

Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids

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Background: Although inhaled corticosteroids (ICSs) are effective in preventing deterioration in asthma control, at least half of subjects with mild-to-moderate asthma will remain stable when these agents are discontinued.

Objective: We sought to determine whether noninvasive markers of inflammation predict which individuals maintain asthma control after discontinuation of ICSs.

Methods: We analyzed data obtained from 164 subjects with mild-to-moderate asthma who participated in a 16-week trial comparing the effects of continued ICS use with the effects of a switch to salmeterol or placebo.

Results: In comparison with continued ICS use, a switch to salmeterol or placebo was associated with increased rates of asthma deterioration over 16 weeks (9.3% vs 24.1% and 37.5%, respectively; $P = .04$ and $P < .001$, respectively). We found that neither exhaled nitric oxide nor methacholine PC₂₀,

when measured at randomization or 2 weeks after randomization, were significant predictors of subsequent asthma control in subjects who discontinued ICSs. However, both induced sputum eosinophil counts measured 2 weeks after a switch from ICS to placebo and changes in sputum eosinophil counts from before cessation of ICSs to after a switch to placebo predicted subsequent asthma deterioration (area under the receiver-operating characteristic curve, 0.771 [$P < .001$] and 0.825 [$P < .001$], respectively).

Conclusion: On the basis of a model treatment strategy, we estimate that allocating subjects to ICS therapy on the basis of changes in sputum eosinophil counts after a trial discontinuation could allow 48% of subjects with mild-to-moderate asthma to discontinue ICS therapy without an increased risk of asthma deterioration over a period of at least 14 weeks. (*J Allergy Clin Immunol* 2005;115:720-7.)

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Increases in the fraction of exhaled nitric oxide (FENO), sputum eosinophil counts, and airway reactivity are associated with asthma and are believed to reflect the underlying airway inflammation that characterizes this disease.¹⁻⁶ Levels of these markers further increase during experimental and clinical deteriorations of asthma and are reduced by treatment with anti-inflammatory asthma therapies.⁷⁻¹¹ Previous studies have examined the utility of multiple serial measurements of these markers with respect to predicting asthma outcomes in small groups of subjects over short observation periods; the results of these trials are equivocal.¹²⁻¹⁴

Approximately 15 million Americans have asthma,¹⁵ and of these individuals, it is estimated that 50% meet the definition of mild-to-moderate persistent disease.^{16,17} For patients with this severity of disease, current international guidelines recommend continuous therapy with inhaled corticosteroids (ICSs).^{18,19} In light of the improved understanding of the potential toxicities of long-term ICS use²⁰⁻²² and the results of several studies demonstrating that 45% to 85% of asthmatic subjects whose symptoms are controlled with ICSs will maintain control after cessation of these agents,²³⁻²⁶ the ability to prospectively identify individuals with asthma who require ICSs for maintenance of asthma control over several months would be clinically valuable.

To further define the clinical utility of early changes in FENO, induced sputum markers, and methacholine airway responsiveness in identifying subjects at risk for deterioration in asthma symptoms after ICS cessation, we constructed receiver-operating characteristic (ROC) curves to analyze the ability of these markers to predict subsequent asthma deterioration in subjects undergoing ICS withdrawal in the previously published Asthma Clinical Research Network's Salmeterol or Corticosteroids (SOCS) trial.²³

METHODS

SOCS trial subjects and study design

The SOCS trial enrolled clinically stable, nonsmoking individuals meeting the American Thoracic Society definition of mild-to-moderate asthma and not using any controller medications with the exception of ICSs, as previously described.²³ In brief, the SOCS trial was a 28-week, randomized, double-blind, placebo-controlled, multicenter trial in subjects with persistent asthma comparing the efficacy of an ICS (triamcinolone acetonide [TAA], 400 μ g twice daily) with that of an inhaled long-acting β -adrenergic agonist (salmeterol xinafoate, 42 μ g twice daily) and placebo during 16 weeks of active therapy.

