

Long-Acting β_2 -Agonist Monotherapy vs Continued Therapy With Inhaled Corticosteroids in Patients With Persistent Asthma

A Randomized Controlled Trial

Stephen C. Lazarus, MD

Homer A. Boushey, MD

John V. Fahy, MD

Vernon M. Chinchilli, PhD

Robert F. Lemanske, Jr, MD

Christine A. Sorkness, PharmD

Monica Kraft, MD

James E. Fish, MD

Stephen P. Peters, MD, PhD

Timothy Craig, DO

Jeffrey M. Drazen, MD

Jean G. Ford, MD

Elliot Israel, MD

Richard J. Martin, MD

Elizabeth A. Mauger, PhD

Sami A. Nachman, MD

Joseph D. Spahn, MD

Stanley J. Szeffler, MD

for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute

REGULAR USE OF LONG-ACTING β_2 -agonists has been shown to be more effective than regular use of albuterol sulfate, a short-acting β_2 -agonist, at improving peak expiratory flow (PEF) and reducing asthma symptoms.^{1,2} Asthma treatment guidelines³ recommend addition of a long-acting β_2 -agonist for asthma inad-

Context Long-acting β_2 -agonists are prescribed for patients with persistent asthma and are sometimes used without inhaled corticosteroids (ICSs). No evidence exists, however, to support their use as monotherapy in adults with persistent asthma.

Objective To examine the effectiveness of salmeterol xinafoate, a long-acting β_2 -agonist, as replacement therapy in patients whose asthma is well controlled by low-dose triamcinolone acetonide, an ICS.

Design and Setting A 28-week, randomized, blinded, placebo-controlled, parallel group trial conducted at 6 National Institutes of Health–sponsored, university-based ambulatory care centers from February 1997 to January 1999.

Participants One hundred sixty-four patients aged 12 through 65 years with persistent asthma that was well controlled during a 6-week run-in period of treatment with inhaled triamcinolone (400 μ g twice per day).

Interventions Patients were randomly assigned to continue triamcinolone therapy (400 μ g twice per day; n=54) or switch to salmeterol (42 μ g twice per day; n=54) or to placebo (n=56) for 16 weeks, after which all patients received placebo for an additional 6-week run-out period.

Main Outcome Measures Change in morning and evening peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV₁), self-assessed asthma symptom scores, rescue albuterol use, asthma-specific quality-of-life scores, treatment failure, asthma exacerbation, bronchial reactivity, and markers of airway inflammation, compared among the 3 treatment groups.

Results During the 16-week randomized treatment period, no significant differences between the salmeterol and triamcinolone groups were observed for conventional outcomes of clinical studies of asthma therapy—morning PEF, evening PEF, asthma symptom scores, rescue albuterol sulfate use, or quality of life. Both active treatments were superior to placebo. However, the salmeterol group had more treatment failures than the triamcinolone group (13/54 [24%] vs 3/54 [6%]; $P=.004$), as well as more asthma exacerbations (11/54 [20%] vs 4/54 [7%]; $P=.04$), greater increases in median (interquartile range) sputum eosinophils (2.4% [0.0% to 10.6%] vs -0.1% [-0.7% to 0.3%]; $P<.001$), eosinophil cationic protein (71 [-2 to 430] U/L vs -4 [-31 to 56] U/L; $P=.005$), and tryptase (3.1 [2.1 to 7.6] ng/mL vs 0.0 [0.0 to 0.7] ng/mL; $P<.001$). The duration of benefit when patients were switched from active treatment to placebo after 22 weeks of randomized treatment was not significantly longer in the triamcinolone group than in the salmeterol group.

Conclusions Patients with persistent asthma well controlled by low doses of triamcinolone cannot be switched to salmeterol monotherapy without risk of clinically significant loss of asthma control.

JAMA. 2001;285:2583-2593

www.jama.com

See also pp 2594 and 2637.

Author Affiliations and Financial Disclosures are listed at the end of this article.
Corresponding Author and Reprints: Stephen C.

Lazarus, MD, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143-0111 (e-mail: lazma@itsa.ucsf.edu).

Box 1. Inclusion Criteria**Inclusion Criteria for Study Entry (Triamcinolone Run-in Period)**

1. Age 12 through 65 years
2. For patients not already receiving an ICS:
FEV₁ \leq 80% of predicted value; and
Documentation of \geq 12% increase in FEV₁ after aerosolized albuterol treatment
3. For patients already receiving an ICS:
FEV₁ \geq 40% of predicted value
If FEV₁ is 40%-80% of predicted value, patient must demonstrate \geq 12% increase in FEV₁ after aerosolized albuterol treatment
If FEV₁ is $>$ 80% of predicted value, patient must demonstrate a 20% reduction in FEV₁ in response to a concentration of inhaled methacholine \leq 8 mg/mL (PC₂₀ FEV₁ \leq 8 mg/mL)
4. Nonsmoker (total lifetime smoking history $<$ 10 pack-years; no smoking for at least 1 year)
5. No regular use of other medications except oral contraceptives and nasal beclomethasone
6. No respiratory tract infection or asthma exacerbation within 6 weeks of run-in period
7. No serious medical illness other than asthma

Inclusion Criteria for Allocation Into the SOCS Study After 6-Week Triamcinolone Run-in Period

1. FEV₁ $>$ 80% of predicted value; and
2. Average peak expiratory flow (PEF) variability \leq 20%, calculated as [(PM PEF – AM PEF)/(PM PEF + AM PEF)/2] \times 100, during the final 2 weeks of the run-in period; and
3. Ability of the patient to measure his/her AM PEF and PM PEF on schedule using assigned device, to appropriately mark the PEF measurements using the post-medication marker, and to accurately transcribe the PEF measurements onto diary cards at least 85% of the time during the last 2 weeks of the run-in period

equately controlled by low-to-moderate dosages of an inhaled corticosteroid (ICS) because addition of salmeterol xinafoate or formoterol fumarate, 2 long-acting β_2 -agonists, was shown to be more effective than increasing the dose of the ICS.⁴⁻⁶ In the first half of 1999, more prescriptions were written in the United States for salmeterol for patients with asthma than for any other asthma medication except albuterol (IMS Health, Plymouth Meeting, Pa, unpublished data, September 2, 1999). The role of long-acting β_2 -agonists as monotherapy, however, is unclear,⁷⁻⁹ since most studies of salmeterol have included a significant proportion of patients taking other controller medications, including ICSs.^{1,2} A recent study suggests that salmeterol may be equivalent to low-dose beclomethasone dipropionate in corticosteroid-naïve patients with persistent asthma.¹⁰

Current asthma treatment guidelines suggest use of controller medications for patients who require rescue albuterol more than 2 to 3 times per week.^{3,11} These recommendations are based on recognition of the inflammatory basis of asthma and on several studies suggesting that a delay in initiation of ICS therapy could lead to irretrievable loss of airway function, attributable to “airway remodeling” that results from untreated inflammation.¹²⁻¹⁵ Inhaled corticosteroids are widely used as controller therapy, but long-acting β_2 -agonists are also classified as long-term controller medications³ even though they are generally believed to have little effect on inflammatory mediators or cells.¹⁶⁻¹⁸

How differences in the mechanisms of action of long-acting β_2 -agonists and ICSs translate into differences in effectiveness of long-term treatment of adults with

asthma is not known. For patients whose asthma is well controlled by low-to-moderate doses of an ICS, must the ICS be continued, or might monotherapy with a long-acting β_2 -agonist be equally or more effective? To our knowledge, no evidence from clinical trials supports replacement of ICS therapy with salmeterol monotherapy in patients with persistent asthma, but this approach has begun to appear in clinical practice. To study these questions, the Asthma Clinical Research Network (ACRN) of the National Heart, Lung, and Blood Institute (NHLBI) undertook a 28-week, randomized, multicenter, blinded, placebo-controlled trial in patients with moderate persistent asthma that was well controlled with an ICS. The trial compared the effects of continuing the ICS, triamcinolone acetonide, after a 6-week run-in period; switching to a long-acting β_2 -agonist, salmeterol; or switching to placebo on asthma symptoms, pulmonary function, bronchial reactivity, markers of airway inflammation, and frequency of exacerbations during treatment and after treatment was withdrawn. The trial tested the null hypothesis that in patients with moderate persistent asthma whose symptoms are well controlled with regularly scheduled triamcinolone and as-needed inhaled rescue albuterol, continued treatment with triamcinolone does not differ in efficacy from a change to monotherapy with salmeterol.

