Inhaled Corticosteroid Reduction and Elimination in Patients With Persistent Asthma Receiving Salmeterol: A Randomized Controlled Trial

Robert F. Lemanske, Jr, MD
Christine A. Sorkness, PharmD
Elizabeth A. Mauger, PhD
Stephen C. Lazarus, MD
Homer A. Boushey, MD
John V. Fahy, MD
Jeffrey M. Drazen, MD
Vernon M. Chinchilli, PhD
Timothy Craig, DO
James E. Fish, MD
Jean G. Ford, MD
Elliot Israel, MD
Monica Kraft, MD
Richard J. Martin, MD
Sami A. Nachman, MD
Stephen P. Peters, MD, PhD
Joseph D. Spahn, MD
Stanley J. Szefler, MD
for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute

Context Inhaled long-acting β₂-agonists improve asthma control when added to inhaled corticosteroid (ICS) therapy.

Objective To determine whether ICS therapy can be reduced or eliminated in patients with persistent asthma after adding a long-acting β₂-agonist to their treatment regimen.


Participants One hundred seventy-five patients aged 12 through 65 years with persistent asthma that was suboptimally controlled during a 6-week run-in period of treatment with inhaled triamcinolone acetonide (400 µg twice per day).

Intervention Patients continued triamcinolone therapy and were randomly assigned to receive add-on therapy with either placebo (placebo-minus group, n=21) or salmeterol xinafoate, 42 µg twice per day (n=154) for 2 weeks. The entire placebo-minus group was assigned and half of the salmeterol group (salmeterol-minus group) was randomly assigned to reduce by 50% (for 8 weeks) then eliminate (for 8 weeks) triamcinolone treatment. The other half of the salmeterol group (salmeterol-plus group) was randomly assigned to continue both salmeterol and triamcinolone for the remaining 16 weeks (active control group).

Main Outcome Measure Time to asthma treatment failure in patients receiving salmeterol.

Results Treatment failure occurred in 8.3% (95% confidence interval [CI], 2%-15%) of the salmeterol-minus group 8 weeks after triamcinolone treatment was reduced compared with 2.8% (95% CI, 0%-7%) of the salmeterol-plus group during the same period. Treatment failure occurred in 46.3% (95% CI, 34%-59%) of the salmeterol-minus group 8 weeks after triamcinolone therapy was eliminated compared with 13.7% (95% CI, 5%-22%) of the salmeterol-plus group. The relative risk (95% CI) of treatment failure at the end of the triamcinolone elimination phase in the salmeterol-minus group was 4.3 (2.0-9.2) compared with the salmeterol-plus group (P<.001).

Conclusions Our results indicate that in patients with persistent asthma suboptimally controlled by triamcinolone therapy alone but whose asthma symptoms improve after addition of salmeterol, a substantial reduction (50%) in triamcinolone dose can occur without a significant loss of asthma control. However, total elimination of triamcinolone therapy results in a significant deterioration in asthma control and, therefore, cannot be recommended.

JAMA. 2001;285:2594-2603

See also pp 2583 and 2637.
The concept that continual long-acting β2-agonist therapy treats symptoms but not the underlying disease has generated controversy. Although some studies have evaluated ICS reduction in patients treated with salmeterol xinafoate, the disparate and complex nature of the reduction and elimination strategies, the outcome measures used, and the small numbers of patients evaluated have not provided sufficient information for clinical decision making. To address these issues, the National Heart, Lung, and Blood Institute ( NHLBI ) Asthma Clinical Research Network ( ACRN ) conducted the clinical trial Salmeterol ± Inhaled Corticosteroids ( SLIC ). The trial tested the hypothesis that in patients with persistent asthma whose symptoms are suboptimally controlled with a regularly scheduled ICS (triamcinolone acetonide) but subsequently controlled following the addition of a scheduled long-acting β2-agonist (salmeterol), the dosage of ICS can be reduced or eliminated without increasing the risk of treatment failure. The trial, which used clinically relevant ICS reduction and elimination strategies that are readily adaptable to patient care, allowed us to show that while being treated with salmeterol, triamcinolone dosages could be safely reduced but not eliminated.

**METHODS**

**Study Design and Patients**

We conducted a 24-week, randomized, controlled, blinded, double-dummy, parallel group trial from February 1997 to January 1999 at the 6 ACRN clinical centers (FIGURE 1). The study was approved by the ACRN protocol review committee and human subjects review boards at each participating institution. Patients with asthma as defined by the American Thoracic Society guidelines who met recommended criteria for treatment with ICSs were recruited at each ACRN clinical center. Written informed consent was obtained from all patients enrolled in the study. The study entry criteria and the initial triamcinolone run-in period are described in an accompanying article. Briefly, entry criteria included being aged 12 through 65 years and having persistent asthma defined for patients not receiving ICSs at study entry as having a forced expiratory volume in 1 second (FEV1) of 80% of the