A schematic of the study design is presented in Fig 1. On entry into the trial, subjects completed a 6-week run-in period during which they received open-label TAA, 400 μ g twice daily. At the end of the run-in period, protocol-adherent subjects with an FEV₁ of greater than 80% of predicted value and an average peak expiratory flow variability of 20% or less were randomized to receive either TAA (400 μ g twice daily plus salmeterol placebo), salmeterol (42 μ g twice

Abbreviations used

ECP: Eosinophil cationic protein
FENO: Fraction of exhaled nitric oxide
ICS: Inhaled corticosteroid
ROC: Receiver-operating characteristic
SOCS trial: Salmeterol or Corticosteroids trial
TAA: Triamcinolone acetonide

daily plus TAA placebo), or long-acting β -agonists and ICS placebos for the next 16 weeks. After randomization, subjects returned to the study centers every 2 to 4 weeks for follow-up reassessment. Among other time points,²³ subjects provided exhaled gas for nitric oxide measurements and underwent methacholine bronchial provocation and sputum induction for quantification of sputum differential counts at 2 and 4 weeks after randomization. Methacholine provocation was conducted as previously described.^{23,27} Detailed descriptions of the exhaled nitric oxide measurements and sputum induction techniques are presented in the Journal's Online Repository at www.mosby.com/jaci.

Clinical outcomes

In the SOCS trial the criteria for determining asthma exacerbations and asthma treatment failures were predefined. Because both exacerbations and treatment failures represent clinical events that would induce physicians to intensify asthma therapy, we defined a combined end point for this analysis, asthma deteriorations, as worsening of asthma meeting the criteria for either asthma exacerbation or asthma treatment failure. The specific criteria for asthma deterioration are presented in Table I.

Statistical analysis

Comparisons of marker values before and after withdrawal of corticosteroids were performed by using the Student *t* test or Sign test, as appropriate. Rates of asthma deteriorations in each treatment group were compared with the χ^2 test.

ROC curves were constructed by plotting the sensitivity of the marker test compared with its specificity across the range of values observed to determine the accuracy of the various markers examined to predict the occurrence of asthma deterioration.²⁸ The area under the ROC curve, which varies from 0.5 to 1.0, is a measure of the accuracy of the test for the outcome under examination. ROC analysis has been used to describe predictive tests for common clinical conditions, such as myocardial ischemia, and the presence of allergies, asthma, and asthma exacerbations.^{3,12,29-35} In this study areas under the ROC curves were compared by using the method of Hanley and McNeil.³⁶ Construction of the ROC curves, comparison between areas under the ROC curve, and tests of significant prediction were performed with Analyse-it version 1.61 (February 2001; Analyse-it, Inc, Leeds, England).

RESULTS

Study population

As previously reported, 164 subjects successfully completed the single-blind triamcinolone run-in period and were randomized into the SOCS trial.²³ Of these individuals, 56 were randomly allocated to receive double-blind placebo therapy, 54 were randomized to receive therapy with salmeterol, and 54 were allocated to

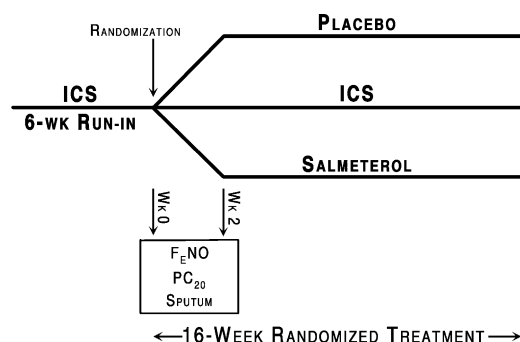


FIG 1. Schematic diagram of the SOCS study and the time points for F_ENO measurement, methacholine PC₂₀ measurement, and sputum induction included in the analysis.