METHODS**Study Design and Patients**

This 28-week, randomized placebo-controlled trial, the Salmeterol or Corticosteroids (SOCS) study, was conducted from February 1997 to January 1999 at the 6 clinical sites that comprise the ACRN. The study was approved by the NHLBI-ACRN Protocol Review Committee and by the committees on human research at each clinical site. Written informed consent was obtained from all enrolled patients. Patients with asthma as defined by the American Thoracic Society¹⁹ who met recommended criteria for treatment with an ICS²⁰ were recruited. Four hundred twenty-two patients who met the inclu-

sion criteria (BOX 1) entered a 6-week run-in phase during which all patients received 400 μg (4 puffs) twice per day of open-label triamcinolone acetate. Patients whose asthma was well controlled, defined objectively (Box 1), following the 6-week run-in period were entered into the SOCS study. Patients whose asthma was not well controlled after the run-in were assigned to a concurrent study, the Salmeterol \pm Inhaled Corticosteroids (SLIC) study.²¹

Patients eligible to continue in the SOCS study were randomly assigned to receive either 400 μg (4 puffs) twice per day by metered-dose inhaler (MDI) of triamcinolone; 42 μg (2 puffs) twice per day by MDI of salmeterol xinafoate; or 2 puffs twice per day by MDI of placebo for the next 16 weeks. After 16 weeks, all active scheduled medications were stopped for an additional 6-week, single-blind placebo run-out period.

Patient randomization was performed online via an Internet connection to the computer system at the data coordinating center. Patients were stratified according to clinical center, methacholine responsiveness (PC_{20} , the provocative concentration of methacholine required to decrease forced expiratory volume in 1 second [FEV_1] by 20%), race/ethnicity, sex, and age by a permuted-blocks scheme, with blocks of random size within each stratum. When a patient was deemed eligible for study entry, a clinical center staff member entered and verified the pertinent data and received a drug packet number to give the patient.

The study was triple-blinded: patients, clinical center personnel, and data analysts were all blinded to treatment identity and dosages. Each patient received 2 inhalers, either active triamcinolone plus placebo salmeterol, placebo triamcinolone plus active salmeterol, or placebo triamcinolone plus placebo salmeterol. All patients were given albuterol inhalers to use for rescue treatment throughout the study. Triamcinolone and triamcinolone placebo were administered through a built-in spacer; all other MDIs were used without spacers. All inhalers used chlorofluorocarbon propellant. Patients were trained in each

technique, and techniques were assessed at each visit. Treatment medication for each patient was packaged together, labeled with a unique number, and distributed to the clinical centers. The contents of the drug packages were known only to administrative personnel at the data coordinating center.

Procedures

Throughout the study, patients rated the severity of 5 asthma symptoms (shortness of breath, chest tightness, wheezing, cough, and phlegm/mucus) on a scale of 0 (none) to 3 (severe). Patients recorded daytime and nighttime asthma symptom scores, morning (AM) and evening (PM) PEF using an Airwatch device (Enact, Palo Alto, Calif), rescue albuterol use, intercurrent illnesses, and hospitalizations. Patients were evaluated every 2 to 4 weeks (after a 6-hour albuterol hold and 48-hour salmeterol hold) for interval history, physical examination, diary review, spirometry (Collins Eagle 2 spirometer, Quincy, Mass), and measurement of exhaled nitric oxide (NOA 280, Sievers, Boulder, Colo).²² An asthma-specific quality-of-life questionnaire²³ was administered at the beginning of the run-in period (baseline), at the end of the run-in period (week 6), at the end of the randomized treatment period (week 22), and 2 and 6 weeks after cessation of therapy (run-out period, study weeks 24 and 28). Methacholine responsiveness²⁴ and sputum induction for analysis of total and differential cell counts, eosinophil cationic protein (ECP), and tryptase²⁵ were performed at baseline; at the end of the run-in period; after 2, 8, and 16 weeks of randomized treatment; and 2 and 6 weeks after cessation of therapy (FIGURE 1).

All testing was performed at each site with standardized equipment and procedures. Network staff were trained and tested to ensure proficiency and uniformity in all procedures. All spirometric testing, including that for PC_{20} , was over-read by a single member of the network. The function of the PEF measurement device was confirmed at each clinic visit, and the devices were replaced if they failed to meet predetermined standards.

A distributed data entry system allowed each clinical center to submit data electronically to the data coordinating center. The data coordinating center entered the data a second time for verification.

Outcomes

The primary outcome variable was change in AM PEF from the final week of the run-in period (week 6) to the final week of the randomized treatment period (week 22). To examine the duration of benefit after treatment was stopped, we also compared the change in AM PEF from the final week of the run-in period (week 6) to the final week of the run-out period (week 28). Similar analyses were applied to other markers of asthma severity and asthma control, including FEV_1 , asthma symptom scores, rescue albuterol use, quality-of-life scores, and PC_{20} . Other outcomes included the number of asthma exacerbations in the treatment and off-treatment periods.

To determine whether differences in efficacy or duration of benefit reflected differences in anti-inflammatory activity, we compared total and differential cell counts as well as concentrations of ECP and tryptase from induced sputum samples²⁵ and measured exhaled nitric oxide at each visit.²²

Treatment Failure and Asthma Exacerbation

Specific criteria were established prospectively to define treatment failure, asthma exacerbation, and run-out failure (BOX 2). Patients who met treatment failure criteria were treated with a short burst of prednisone or 400 μg twice per day of open-label, inhaled triamcinolone acetate, and continued open-label triamcinolone instead of study triamcinolone for the remainder of the study. Study inhalers of salmeterol or placebo were continued. Data collected during and after treatment failure were included in the primary intention-to-treat (ITT) analysis for all outcome variables. Patients who developed an asthma exacerbation during the run-in period (prior to randomization) were withdrawn from the study; asthma exacerbations following ran-

domization were managed according to specific predefined rescue algorithms.³ Trial drugs were continued during exacerbations unless a physician believed it appropriate to suspend such therapy until the exacerbation had resolved. Patients with asthma exacerbations, as in the case of treatment failure, were included in the ITT analysis. Patients who met failure criteria during the run-out phase were dropped from further study participation. All data collected prior to study withdrawal were included in the analyses.

