressive increase until asthma became uncontrolled (P<0.001) (Figures 1 and 2). This increase in eosinophils was observed as early as three visits before asthma became uncontrolled (approximately 30 days), but this only became significantly different between groups (mean increase in the exacerbated group was 1%) two visits before (approximately 20 days, P=0.021). The increase in sputum eosinophils preceded clinical deterioration in all but one patient (patient 8) who already had moderate eosinophilia at baseline. At exacerbation, there was a significant increase in sputum IL-5 levels (an increase of 11.5 pg/mL; P=0.04), but no significant change in blood IL-5 or blood GM-CSF levels. Sputum GM-CSF levels were undetectable at any time. The changes in sputum eosinophil

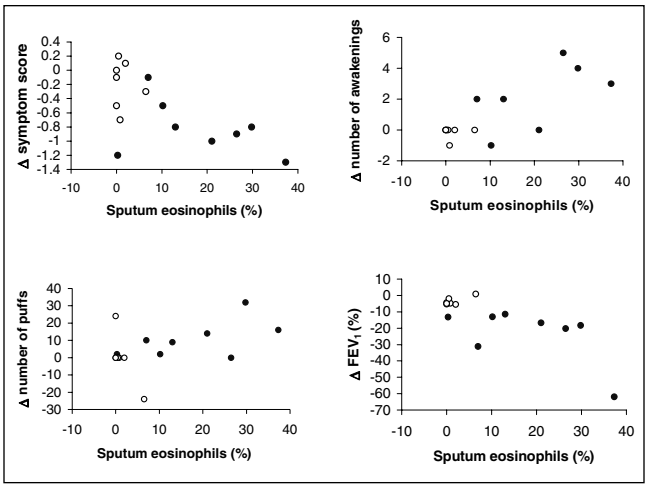

Figure 2) *Correlation between sputum eosinophil percentage at the last visit and changes (Δ) in the measures of asthma control from baseline (symptom score, beta-agonist use, noctural awakenings and forced expiratory volume in 1 s [FEV_1]). The solid circles represent patients whose asthma became uncontrolled and open circles represent patients whose asthma was controlled*

TABLE 2
Symptoms, airway function and inflammatory measurements at baseline, at exacerbation/last visit (Ex/L) and at the two visits before this (Ex-1 and Ex-2)

	Baseline	Ex-1	Ex-2	Ex/L
Exacerbated group				
Symptoms score	8.25 (0.72)	8.31 (0.59)	8.34 (0.61)	7.55 (0.82)
PEF (L/min)	405 (59)	403 (56)	403 (49)	367 (49)
FEV_1 (%)	84.8 (13.9)	84.8 (16.0)	83.8 (18.8)	61.6 (19.4)
PC_{20} (mg/mL)	1.90 (3.33)	1.69 (4.0)	1.75 (1.25)	0.51 (0.12)
Sputum Eo (%)	1.0 (13.2)	2.0 (8.5)	3.9 (4.6)	17.0 (12.6)
ENO (ppb)	19.9 (17.9)	19.9 (20)	23.4 (11.8)	54.3 (31.0)
Blood Eo ($\times 10^9$/L)	0.36 (0.26)	0.44 (0.36)	0.51 (0.53)	0.55 (0.35)
Nonexacerbated group				
Symptoms score	8.01 (1.13)	7.69 (1.19)	7.93 (1.24)	7.83 (1.42)
PEF (L/min)	474 (61)	467 (51)	457 (55)	454 (59)
FEV_1 (%)	90.1 (9.5)	90.9 (12.7)	90.9 (12.7)	86.4 (10.1)
PC_{20} (mg/mL)	2.76 (2.72)	2.78 (3.17)	1.76 (1.13)	1.20 (0.70)
Sputum Eo (%)	0.0 (0.8)	0.0 (0.5)	1.0 (0.6)	0.5 (2.3)
ENO (ppb)	16.1 (5.7)	13.3 (4.7)	19.1 (12.1)	16.4 (10.8)
Blood Eo ($\times 10^9$/L)	0.14 (0.07)	0.15 (0.06)	0.22 (0.10)	0.20 (0.06)

ENO Exhaled nitric oxide; Eo Eosinophils; FEV_1 Forced expiratory volume in 1 s; PC_{20} Provocative concentration of methacholine causing a 20% fall in FEV_1; PEF Peak expiratory flow; ppb Parts per billion

counts before and after the loss of control were directly related to the change in blood IL-5 levels (r=0.48; P=0.034), but not to the change in blood GM-CSF levels. All other variables only changed at the time of loss of asthma control (Table 2).

The proportions of sputum eosinophils in both groups at the end of the study were significantly related to the change in the symptoms score (r=–0.50, P=0.045), number of awakenings (r=0.78, P=0.001), number of inhalations of rescue medication (r=0.52, P=0.047) and FEV_1 (r=–0.77, P=0.001) (Figure 2).