TABLE I. Criteria for determining asthma deterioration

Increased cough, chest tightness, and wheezing with one or more of the following:
• ≥ 8 Puffs of rescue albuterol over reference value* in a 24-h period
• ≥ 16 Puffs of rescue albuterol in a 48-h period
• Peak flow expiratory flow rate $< 65\%$ of reference value*
• Symptoms despite 60 min of treatment
• Requirement for systemic corticosteroids
>1 Emergency department or urgent care visit for treatment of asthma exacerbation
Hospitalization for the treatment of asthma
Physician clinical judgment for safety

*The reference value was defined as the average value measured during the last 2 weeks of the run-in period.

TABLE II. Characteristics at randomization of subjects in the SOCS trial

Characteristic	Placebo (n = 56)			Salmeterol (n = 54)			Triamcinolone (n = 54)			P value
Female sex, n (%)	38	(67.9)		33	(61.1)		36	(66.6)		.768
Nonwhite, n (%)	18	(32.1)		13	(24.1)		18	(33.3)		.552
Use of ICS on entry, n (%)	52	(92.9)		53	(98.2)		54	(100)		.128
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Age (y)	56	31.2	10.6	54	31.2	10.8	54	31.3	11.0	.978¶
Puff β -agonist/d*	56	0.445	0.000-2.307	54	1.129	0.067-3.133	54	0.750	0.200-2.476	.501#
FEV ₁ (L)†	56	3.066	0.623	54	3.105	0.786	54	3.213	0.646	.513¶
FEV ₁ (% predicted)†	56	93.25	8.286	54	92.54	8.645	54	95.67	10.35	.178¶
Methacholine PC ₂₀ (mg/mL)†‡	52	0.767	0.277-1.668	53	0.885	0.300-1.970	54	0.966	0.395-2.050	.498#
Sputum eosinophils (%)†§	50	0.7	0.2-2.0	46	0.6	0.0-1.8	46	0.6	0.0-1.8	.833#
Sputum ECP†§	48	72.00	35.50-189.0	46	66.50	35.00-148.0	46	62.50	35.00-140.0	0.868#
FENO (ppb)†§	26	14.3	11.4-24.5	27	14.1	8.8-29.7	26	15.7	11.3-28.4	.939#
Dose of ICS at entry (μ g/d)	52	565.3	391.4	53	488.2	237.6	54	507.5	309.8	.438¶

*Average over weeks 5 and 6 of the run-in period.

†Average from week 6 of the run-in period.

‡Geometric mean and first and third quartile reported.

§Median and first and third quartile reported.

||Fisher exact test (2-tailed) for differences in proportions across treatment groups.

¶One-way ANOVA testing for differences across treatment groups.

#Kruskal-Wallis test for differences across treatment groups.

receive therapy with continued triamcinolone. The baseline characteristics at randomization of the subjects in each of these treatment groups are provided in Table II. There were no significant differences among the groups with regard to age, sex, race, or baseline physiologic parameters.

Changes in inflammatory markers after randomization

We assessed the change in sputum eosinophil counts and eosinophil cationic protein (ECP) levels, FENO, and methacholine PC₂₀ that occurred during the first 2 weeks of randomized therapy in the subjects who had maintained per-protocol treatment and had available inflammatory marker data. Sputum eosinophil counts did not change during 2 weeks of continued double-blind treatment with triamcinolone (Fig 2, A). In contrast, sputum eosinophil counts increased when subjects stopped ICSs and switched to salmeterol treatment. In these subjects sputum

eosinophil counts increased from 0.6% (first and third quartiles, 0.0% and 1.6%) to 1.9% (first and third quartiles, 0.4% and 9.6%; $P < .0001$). Similarly, in subjects who discontinued triamcinolone and switched to placebo therapy, sputum eosinophil counts significantly increased from 0.3% (first and third quartiles, 0.1% and 1.8%) at randomization to 1.6% (first and third quartiles, 0.3% and 7.7%) when measured 2 weeks later ($P = .004$).