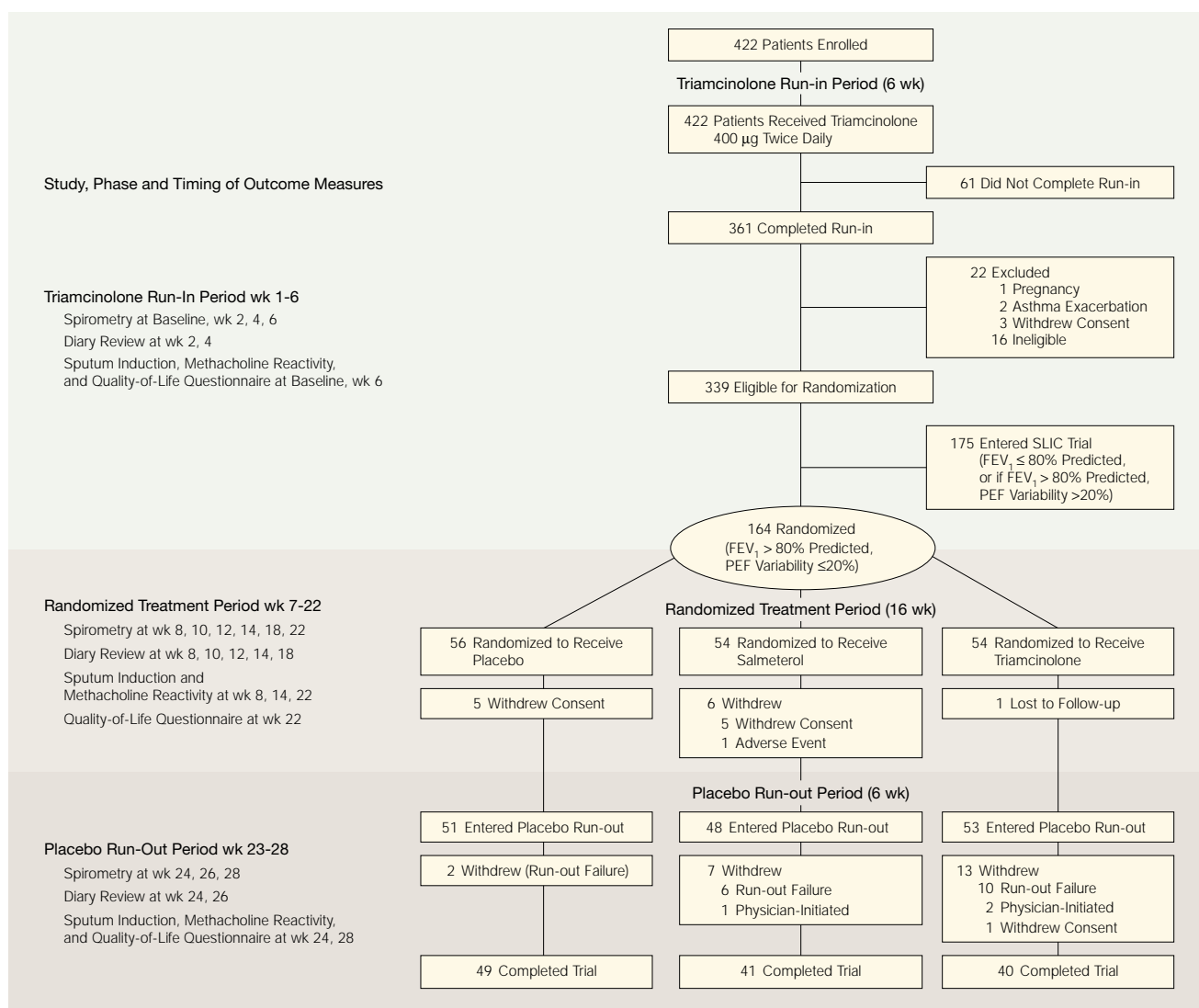
Statistical Analysis

The primary analyses were conducted using longitudinal data analysis based on fitting a mean for each treatment group at each point.²⁶ Daily daytime and nighttime symptom scores for each patient were averaged, yielding a 15-point scale between 0 and 3, and then averaged over each week for each patient, yielding a 105-point score that was used in the longitudinal data analysis. Within-group differences were constructed from model-based estimates, eg, end of treatment minus end of run-

in, and these within-group differences were compared across groups. Variables that displayed a high level of skewness or discreteness were analyzed via rank tests. All available data on all randomized patients were included in the primary statistical analysis and analyzed according to treatment group assignments at randomization. Values were not imputed for missing data.

Patients who were assigned treatment failure or asthma exacerbation status received protocol-defined treatment with prednisone, inhaled

Figure 1. Flow Diagram of the Salmeterol or Corticosteroids (SOCS) Trial



FEV₁ indicates forced expiratory volume in 1 second; PEF, peak expiratory flow; and SLIC, the Salmeterol ± Inhaled Corticosteroids study.

triamcinolone, or both. Because this rescue therapy was likely to affect outcomes, we planned a secondary analysis, performed by the last-observation-carried-forward (LOCF) method, carrying forward the last value prior to treatment failure or asthma exacerbation, or by excluding data collected after treatment failure or asthma exacerbation (truncation). The cumulative incidences of treatment failure and asthma exacerbation were analyzed using Kaplan-Meier survival curves.

Based on published data,¹³ we estimated that a total of 150 randomized patients were required to provide an 80% likelihood of detecting clinically significant changes in AM PEF. This sample size would detect a 15.7-L/min difference in AM PEF in a 3-armed trial, assuming a withdrawal rate of 20%. This sample size also yielded effect sizes for FEV₁ of 0.17 L and PC₁₅ of 0.68 dose steps (less than 1 doubling dose). Because we applied a Bonferroni correction to account for 3 pairwise comparisons and conducted an interim analysis at the trial midpoint based on the O'Brien-Fleming group sequential method,²⁷ a *P* value of less than .016 was required for statistical significance for all 3-way comparisons. Although descriptive statistics and *P* values are reported for within-group changes, the *P* values also should be considered as descriptive statistics because changes over time within a treatment group are not necessarily due to the effect of that particular treatment.

RESULTS

Enrollment, Retention, and Adherence

Four hundred twenty-two patients were enrolled, 389 (92%) of whom were already receiving an ICS at enrollment. Of the 422 patients enrolled, 361 completed the run-in period (Figure 1). Of these, 164 met entry criteria for the SOCS study and were randomly assigned to blinded treatment with placebo (*n*=56), salmeterol (*n*=54), or triamcinolone (*n*=54). The groups were well matched with regard to age, sex, and race/ethnicity and did not differ by airway function, asthma symptoms, or inflam-

Box 2. Criteria for Treatment Failure and Asthma Exacerbation

Criteria for Treatment Failure Status During the Randomized Treatment Period

Any of the following:

1. Requirement for ≥ 1 course of prednisone for treatment of asthma exacerbations
2. More than 1 emergency department or urgent care visit for treatment of asthma exacerbation
3. Hospitalization for treatment of asthma exacerbation
4. Physician clinical judgment for safety

Criteria for Asthma Exacerbations

Increased cough, chest tightness, or wheezing in association with 1 or more of the following:

1. Rescue albuterol use of ≥ 8 puffs per 24 hours over baseline use* for a period of 48 hours
2. Rescue albuterol use of ≥ 16 puffs per 24 hours for a period of 48 hours
3. Peak expiratory flow (PEF) $< 65\%$ of reference levels† despite 60 minutes of rescue treatment
4. Symptoms despite 60 minutes of rescue treatment
5. Requirement for systemic corticosteroids

Criteria for Failure During Placebo Run-out Period

Any of the following:

1. FEV₁ $\leq 50\%$ of predicted and inability to reverse to within 5% of baseline FEV₁
2. Emergency department or urgent care visit requiring treatment for asthma exacerbation
3. PEF of $\leq 65\%$ of reference PEF level† despite albuterol treatment (2-4 puffs every 20 minutes up to 1 hour)
4. Increased symptoms associated with increased rescue albuterol use of ≥ 8 puffs per 24 hours over baseline* for a period of 48 hours
5. Increased symptoms associated with increased rescue albuterol use to ≥ 16 puffs per 24 hours for a period of 48 hours
6. Use of oral or parenteral corticosteroids for asthma exacerbation
7. Physician clinical judgment for safety

*Baseline rescue albuterol use refers to the average from the last 2 weeks of the triamcinolone run-in period.

†Reference PEF level was the average prebronchodilator AM PEF from the last 2 weeks of the triamcinolone run-in period.

matory cells in induced sputum (TABLE 1). During the 22 weeks of randomized treatment and the placebo run-out period, 34 patients withdrew from the trial, 7 in the placebo group, 13 in the salmeterol group, and 14 in the triamcinolone group. Twelve of 34 withdrawals occurred during the randomized treatment period; 3 were for dissatisfaction with asthma control, 1 was physician-initiated, and the remainder were for personal or administrative reasons. One serious adverse event (not asthma-related) occurred in the salmeterol group. Of 792 scheduled visits in the triamcinolone run-in period, none were missed. During the treatment pe-

riod, 1314 (99%) of 1327 scheduled visits were completed and 91% occurred within preassigned time windows. Over the duration of the study, patients reported their AM PEF on 94.7% of days and reported taking their inhaled medications as directed on 81.1% of days.

Triamcinolone Run-in Period

Even though 159 (97%) of the 164 patients who entered the SOCS study were already receiving an ICS at enrollment, AM PEF, FEV₁, PC₂₀, and sputum eosinophil concentration all improved significantly after 6 weeks of run-in therapy with 400 μ g twice per day of open-label triamcinolone (TABLE 2).