DISCUSSION

The results illustrate that the reduction of corticosteroid treatment caused a mild loss of control of asthma in approximately one-half of the patients who were previously well controlled. These patients had a higher baseline blood eosinophil count, as well as higher blood and sputum IL-5 levels, and tended to have higher sputum eosinophil counts and ENO levels, and a lower PEF, FEV_1 and methacholine PC_{20}. Sputum eosinophil counts increased first (before asthma became uncontrolled) followed by a fall in the mean daily PEF (before worsening of symptoms and other parameters). The magnitude of the increase of eosinophils correlated with the loss of control. The results suggest that it may not be advisable to reduce the dose of corticosteroids further in patients with stable asthma if they have a raised blood eosinophil count or show a trend toward an increased sputum eosinophil count.

The results confirm the observations of others that a reduction in inhaled corticosteroid treatment in corticosteroid-dependent patients with asthma can be followed by a worsening of symptoms and airway function, as well as airway inflammation (12-15). The observation that sputum eosinophilia precedes the clinical loss of asthma control is similar to the observations of Leuppi et al (14) and Jatakanon et al (15). In these studies, inhaled corticosteroids were reduced until 200 μg/day or by 50%. We went further by completely withdrawing inhaled corticosteroids in a progressive, stepwise and safe manner that is easy to apply in clinical settings similar to that used by Leuppi et al (14). Similar to previous reports (14,15), we found that the deterioraton of airflow limitation was related to eosinophilic airway inflammation. In addition, we observed that airway eosinophilia was also related to the severity of symptoms; moreover, in agreement with previous reports (14-16), it preceded both airflow limitation and symptoms. The increase in sputum eosinophil count may have been facilitated by an increase in blood IL-5 levels, but other mechanisms, such as decreased apoptosis and increased survival, may have played a role. The observation that sputum eosinophils increased before ENO levels increased is in keeping with the greater sensitivity of ENO to treatment with inhaled corticosteroid and indicates that ENO is not a sensitive marker of an exacerbation of eosinophilic bronchitis when the patient is already on corticosteroid treatment (17). However, raised ENO levels may be a baseline predictor of exacerbation. The present study may not have had the power to detect this.

We used the corticosteroid reduction model that was described by Gibson et al (18) and used by in't Veen et al (19) to study the kinetics of change in clinical and inflammatory parameters during a mild exacerbation of asthma. However, rather than making 50% reductions every week, we reduced the inhaled corticosteroid more slowly, by 50% every 20 days. This approach allowed us to study the kinetics of changes in clinical and inflammatory markers more carefully. We reduced the inhaled corticosteroid in a single-blind manner to overcome the expectation that patients' symptoms should become worse. The effectiveness of this approach is illustrated by the lack of symptomatic exacerbations in just under one-half of the patients. We also performed the sputum cell counts blind to the clinical details; the appropriateness of this is illustrated by the observation that the proportion of sputum eosinophils only increased in patients with clinical deterioration. Finally, because we wished to examine loss of asthma control due to a reduction of corticosteroid treatment, we withdrew two patients from the analysis who had exacerbations that seemed to be clinically associated with confounding infections. This may not have been appropriate because, in retrospect, their

clinical and inflammatory findings were similar to the other exacerbations. Our observations that baseline sputum eosinophil count was not a predictor of loss of control may be due to the fact that that all but two patients whose asthma became uncontrolled had normal values. The study may also have been underpowered to detect differences in other baseline variables.

The results of the present study are relevant to asthma treatment and confirm previous observations that sputum eosinophil counts are useful in monitoring the dose of inhaled corticosteroids in patients with asthma. Specifically, just as they are useful in titrating up the dose of corticosteroids to maintain eosinophil counts less than 2%, they are also helpful in reducing the dose of corticosteroids when asthma control is established (3,4). However, there are no precise guidelines on stepping down corticosteroids. The present study suggests that it may be possible to reduce the dose of inhaled corticosteroids in approximately 50% of patients with asthma. However, caution should be exercised in reducing the dose in patients who have a raised blood eosinophil count and in those whose sputum eosinophil count increases by as little as 1% because these are predictors of loss of asthma control. This is in agreement with the recent observation by Deykin et al (20), who reported that a 0.8% increase in sputum eosinophil count two weeks after discontinuation of inhaled triamcinolone is a predictor of loss of asthma control over the ensuing 16 weeks. These observations suggest that it may be appropriate to maintain sputum eosinophilia at less than 1% (instead of the 2% or 3% reported by Green et al [3] and Jayaram et al [4]) for more optimal asthma control; however, this needs to be tested in clinical trials.

In summary, in patients whose asthma is well controlled on their current dose of inhaled corticosteroids, it is prudent not to reduce the dose further if their blood eosinophils are increased or if their sputum eosinophils increase with reduction by as little as 1%.

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