Similar to sputum eosinophil counts, sputum ECP levels did not change during 2 weeks of continued double-blind treatment with triamcinolone (Fig 2, B). In contrast, sputum ECP levels increased when subjects stopped ICSs and switched to salmeterol treatment. In these subjects sputum ECP levels increased from 66.5 μ g/L (first and third quartiles, 37.0 and 180.0 μ g/L) to 166 μ g/L (first and third quartiles, 55.5 and 640.0 μ g/L; $P < .0001$). Similarly, in subjects who discontinued triamcinolone and switched to placebo therapy, sputum ECP levels increased from 72.0 μ g/L (first and third quartiles, 14.5

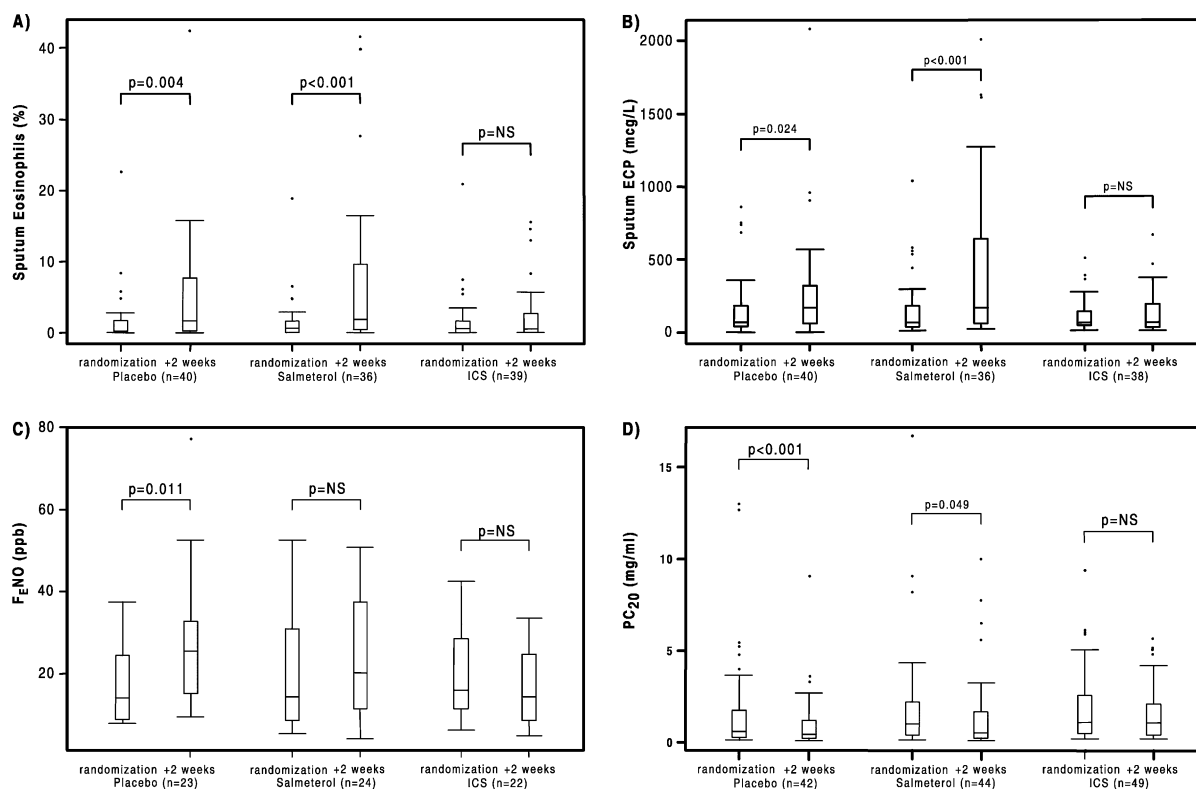


FIG 2. Box plots of sputum eosinophil counts (**A**), sputum ECP levels (**B**), FENO values (**C**), and methacholine PC₂₀ values (**D**) in each of the treatment groups at randomization and after 2 weeks of double-blind therapy. By convention, the horizontal bar represents the median value, the length of the box represents the interquartile range, and the whiskers are drawn to the nearest value not beyond 1.5 interquartile range from the quartiles. Differences between time points were assessed by using the Sign test for FENO values and sputum eosinophil counts and the Student *t* test for methacholine PC₂₀ values.

and 187.50 $\mu\text{g/L}$) at randomization to 170.5 $\mu\text{g/L}$ (first and third quartiles, 63.5 and 320.0 $\mu\text{g/L}$) when measured 2 weeks after a switch to placebo ($P = .024$).