Table 1. Patient Characteristics at Randomization^a

Characteristics	Treatment Group			P Value
	Placebo (n = 56)	Salmeterol (n = 54)	Triamcinolone (n = 54)	
Male, No. (%)	18 (32.1)	21 (38.9)	18 (33.3)	.77 ^b
Age at randomization, mean (SD), y	31.19 (10.62)	31.62 (10.77)	31.32 (10.95)	.99 ^c
Patients aged <18 y, No. (%)	5 (8.9)	5 (9.3)	6 (11.1)	.95 ^b
Race or ethnicity, No. (%)				
White	38 (67.9)	41 (75.9)	36 (66.6)	.55 ^b
Asian or Pacific Islander	4 (7.1)	2 (3.7)	3 (5.6)	
Black	9 (16.1)	7 (12.9)	8 (14.8)	
Hispanic	5 (8.9)	3 (5.6)	5 (9.3)	
Other	0	1 (1.9)	2 (3.7)	
Previous inhaled corticosteroid use, No. (%)	52 (92.9)	53 (98.2)	54 (100)	.13 ^b
Previous inhaled corticosteroid use, mean (SD), $\mu\text{g}/\text{d}^{\text{m}}$	565.3 (391.4)	488.2 (237.6)	507.5 (309.8)	.44 ^c
PEF, mean (SD), L/min ^d				
AM PEF	446.5 (101.4)	443.9 (112.3)	459.4 (107)	.72 ^c
PM PEF	452.9 (96.3)	454.3 (112.6)	473.3 (110.7)	.54 ^c
PEF variability, mean (SD) ^{d,e}	0.108 (0.041)	0.100 (0.048)	0.108 (0.054)	.55 ^c
Daily asthma symptom score, median (IQR) ^{d,f}	0.159 (0.054-0.411)	0.223 (0.064-0.431)	0.253 (0.080-0.463)	.42 ^g
Rescue albuterol use, median (IQR), puffs/d ^d	0.445 (0.000-2.307)	1.129 (0.067-3.133)	0.75 (0.200-2.476)	.50 ^g
FEV ₁ , mean (SD), L ^h	3.066 (0.623)	3.105 (0.786)	3.213 (0.646)	.51 ^c
FEV ₁ % predicted, mean (SD) ^h	93.25 (8.29)	92.54 (8.65)	95.67 (10.35)	.18 ^c
PC ₂₀ , geometric mean (IQR), mg/mL ^{h,i}	0.767 (0.277-1.670)	0.885 (0.299-1.970)	0.966 (0.395-2.050)	.50 ^g
Asthma quality-of-life score, median (IQR) ^{h,j}	1.934 (1.688-2.859)	2.141 (1.563-2.844)	2.203 (1.556-2.625)	.94 ^g
Sputum eosinophils, median (IQR), % ^{h,k}	0.7 (0.2-2.0)	0.6 (0.0-1.8)	0.6 (0.0-1.8)	.83 ^g
Exhaled nitric oxide, median (IQR), ppb ^{h,l}	14.3 (11.4-24.5)	14.1 (8.8-29.7)	15.7 (11.3-28.4)	.94 ^g

^aPEF indicates peak expiratory flow; IQR, interquartile range; FEV₁, forced expiratory volume in 1 second; and PC₂₀, methacholine responsiveness (the provocative concentration of methacholine required to decrease FEV₁ by 20%).

^bData calculated using the Fisher exact test (2-tailed) for differences in proportions across treatment groups.

^cData calculated using 1-way analysis of variance for differences across treatment groups.

^dAverage for the last 2 weeks of run-in period.

^ePEF variability was calculated as
$$\frac{\text{PEF}_{\text{PM}} - \text{PEF}_{\text{AM}}}{(\text{PEF}_{\text{PM}} + \text{PEF}_{\text{AM}})/2}$$

^fAsthma symptoms were graded by the patients each day from 0 (no symptoms) to 3 (severe symptoms).

^gData calculated using the Kruskal-Wallis test for differences across treatment groups.

^hAverage for the last week of the run-in period.

ⁱIn the placebo group, 52 patients had PC₂₀ data.

^jA score of 1.0 indicates no limitation; a score of 7.0 indicates total limitation.

^kIn the placebo, salmeterol, and triamcinolone groups, 50, 46, and 46 patients had sputum eosinophil data, respectively.

^lIn the placebo, salmeterol, and triamcinolone groups, 26, 27, and 26 patients had exhaled nitric oxide data, respectively.

^mIn the placebo and salmeterol groups, 52 and 53 patients had previous inhaled corticosteroid use data, respectively.

Table 2. Interval Change in Outcome Measures During Triamcinolone Run-in Period*

	n	Median (Interquartile Range)	P Value
AM PEF, L/min	164	3.23 (-19.09 to 45.06)	.008
PM PEF, L/min	164	3.95 (-25.50 to 33.65)	.21
FEV ₁ , L	164	0.16 (0 to 0.35)	<.001
PC ₂₀ , mg/mL	155	0.14 (-0.04 to 0.77)	<.001
Sputum eosinophils, %	132	-0.30 (-1.50 to 0.20)	<.001

*Interval change is expressed as end of run-in - baseline. Statistical analysis was done with the Wilcoxon signed rank test; P values are 2-sided. PEF indicates peak expiratory flow; FEV₁, forced expiratory volume in 1 second; and PC₂₀, methacholine responsiveness (the provocative concentration of methacholine required to decrease FEV₁ by 20%).

Randomized Treatment Period

Primary ITT Analysis. During the randomized treatment period, the primary outcome variable, AM PEF, increased in the salmeterol and triamcinolone groups and decreased initially then increased in the placebo group (FIGURE 2A). We found no statistically significant differ-

ences either within or among the 3 groups (TABLE 3).

In the Kaplan-Meier analysis, the treatment failure rate for the triamcinolone group was significantly lower than the treatment failure rates in the placebo ($P < .001$) and salmeterol ($P = .004$) groups (FIGURE 3A). Treatment failure

occurred in 20 patients (36%) in the placebo group, 13 (24%) in the salmeterol group, and 3 (6%) in the triamcinolone group. Nineteen of these 36 patients were judged to have treatment failure because of an asthma exacerbation that met our preestablished criteria for prednisone therapy; in the remaining 17, the patient's asthma control was considered to be sufficiently unstable to warrant a change in therapy by physician clinical judgment for safety. The difference in treatment failure rates between the placebo and salmeterol groups was not significant ($P = .18$). The pattern of asthma exacerbations paralleled that of treatment failures (Figure 3B). Asthma exacerbations were experienced by 16 patients (29%) in the placebo group, 11 (20%) in the salmeterol group, and 4

(7%) in the triamcinolone group. The rate of asthma exacerbations was significantly lower in the triamcinolone group compared with the salmeterol ($P=.04$) and placebo ($P=.003$) groups.

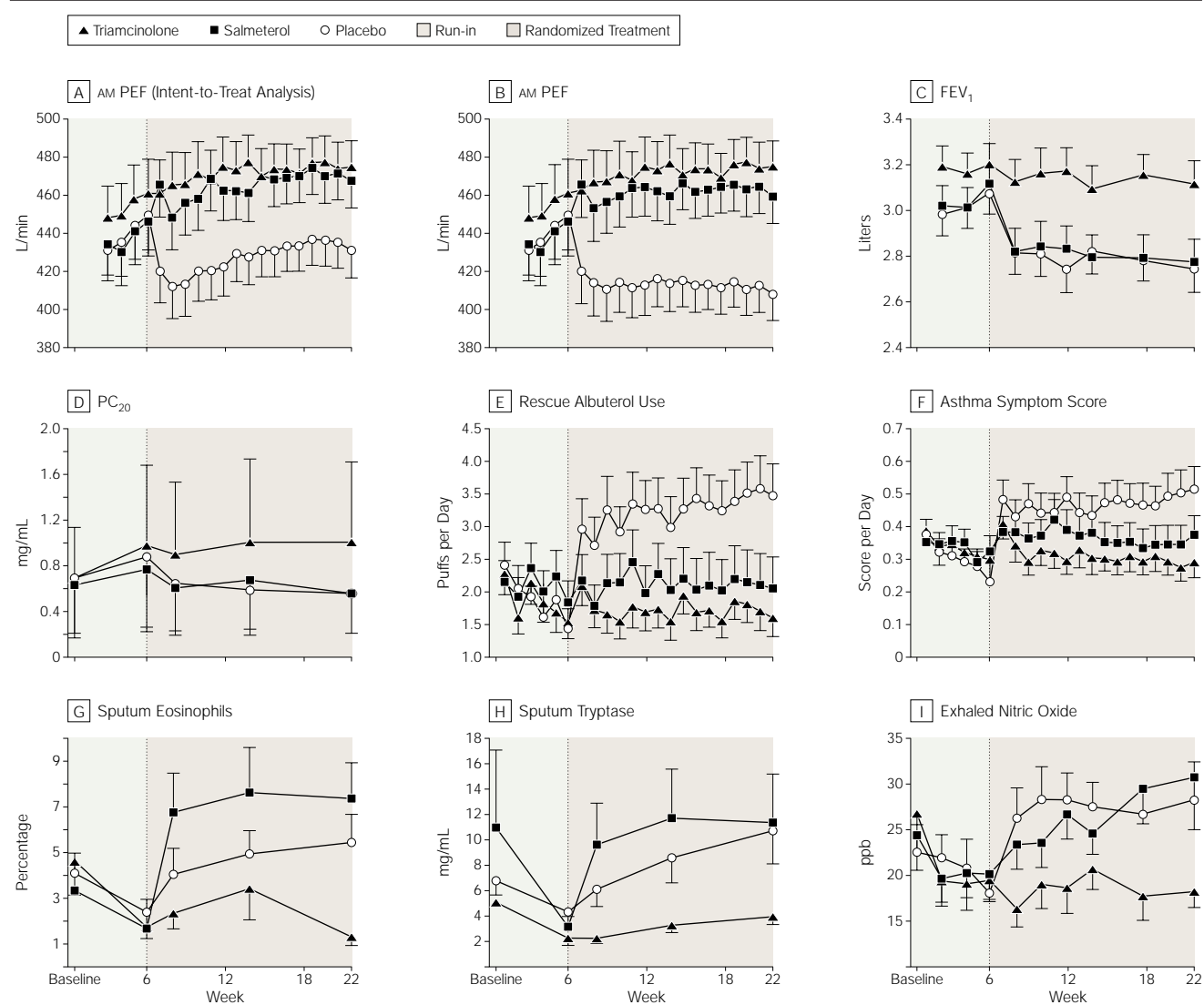
Secondary LOCF Analysis: Outcomes Prior to Treatment Failure or Asthma Exacerbation. In the LOCF analyses, there were statistically significant within-group changes in every outcome in the placebo group during the randomized treatment period (Figure 2

and FIGURE 4); AM PEF, PM PEF, FEV₁, PC₂₀, and quality of life all decreased; rescue albuterol use, daily asthma symptom scores, sputum eosinophils, ECP, and tryptase, and exhaled nitric oxide all increased ($P\leq.03$ for all). In contrast, no significant within-group change occurred in any outcome in the triamcinolone group. In the salmeterol group, AM PEF, PM PEF, rescue albuterol, asthma symptom scores, and quality of life did not change significantly within

the group, but FEV₁ and PC₂₀ (both measured after β_2 -agonist hold) decreased and exhaled nitric oxide and sputum eosinophils, ECP, and tryptase all increased ($P<.04$ for all).

During the randomized treatment period (end of week 6 through week 22), increases in markers of inflammation—sputum eosinophils (median [interquartile range {IQR}], 2.4% [0% to 10.6%]) vs -0.1% [-0.7% to 0.3%]; $P<.001$), sputum ECP (71 [-2 to 430]

Figure 2. Primary and Secondary Outcome Measures During Triamcinolone Run-in and Randomized Treatment Periods



A, AM peak expiratory flow (PEF) calculated using the intention-to-treat analysis; B-I, outcome data calculated using last-observation-carried-forward analysis. Forced expiratory volume in 1 second (FEV₁) and methacholine responsiveness (PC₂₀, the provocative concentration of methacholine required to decrease FEV₁ by 20%) were measured after β_2 -agonist hold. Data are mean values; error bars indicate SE.

U/L vs -4 [-31 to 56] U/L; $P=.005$), and sputum tryptase (3.1 [2.1 to 7.6] ng/mL vs 0 [0 to 0.7] ng/mL; $P<.001$)—were significantly greater in the salmeterol group than in the triamcinolone group. There were no significant differences in the salmeterol vs triamcinolone groups for interval changes in any of the other outcomes. Similar results were obtained for the salmeterol vs triamcinolone comparisons using ITT and truncation analyses, except that changes in ECP in the 2 groups were no longer significantly different. When we compared changes in the placebo and salmeterol groups during the randomized treatment period using the LOCF analysis, we found significant differences for AM PEF, rescue albuterol use, daily

asthma symptom scores, and quality of life ($P<.01$ for all); there were no significant differences between placebo and salmeterol for PM PEF, FEV₁, PC₂₀, exhaled nitric oxide, sputum eosinophils, ECP, or tryptase. Changes during the randomized treatment period were significantly different between the placebo and triamcinolone groups for AM PEF, rescue albuterol use, daily asthma symptom scores, quality of life, sputum eosinophils, and tryptase ($P<.01$ for all); there were no significant differences for PM PEF, FEV₁, PC₂₀, exhaled nitric oxide, or ECP.

Placebo Run-out Period

During the placebo run-out period (weeks 23-28), when all patients re-

ceived placebo, there were 18 run-out failures, 2 in the placebo group, 6 in the salmeterol group, and 10 in the triamcinolone group. Sixteen patients met objective criteria for run-out failure; 2 others were identified because of unstable asthma by physician clinical judgment for safety. Four additional patients withdrew during the run-out period for personal or administrative reasons. The differences in failure rates between the salmeterol and triamcinolone groups and between the placebo and salmeterol groups were not significant ($P=.05$ for both); the difference between the placebo and triamcinolone groups was significant ($P=.004$).

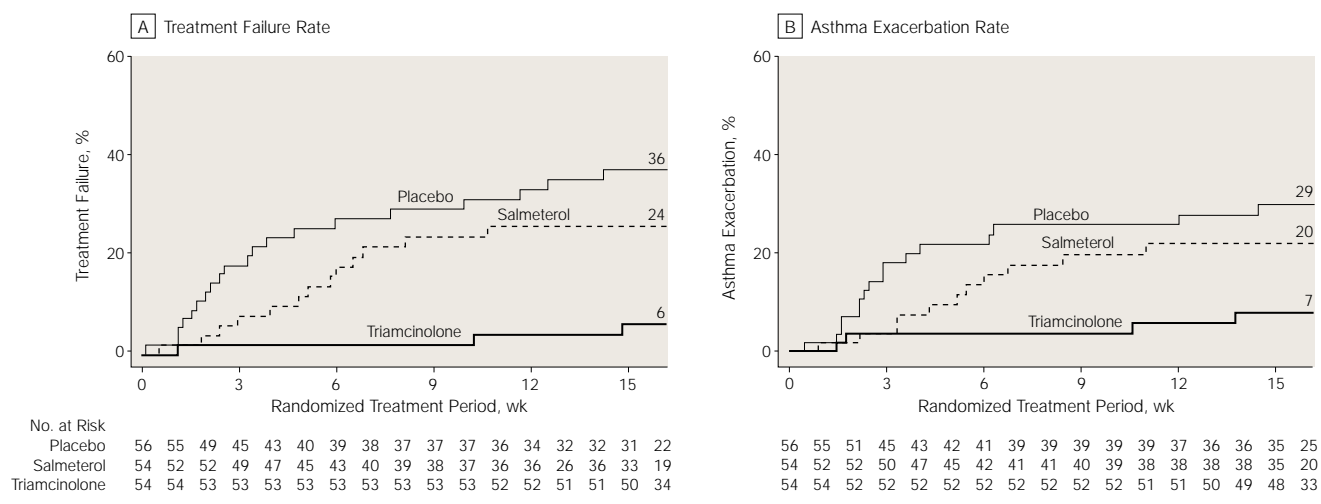
When patients were switched from triamcinolone to placebo, there were