FENO values did not increase significantly during the 2 weeks after randomization when ICSs were continued or when salmeterol was substituted for ICSs (Fig 2, C). In contrast, in subjects who discontinued use of ICSs at randomization and switched to placebo, FENO values increased during the 2 weeks after the switch. In these subjects FENO values increased from 14.2 ppb (first and third quartiles, 8.8 and 24.5 ppb) to 25.6 ppb (first and third quartiles, 15.0 and 30.7 ppb; $P = .011$).

After 2 weeks of randomized therapy, the methacholine PC₂₀ value was 1.000 mg/mL (first and third quartiles, 0.307 and 2.040 mg/mL) and was unchanged compared with randomization baseline (1.040 mg/mL [first and third quartiles, 0.429 and 2.500 mg/mL]) in the subjects who continued ICSs. In contrast, airway hyperresponsiveness increased (as indicated by a decrease in the PC₂₀ value) in comparison with randomization values in those subjects who discontinued ICSs and switched to either salmeterol or placebo (Fig 2, D). In the subjects who switched to salmeterol, methacholine PC₂₀ values measured 2 weeks after discontinuation of ICSs decreased from 0.974 mg/mL (first and third quartiles, 0.365 and 2.180 mg/mL) to

0.493 mg/mL (first and third quartiles, 0.194 and 1.640 mg/mL; $P = .049$). In the subjects who discontinued triamcinolone and switched to placebo, methacholine PC₂₀ values decreased from 0.611 mg/mL (first and third quartiles, 0.284 and 1.780 mg/mL) to 0.436 mg/mL (first and third quartiles, 0.214 and 1.210 mg/mL) measured 2 weeks after randomization ($P < .001$).

Prediction of asthma control

As demonstrated in Table III, more subjects who continued triamcinolone therapy did not meet the deterioration criteria and maintained asthma control compared with those subjects who switched to salmeterol or placebo ($P < .05$ and $P < .001$, respectively).

To explore the ability of FENO, methacholine PC₂₀, and sputum markers measured at randomization and 2 weeks after randomization to predict subsequent asthma control occurring over the remaining 14 weeks of the trial in the subjects who switched to placebo, we constructed ROC curves for the occurrence of clinical asthma deterioration by using these marker data. The areas under the ROC curves for each of these markers in the subjects who switched from ICSs to placebo are presented in Table IV. Of the 56 subjects randomized to discontinue triamcinolone and switch to placebo, 46 subjects had not experi-

TABLE III. Asthma deteriorations in the 3 treatment groups

Therapy	No. of subjects with asthma deteriorations		Total
	Initial 2 wk	Subsequent 14 wk	
Triamcinalone (n = 54)	2*	3*†	5†‡
Salmeterol (n = 54)	2*	11	13§
Placebo (n = 56)	10	11	21

**P* < .05 versus placebo.†*P* < .05 versus salmeterol.‡*P* < .001 versus placebo.§*P* = .13 versus placebo.

enced asthma deterioration 2 weeks after randomization. These subjects were included in the ROC analysis indicated in Table IV.

Although FENO and methacholine PC₂₀ values provided no predictive information, sputum eosinophil counts and sputum ECP levels predicted subsequent asthma control (Table IV and Figure E1 available in the Journal's Online Repository at www.mosby.com/jaci). Sputum eosinophils, when measured 2 weeks after discontinuation of ICSs and when expressed as the change in sputum eosinophil counts from randomization to 2 weeks after randomization, were powerful predictors of subsequent asthma control between weeks 2 and 16, with respective areas under the ROC curve of 0.771 (95% CI, 0.603-0.940) and 0.825 (95% CI, 0.686-0.964; *P* < .001 for prediction). The sensitivity and specificity of the change in sputum eosinophil counts at a cutoff value of 0.8% for subsequent loss of asthma control was 90% and 65%, respectively.