Table 3. Intention-to-Treat Analysis of Mean AM PEF and Change in AM PEF*

AM PEF, L/min	Treatment Group					
	Placebo	Salmeterol	Triamcinolone	Placebo vs Salmeterol	Placebo vs Triamcinolone	Salmeterol vs Triamcinolone
Model estimate, mean (SE)						
End of run-in (wk 6)	449.2 (16.8)	446.4 (17.1)	460.4 (17.1)			
End of randomized treatment (wk 22)	430.8 (14.3)	467.7 (14.5)	474.6 (14.3)			
End of run-out (wk 28)	429.6 (15.5)	447.5 (16.1)	449.4 (15.7)			
Change in mean AM PEF at end of treatment vs end of run-in, model estimate (95% confidence interval) [P value]	-18.4 (-50.1 to 13.3) [.26]	21.3 (-11.3 to 53.9) [.20]	14.2 (-17.5 to 46.0) [.38]	-39.7 (-85.2 to 5.8) [.09]	-32.6 (-77.5 to 12.2) [.15]	7.1 (-38.4 to 52.6) [.76]

*PEF indicates peak expiratory flow.

Figure 3. Kaplan-Meier Survival Curves for Treatment Failure and Asthma Exacerbation During the Randomized Treatment Period



A, For placebo vs triamcinolone, $P<.001$; for salmeterol vs triamcinolone, $P=.004$; and for placebo vs salmeterol, $P=.18$. B, For placebo vs triamcinolone, $P=.003$; for salmeterol vs triamcinolone, $P=.04$; and for placebo vs salmeterol, $P=.29$. Statistical comparisons are based on the log-rank test.

statistically significant decreases in AM PEF, FEV₁, and PC₂₀, and increases in rescue albuterol use and daily asthma symptom scores in all analyses (within-group, ITT, and LOCF) (FIGURE 5). When patients were switched from salmeterol to placebo, there were significant within-group changes in FEV₁, rescue albuterol use, and daily asthma symptom scores. The placebo group, having already worsened during the randomized treatment period, demonstrated no further significant change in any outcome. When changes during the placebo run-out period were compared between groups, there were significant differences between the placebo and triamcinolone groups for FEV₁ ($P = .015$ by ITT), and PC₂₀ ($P = .003$ by ITT; $P = .01$ by LOCF). Percentage of eosinophils and tryptase concentration in sputum and exhaled nitric oxide all increased significantly (within group, $P = .002$ for all) when the triamcinolone group was switched to placebo, and the pattern mirrored that seen in

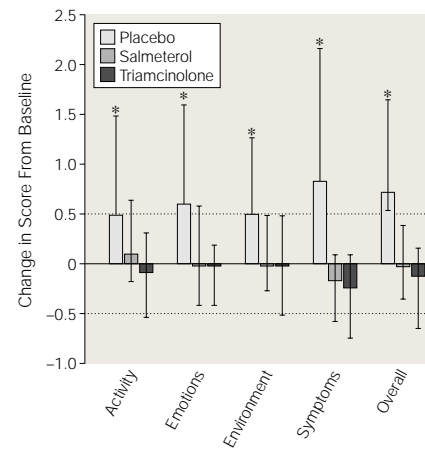
the placebo and salmeterol groups when triamcinolone was stopped at the end of the triamcinolone run-in period.

To determine whether the duration of active treatment affected airway function after treatment was stopped, we compared ITT changes in AM PEF, FEV₁, and PC₂₀ between the end of the placebo run-out (week 28) and the end of the triamcinolone run-in (week 6) periods. There were no significant differences among groups, indicating no long-term carryover benefit from up to 22 weeks of triamcinolone treatment.

COMMENT

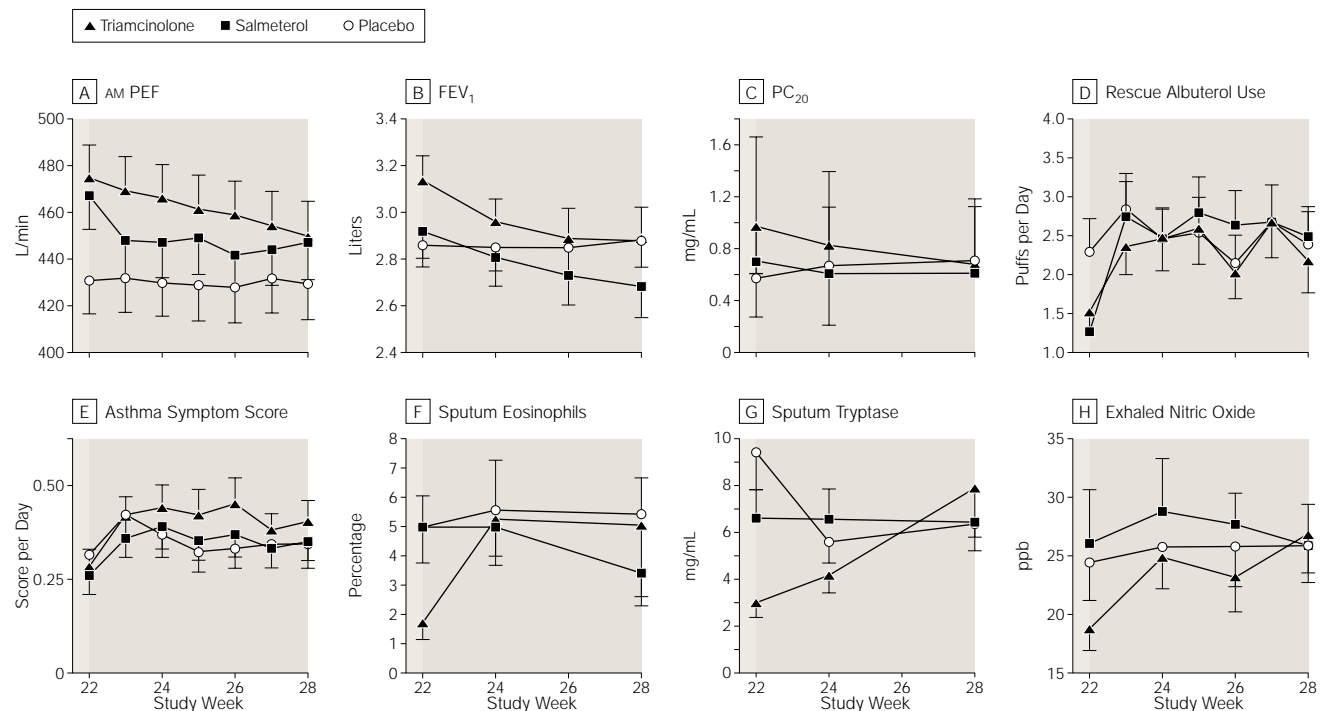
Although use of long-acting β_2 -agonists as additive therapy in patients whose asthma is not controlled by inhaled corticosteroids is well supported by the results of clinical trials,⁴⁻⁶ their use as monotherapy in persistent asthma is not. Indeed, US guidelines for diagnosis and management of asthma recommend long-acting β_2 -agonists only as additive therapy,³ but this recommendation was

Figure 4. Change in Asthma Quality-of-Life Scores During the Randomized Treatment Period



Quality of life was assessed using a 32-item questionnaire, with each item scored from 1 (no limitations) to 7 (totally limited); a separate average score for each of 4 individual domains was calculated and an overall score was calculated by averaging the responses to all 32 items. The dotted lines represent the change believed to be clinically significant.²⁸ Data are median values; error bars indicate interquartile range. Asterisk indicates $P < .001$ for within-group change using the Wilcoxon signed rank test.

Figure 5. Primary and Secondary Outcome Measures During the Placebo Run-out Period



Outcome data in this figure were calculated using intention-to-treat analysis. Forced expiratory volume in 1 second (FEV₁) and methacholine responsiveness (PC₂₀, the provocative concentration of methacholine required to decrease FEV₁ by 20%) were measured after β_2 -agonist hold. Data are mean values; error bars indicate SE.

based on expert opinion, not on evidence from clinical trials. Our study demonstrates that patients with persistent asthma that is well controlled by low-dose triamcinolone monotherapy cannot be switched to salmeterol monotherapy without risk of clinically significant loss of asthma control.

Although most of the 164 patients in this study reported using an ICS prior to entry, significant improvements were still noted in AM PEF, FEV₁, PC₂₀, and sputum eosinophil concentration during the triamcinolone run-in period, presumably reflecting greater compliance with regular ICS treatment in the setting of a clinical trial. In the randomized treatment period, patients who continued treatment with triamcinolone had better asthma control than those treated with placebo or salmeterol. Treatment failure and asthma exacerbations were the most robust indicators of the difference in asthma control achieved by treatment with triamcinolone vs salmeterol. Thus, although patients who received salmeterol had fewer asthma symptoms, less need for rescue albuterol, and better airway function than patients who received placebo, they experienced treatment failures and asthma exacerbations at a rate similar to the placebo group. Similarly, methacholine responsiveness worsened significantly in the salmeterol and placebo groups but not in the triamcinolone group. In the placebo run-out period, all patients whose treatment had not failed were switched to inhaled placebo, and most elements of asthma control predictably worsened in both active treatment groups. Notably, the duration of treatment benefit was not significantly longer in the triamcinolone group than in the other 2 groups. Fourteen (25%) of the patients assigned to receive placebo at the end of the 6-week triamcinolone run-in period met criteria for treatment failure within 6 weeks; 12 (24%) of the patients who received triamcinolone for 22 weeks also qualified as failures during the 6-week placebo run-out period. We thus found no evidence that an additional 16 weeks of continuous corticosteroid treatment conferred persistent benefit.

This study illustrates some limitations of traditional asthma outcome measures in clinical trials. Although treatment with salmeterol resulted in greater improvements in AM and PM PEF, asthma symptoms, and rescue albuterol use than treatment with placebo, the differences in the rates of treatment failure and asthma exacerbations between these 2 groups were small and insignificant. A similar dissociation between symptom control and asthma exacerbations was observed when salmeterol was given as monotherapy to children for 1 year. In that study, salmeterol was less effective than beclomethasone in preventing exacerbations.²⁹

The effect of long-acting β_2 -agonists on asthmatic inflammation is controversial. In this study, airway inflammation, as inferred from analysis of induced sputum, decreased during triamcinolone treatment in the run-in period and increased in both the placebo and salmeterol groups during the randomized treatment period when triamcinolone was stopped. The authors of a recent small study proposed that treatment with long-acting β_2 -agonists may mask worsening airway inflammation and delay awareness of worsening asthma.⁹ We observed an increase in markers of inflammation when patients were switched from triamcinolone to salmeterol. This change appears to reflect cessation of triamcinolone treatment rather than a direct salmeterol effect, since we saw a similar increase in inflammatory markers when patients were switched from triamcinolone to placebo in the run-out period. Other recent studies have shown no increase in markers of inflammation and a reduction in some inflammatory cell types in airway mucosal biopsy specimens after combined treatment with salmeterol and an ICS³⁰ or with the long-acting β_2 -agonist formoterol alone.³¹

Our findings indicate that salmeterol should not be used as monotherapy for treatment of persistent asthma. Although salmeterol was highly effective at maintaining improvement in some conventional asthma outcome measures, including PEF, asthma symptoms, and rescue albuterol use, salmeterol was no more

effective than placebo at preventing treatment failures and asthma exacerbations or at suppressing airway inflammation. These data support the concept that an ICS is preferable to a long-acting bronchodilator as monotherapy in patients with persistent asthma.

Author Affiliations: University of California, San Francisco (Drs Lazarus, Boushey, and Fahy); Milton S. Hershey Medical Center, Hershey, Pa (Drs Chinchilli, Craig, and Mauger); University of Wisconsin Medical School (Dr Lemanske) and School of Pharmacy (Dr Sorkness), Madison; National Jewish Medical and Research Center, Denver, Colo (Drs Kraft, Martin, Spahn, and Szefler); Thomas Jefferson University, Philadelphia, Pa (Drs Fish and Peters); Brigham and Women's Hospital and Harvard Medical School, Boston, Mass (Drs Drazen and Israel); and Harlem Hospital Center, New York, NY (Drs Ford and Nachman).

Financial Disclosures: *Lazarus:* Abbott (research funding and honoraria), Astra (honoraria), Aventis (consultant), Boehringer Ingelheim (research funding), Fujisawa (consultant), Genentech (research funding), GlaxoSmithKline (consultant), Immunex (consultant), Merck (consultant), Merck Frosst (honoraria), Novartis (consultant), Pfizer (research funding), Pharmacia-Upjohn (research funding), and Zeneca Pharmaceuticals (research funding and honoraria).

Boushey: Aventis (consultant), GlaxoSmithKline (research funding), Kosan Biosciences (scientific advisory board membership), Novartis/Genentech (consultant), Roche (consultant), and Schering-Plough (data monitoring board for research study).

Fahy: Amgen (consultant), Astra-Zeneca (research funding and honoraria), Boehringer Ingelheim (research funding), Fujisawa (consultant), Genelabs Inc (research funding), Genentech (consultant), GlaxoSmithKline (research funding), Merck (honoraria), Novartis (research funding), Rhone-Poulenc Rorer (consultant), Roche Bioscience (Syntex) (consultant), and Texas Biotechnology (consultant).

Chinchilli: GlaxoSmithKline (consultant) and Robert Wood Johnson Pharmaceutical Research Institute (consultant).

Lemanske: Abbott (patent pending), Astra-Zeneca (honoraria), Aventis (honoraria), GlaxoSmithKline (honoraria and research funding), Merck (honoraria and research funding), and Novartis (consultant).

Sorkness: Astra-Zeneca (consultant and honoraria), GlaxoSmithKline (consultant and honoraria), and Merck (consultant and honoraria).

Kraft: Abbott (research funding), Astra-Zeneca (speaker's bureau), Aventis (consultant), Forrest (consultant), Genentech (consultant), GlaxoSmithKline (speaker's bureau and consultant), Immunex (research funding), Merck (research funding and speaker's bureau), Novartis (research funding), Purdue Frederick (speaker's bureau), Schering-Plough (consultant), and 3M (research funding).

Fish: Astra-Zeneca (speaking honoraria), Aventis (speaking honoraria), Genentech (speaking honoraria and consultant), GlaxoSmithKline (research funding and speaking honoraria), Merck (research funding and consultant), Ortho-McNeil (speaking honoraria), Schering-Plough (speaking honoraria and consultant), and Viropharm (consultant).

Peters: Abbott (clinical trial), Astra-Zeneca (clinical trial, consultant, and speaker's bureau), Aventis (consultant and speaker's bureau), Fujisawa (consultant), Genentech-Novartis (consultant), GlaxoSmithKline (clinical trial and consultant), Health Science Center CME/World Medical Leaders.com (consultant), Merck (clinical trial, advisory board, and speaker's bureau), Schering-Plough (clinical trial, advisory board, and speaker's bureau), 3M (consultant), and Wyeth-Ayerst (consultant).

Craig: Astra-Zeneca (research funding), Aventis (consultant), Aventis-Pasteur (clinical trials), Bayer (research funding), GlaxoSmithKline (speaker's bureau, research funding), Merck (speaker's bureau, research funding), Schering-Plough (speaker's bureau), and SmithKline (clinical trials).

Drazen: Forrest Pharmaceuticals and Sepracor (research funding during SOCS and SLIC trials; grants completed in 1999 and not renewed); 2 US patents covering the use of genetic information to understand the variability in asthma treatment response—all revenues from licensing these patents currently accrue to the Brigham and Women's Hospital and none are distributed to Dr Drazen or his laboratory; no current arrangements with any commercial entity in the health care sector other than his current employer, the Massachusetts Medical Society.

Ford: Boehringer Ingelheim (consultant), GlaxoSmithKline (speaking honoraria and consultant), Merck (speaking honoraria and consultant), and Sepracor (speaking honoraria).