The clinical implications of administering treatment on the basis of a change in sputum eosinophil percentage by using the 0.8% threshold are modeled in Fig 3. By using a traditional, unstratified approach guided by current recommendations,^{18,19} 1000 patients similar to those enrolled in the SOCS trial would currently be prescribed continuous ICSs. On the basis of the findings of the SOCS trial, in which symptoms in 9.3% of patients deteriorated while taking ICSs, 93 of these individuals would experience an asthma deterioration event over 16 weeks of observation (Fig 3, A).

In contrast, a clinical strategy presented in Fig 3, B, that mimics the SOCS study structure and targets readministration of ICSs to those asthmatic subjects with large increases in sputum eosinophil counts after a 2-week period of ICS discontinuation could produce similarly low rates of asthma deteriorations while decreasing the number of individuals treated with ICSs by 48%. On the basis of the results of the SOCS trial, this model (which includes the use of salmeterol during the first 2 weeks of ICS discontinuation) indicates that 37 of 1000 individuals similar to those enrolled in the SOCS trial would experience deterioration during an initial 2-week period of substitution of salmeterol for ICSs. After this period and reassessment of sputum eosinophil counts, the model predicts that 482 of the remaining 963 individuals would be found to have a change in sputum eosinophil percent-

age of 0.8% or less and that with treatment with as-required β -agonists alone, 27 of these 482 subjects would experience asthma deterioration over the subsequent 14 weeks.

In contrast to these patients with small increases in sputum eosinophil percentages, the 481 patients with an increase of greater than 0.8% could be targeted for therapy with ICSs on the basis of their increased risk for experiencing asthma deteriorations. Assuming a slightly higher rate of deterioration in this group with higher eosinophil changes than in the unstratified groups of SOCS subjects who received ICS therapy (6.0% compared with 5.8%), 29 of these 481 patients would be expected to have asthma deteriorations over 14 weeks of observations, whereas 452 would remain free of asthma deteriorations during this time period. Thus the model predicts a total of 93 deteriorations by using an induced sputum eosinophil-guided strategy (Fig 3, B), which is equivalent to the number of deteriorations expected with currently recommended treatment, with which all such patients would receive continuous ICS therapy (Fig 3, A).

DISCUSSION

Current international guidelines recommend that individuals with mild-to-persistent asthma receive continuous therapy with ICSs.^{18,19} Although one of the stated goals of this therapeutic recommendation is the prevention of asthma attacks, several studies have shown that a large proportion of subjects with well-controlled asthma, similar to those we studied, will not have exacerbations when ICSs are withheld.²⁴⁻²⁶

Our retrospective analysis has demonstrated that the change in the percentage of eosinophils in induced sputum during the first 2 weeks after ICS cessation is a useful predictor of subsequent deterioration of asthma control. Neither FENO nor methacholine was a robust predictor in this regard. The ability of the change in sputum eosinophil counts to identify asthmatic subjects who will not maintain asthma control after discontinuation of ICSs compares favorably with other standard tests used in clinical decision making, such as creatine kinase MB, troponin T, and myoglobin as predictors of myocardial infarction.^{30,37,38}

In a previous study we found that sputum eosinophil counts measured at baseline correlated with improvements in airway hyperresponsiveness observed after 21 weeks of ICS therapy.³⁹ The current analysis now suggests that measurement of sputum eosinophil counts might also provide prognostic information with respect to asthma control. Our findings extend those reported by Green et al,⁴⁰ who noted that sputum eosinophil counts performed well as an asthma treatment end point. In their study titration of anti-inflammatory therapy to achieve a sputum eosinophil count of less than 3%, with sputum analyses performed up to monthly, resulted in improved clinical outcomes with equivalent doses of ICSs compared with care standardized to current guidelines. Similarly, Leuppi