Israel: Abbott (patent pending), Astra-Zeneca (research funding), Eli Lilly (research funding), Genentech (research funding), Genetics Institute (research funding), GlaxoSmithKline (consultant), Immunex (research funding), LeukoSite (research funding), Merck (honoraria, consultant, and research funding), Novartis (research funding), Pfizer (research funding), and Sepracor (research funding).

Martin: Abbott (consultant, honoraria, research funding, and speaker's bureau), Astra-Zeneca (consultant, honoraria, research funding, and speaker's bureau), Boehringer Ingelheim (honoraria and research funding), Eli Lilly (research funding), Genentech (consultant), GlaxoSmithKline (consultant, honoraria, research funding, and speaker's bureau), Immunex (consultant), Merck (consultant, honoraria, research funding, and speaker's bureau), Muro (honoraria, research funding, and speaker's bureau), Novartis (consultant), Purdue Frederick (honoraria, research funding, and speaker's bureau), Rhone-Poulenc Rorer (consultant, honoraria, research funding, and speaker's bureau), Schering-Plough (consultant, honoraria, and speaker's bureau), and 3M (consultant, honoraria, research funding, and speaker's bureau).

Spahn: Astra-Zeneca (research funding and speaker's bureau), GlaxoSmithKline (research funding and speaker's bureau), Merck (research funding and speaker's bureau), and Schering-Plough (research funding).

Szefer: Astra-Zeneca (consultant and honoraria), Merck (consultant and honoraria), Schering-Plough (consultant), Sepracor (consultant), and 3M (consultant, honoraria).

Author Contributions: *Study concept and design:* Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Craig, Drazen, Ford, Israel, Martin, Mauger, Nachman, Spahn, Szefer.

Acquisition of data: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Craig, Drazen, Ford, Israel, Martin, Mauger, Nachman, Spahn, Szefer.

Analysis and interpretation of data: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Drazen, Ford, Israel, Martin, Mauger, Nachman, Szefer.

Drafting of the manuscript: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Craig, Drazen, Israel, Martin, Mauger.

Critical revision of the manuscript for important intellectual content: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Drazen, Ford, Israel, Martin, Mauger, Nachman, Spahn, Szefer.

Statistical expertise: Lazarus, Chinchilli, Lemanske, Mauger.

Obtained funding: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Drazen, Ford, Martin.

Administrative, technical, or material support: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Craig, Drazen, Ford, Israel, Martin, Mauger, Nachman, Spahn, Szefer.

Study supervision: Lazarus, Boushey, Fahy, Chinchilli, Lemanske, Sorkness, Kraft, Fish, Peters, Drazen, Ford, Israel, Martin, Mauger, Nachman.

Funding/Support: This study was supported by grants U10 HL-51810, U10 HL-51834, U10 HL-51831, U10 HL-51823, U10 HL-51845, U10 HL-51843, U10 HL-56443, and M01 RR-03186 from the National Heart, Lung, and Blood Institute. Medications/equipment were provided by Aradigm Corp, Enact Health Management Systems, GlaxoWellcome Inc, Hoechst Marion Roussel Inc, Rhône-Poulenc Rorer Pharmaceuticals Inc, and Sievers Instruments Inc.

Acknowledgment: We acknowledge the following individuals for their assistance in the inception, development, conduct, and analyses of the SOCS clinical trial: *ACRN Steering Committee:* Suzanne Hurd, PhD, Reuben Cherniack, MD; *Clinical coordinators and technical personnel:* J. Chang, E. Fischer, RN, E. Freeman, C. Hong, L. Mazzella, J. Oliviero, Boston, Mass; J. Brandorff, C. Duncan, J. Hassell, J. Pak, M. Rex, A. Stevens, Denver, Colo; R. Kelley, L. Mikus, B. Miller, RN, A. Sexton, MPH, Madison, Wis; D. DeGraffiniedt, E. Gilbert, S. Y. Min, New York, NY; C. Czajka, RN, P. Ilves-Corressel, RN, C. Mitchell, M. Pollice, Philadelphia, Pa; J. Liu, L. Musumeci, RN, T. Ward, RN, H. Wong, San Francisco, Calif; *Data Coordinating Center personnel:* T. Ake, T. Armstrong, D. Baker, B. Beers, S. Boehmer, T. Britton, B. Crissinger, A. M. Dyer, L. Engle, R. Evans, P. Forand, H. Hess, S. Kunselman, E. Lehman, S. McKenzie, S. Meyers, D. Peters, R. Pogash, J. Schmidt, R. Zimmerman, Jr; *Protocol Review Committee:* G. Hunninghake (chair), J. Connett, W. Kelly, R. Nicklas, R. Strunk, R. Crapo; *Data Safety Monitoring Board:* N. Anthonisen (chair), T. Casale, B. Layman, S. Redline, M. Schluchter.

REFERENCES

- Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med.* 1992; 327:1420-1425.
- D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA.* 1994;271:1412-1416.
- National Asthma Education and Prevention Program. *Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: National Institutes of Health; 1997.
- Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet.* 1994;344:219-224.
- Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med.* 1996;153:1481-1488.
- Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med.* 1997;337:1405-1411.
- Page CP. One explanation of the asthma paradox: inhibition of natural antiinflammatory mechanism by β_2 -agonists. *Lancet.* 1991;337:717-720.
- Morley J, Sanjar S, Newth C. Viewpoint: untoward effects of β -adrenoceptor agonists in asthma. *Eur Respir J.* 1990;3:228-233.
- Mclvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med.* 1998;158:924-930.
- Nathan RA, Pinnas JL, Schwartz HJ, et al. A six-month, placebo-controlled, comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma. *Ann Allergy Asthma Immunol.* 1999; 82:521-529.
- British Thoracic Society, Research Unit of the Royal

College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for the management of asthma in adults, II: acute severe asthma. *BMJ.* 1990;301:797-800.

12. Haahtela T, Järvinen M, Kava T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med.* 1991;325:388-392.

13. Haahtela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med.* 1994;331:700-705.

14. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med.* 1994;88:373-381.

15. Overbeek SE, Kerstjens HA, Bogaard JM, Mulder PG, Postma DS. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? *Chest.* 1996; 110:35-41.

16. Boulet LP, Turcotte H, Boutet M, Dube J, Gagnon M, Laviolette M. Influence of salmeterol on chronic and allergen-induced airway inflammation in mild allergic asthma: a pilot study. *Curr Ther Res Clin Exp.* 1997;58:240-259.

17. Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH. Effect of eight weeks of treatment with salmeterol on bronchoalveolar lavage inflammatory indices in asthmatics. *Am J Respir Crit Care Med.* 1994;150:1006-1011.

18. Kraft M, Wenzel SE, Bettinger CM, Martin RJ. The effect of salmeterol on nocturnal symptoms, airway function, and inflammation in asthma. *Chest.* 1997; 111:1249-1254.

19. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis.* 1987;136:225-244.

20. National Asthma Education and Prevention Program. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: National Institutes of Health; 1991.

21. Lemanske RF Jr, Sorkness CA, Mauger EA, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA.* 2001;285:2594-2603.

22. Silkoff PE, McClean PA, Slutsky AS, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med.* 1997;155:260-267.

23. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis.* 1993;147:832-838.

24. Tashkin DP, Altose MD, Bleecker ER, et al. The Lung Health Study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. *Am Rev Respir Dis.* 1992;145:301-310.

25. Fahy JV, Liu J, Wong H, Boushey HA. Analysis of cellular and biochemical constituents of induced sputum after allergen challenge: a method for studying allergic airway inflammation. *J Allergy Clin Immunol.* 1994;93:1031-1039.

26. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38:963-974.

27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35:549-556.

28. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol.* 1994;47:81-87.

29. Verbenne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med.* 1997;156:688-695.

30. Li X, Ward C, Thien F, et al. An antiinflammatory effect of salmeterol, a long-acting β_2 -agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *Am J Respir Crit Care Med.* 1999;160:1493-1499.

31. Wallin A, Sandström T, Söderberg M, et al. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Respir Crit Care Med.* 1999;158:79-86.