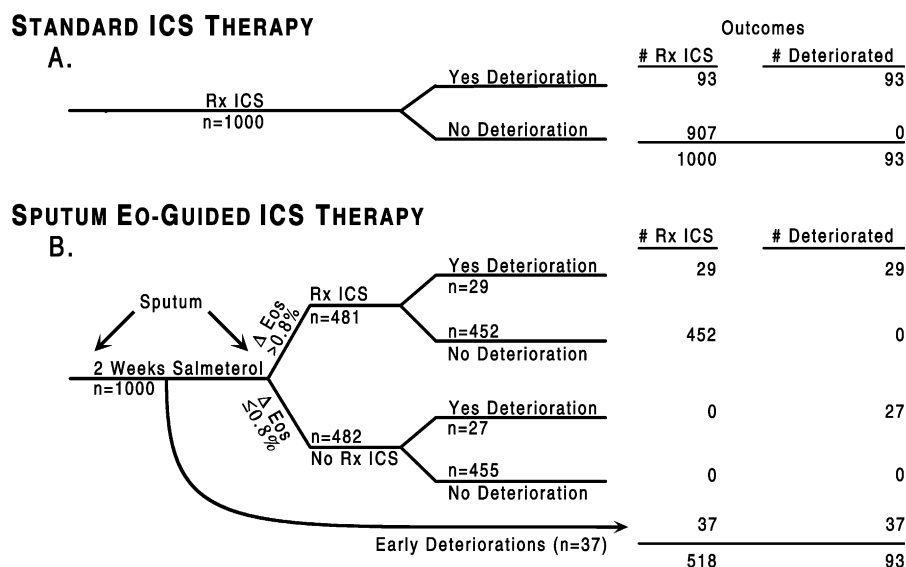


FIG 3. Modeled asthma outcomes on the basis of the data from the SOCS trial of 1000 subjects with mild-to-moderate asthma treated with standard continuous ICSs (**A**) and those of 1000 similar asthmatic subjects selectively withdrawn from ICSs on the basis of sputum eosinophil changes during a short trial discontinuation period (**B**). See text for details.

TABLE IV. Areas under the ROC curves and *P* values for predicting asthma deterioration after cessation of ICS therapy with inflammatory markers

	Inflammatory marker							
	FENO (n = 20)		Sputum eosinophils (n = 36)		Sputum ECP (n = 36)		Methacholine PC ₂₀ (n = 38)	
	AUC ± SE	P value	AUC ± SE	P value	AUC ± SE	P value	AUC ± SE	P value
Randomization	0.660 ± 0.129	.108	0.540 ± 0.109	.356	0.512 ± 0.112	.459	0.598 ± 0.112	.191
+ 2 wk	0.640 ± 0.129	.140	0.771 ± 0.086	.0008	0.669 ± 0.108	.058	0.527 ± 0.117	.409
Delta	0.507 ± 0.166	.484	0.825 ± 0.071	<.0001	0.796 ± 0.075	<.0001	0.548 ± 0.110	.331

et al¹² noted that sputum eosinophil counts, when measured during reduction of ICSs, predicted predefined exacerbations occurring at the next monthly follow-up visit. Our analysis, using data derived from multiple sites, suggests that measurement of sputum eosinophil counts before and 2 weeks after ICS cessation can predict outcomes and thus guide therapy over a longer interval (14 weeks). In this regard and if confirmed, our technique, which involves only 2 measurements of sputum eosinophil counts and provides prognostic information for a longer period of time, might be more clinically feasible and of greater clinical value than those previously reported.

The clinical implications of our findings, as suggested in the model we present, are substantial. We have demonstrated that a change in sputum eosinophil counts of greater than 0.8% in the 2 weeks after ICS discontinuation has a high sensitivity (90%) for subsequent asthma deterioration occurring over the subsequent 14 weeks. In this regard our findings suggest that a sputum eosinophil-guided therapeutic strategy, which allows the 50% of subjects with clinically stable asthma with a change in

eosinophil counts of 0.8% or less during the first 2 weeks after ICS cessation to remain off ICSs and prompts reinstitution of ICSs in those individuals with larger changes in sputum eosinophil counts, would result in overall rates of asthma control no different from those achieved with continuous ICS therapy consistent with current guidelines.^{18,19}

Application of a targeted strategy on the basis of our model to the treatment of mild-to-moderate persistent asthma (comprising approximately 7 million Americans) has important economic implications.¹⁷ At an average cost of \$550 (\$45 per canister), the annual cost for treating all subjects with stable, mild-to-moderate persistent asthma with continuous ICSs is approximately \$4 billion.⁴¹ Under a sputum eosinophil-guided strategy, the number of such individuals who would be treated with continuous ICSs would be reduced by approximately 50%, with potential savings of nearly \$2 billion in medication costs annually. Furthermore, a targeted treatment strategy could provide additional benefits with respect to limiting the small but real risk of bone loss, glaucoma, and cataracts that might occur with long-term exposure to ICSs as well.²⁰⁻²² In this

regard, our findings, if confirmed by future prospective trials with a longer observation period, could inform changes in the current approach to therapy for individuals with mild-to-moderate asthma, the largest group of asthmatic subjects.¹⁷

Although our findings suggest that changes in sputum eosinophil counts can predict loss of asthma control, our present study does not allow us to determine the role of airway eosinophils in propagating asthma instability. Although eosinophils, potentially through elaboration of inflammatory mediators, such as leukotriene E₄, ECP, and RANTES, have the capacity to promote airway narrowing, hyperresponsiveness, and inflammatory cell infiltration, reduction of sputum eosinophils with anti-IL-5 has not been associated with protection against allergen-induced bronchoconstriction or hyperresponsiveness.^{42,43} Thus it is possible that after ICS withdrawal, sputum eosinophilia is a marker for a more complex inflammatory process resulting in asthma deterioration. Our observation that sputum eosinophil counts, but not methacholine PC₂₀ or FENO values, predict loss of asthma control suggests that eosinophils might be more integral to the pathobiology of asthma instability than either of these other markers. This conclusion is further supported by the results of previous studies that have found limited utility for either methacholine responsiveness or FENO with respect to predicting asthma control.^{12,44}

We report that the change in sputum eosinophil counts after cessation of ICSs that predicted an increased risk of subsequent asthma deterioration in our study is numerically small (>0.8%). In this regard we acknowledge that the ability to resolve such a difference in a single individual might appear to be difficult in a clinical setting. However, it is important to recognize that these data were obtained from sputum assays that were performed at 5 distinct sites. Furthermore, the standard protocol used for this measurement has been previously validated, and a 0.8% change in eosinophils is larger than the acceptable interreader variability of this technique.⁴⁵ However, it is clear that before our results can be extended to clinical practice, confirmation of these findings outside a research setting is needed.

We also note that our treatment strategy involves the short-term use of salmeterol during the first 2 weeks after ICS discontinuation. Although we have previously reported that substitution of salmeterol for an ICS provides inadequate protection against asthma exacerbations and treatment failures over 16 weeks,²³ our current analysis suggests that over a 2-week period, salmeterol monotherapy achieves asthma control that is not different from that observed with continued use of ICSs (Table III). In this respect the short-term salmeterol monotherapy component of the treatment strategy we present appears to be safe.

In summary, our retrospective analysis demonstrates that in subjects with clinically stable asthma with normal pulmonary function using ICSs, measurement of sputum eosinophil counts before and 2 weeks after ICS discontinuation identifies individuals who can safely discontinue ICSs, as assessed on the basis of asthma stability, over the

subsequent 14 weeks. Such a strategy produces asthma control outcomes similar to those that would be expected under current recommendations for universal use of ICSs in this population. Although measurement of sputum eosinophil counts is not a current component of routine clinical practice, confirmation of our findings with a future prospective trial of longer duration, in concert with recent evidence suggesting that suppression of sputum eosinophils might be a valid target for asthma therapy,⁴⁰ could provide a rationale for more widespread evaluation of sputum eosinophil counts for the optimal management of asthma.

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