**Figure 1. Flow Diagram of the Salmeterol±Inhaled Corticosteroids (SLIC) Trial**
predicted value or less and a 12% or greater increase after treatment with aerosolized albuterol. For patients already receiving ICs, entry criteria included an FEV₁ of 40% or more of the predicted value, and if FEV₁ was 40% to 80% of the predicted value, a 12% or more increase in FEV₁ after treatment with aerosolized albuterol. If FEV₁ was greater than 80% of the predicted value, patients needed to demonstrate a 20% reduction in FEV₁ in response to a provocative concentration of inhaled methacholine of 8 mg/mL or less (PC₂₀FEV₁ ≤8 mg/mL). Exclusion criteria included smoking (total lifetime smoking history of ≥10 pack-years or smoking within the last year), regular use of other medications except oral contraceptives and nasal beclomethason, respiratory tract infection or asthma exacerbation within 6 weeks of the run-in period, and serious medical illnesses in addition to asthma.

After a 6-week run-in period with open-label triamcinolone acetonide 400 µg (4 puffs) twice per day via metered dose inhaler (MDI) with built-in spacer and chlorofluorocarbon propellant and rescue albuterol by MDI as needed, patients whose asthma was not well-controlled during the final 2 weeks of the run-in period entered the SLIC trial. Suboptimal asthma control was defined as FEV₁ 80% or less of the predicted value, or if FEV₁ was greater than 80% of the predicted value, an average variability in peak expiratory flow (PEF) greater than 20%, calculated as [(PM PEF – AM PEF)/ (PM PEF + AM PEF)/2] × 100. Patients whose asthma was well controlled according to preestablished criteria after the triamcinolone run-in period entered the Salmeterol or Corticosteroids (SOCS) trial. In the first phase of the SLIC trial (Figure 1), the salmeterol introduction phase, all patients continued to receive 400 µg of inhaled triamcinolone acetonide twice per day. Thirteen of every 15 patients were randomly assigned to receive add-on therapy with 42 µg of salmeterol xinafoate (2 puffs) twice per day via MDI (no spacer; chlorofluorocarbon propellant); and 2 of every 15 patients were assigned to receive placebo salmeterol (placebo-minus group). At the end of 2 weeks, half of the patients who had received triamcinolone and add-on salmeterol were randomly assigned to either maintain their triamcinolone dosage throughout the study (active control, salmeterol-plus group) or to undergo a blinded, 1-step, 50% reduction in triamcinolone dose for the first 8 weeks (triamcinolone reduction phase) followed by an 8 week triamcinolone elimination phase during which salmeterol was used as monotherapy (salmeterol-minus group). The patients in the placebo-minus group also underwent the same phases of triamcinolone reduction and elimination. The placebo-minus group was limited in enrollment to safely evaluate whether the rate of treatment failure following triamcinolone reduction and elimination would be similar to that reported by others and to document that patients enrolled in the SLIC trial required IC therapy to maintain adequate asthma control. In all cases, triamcinolone reduction and elimination were only performed if patients did not meet criteria for treatment failure status (Box). Patient randomization was performed online via an Internet connection to the computer system at the data coordinating center. Staff members entered and verified the pertinent data and received a drug packet number to give each eligible patient at the 2 randomizations. The first randomization at the end of the triamcinolone run-in period was stratified according to clinical center, and the second randomization before the triamcinolone reduction phase was stratified according to ethnic group, sex, and age.

This study was triple-blinded in that patients, clinical center personnel, and data analysts were all blinded to treat-
ment identity and dose levels. Each pa-

tient received 2 triamcinolone canis-
ters to be taken twice per day as 2

inhalations of each: (1) 2 canisters of

active triamcinolone for all patients dur-
ing the salmeterol introduction phase;

(2) 1 canister of active triamcinolone

and one canister of placebo drug dur-
ing the reduction phase for the placebo-

minus and the salmeterol-minus groups;

(3) 2 canisters of placebo triamcinolone
during the elimination phase for the placebo-minus and sal-

meterol-minus groups. Patients in the

placebo-minus group received pla-

cebo canisters of salmeterol; patients in

the salmeterol-plus and salmeterol-

minus groups received active salme-

terol canisters. All patients received al-

buterol for rescue therapy as needed.

Medication for each patient was pack-

aged together, labeled with a unique

number, and distributed to the clin-
cal centers. The contents of the drug

packages were known only to admin-

istrative personnel at the data coordi-
nating center.

Outcome Measures

The primary outcome measure was
time-to-treatment failure as defined by
preestablished criteria (Box).16 Pa-

tients who met these criteria received
400 µg of triamcinolone acetonide twice
per day by open-label inhaler and con-
tinued coded inhalers of triamcino-

lone, salmeterol, and/or placebo. These

patients continued to participate in the

study until its termination, but no fur-

ther reductions in triamcinolone dos-

age were attempted.

Secondary outcome measures in-
cluded (1) pre-β₂-agonist FEV₁ (after
8 hour albuterol hold and 48 hour salme-

terol hold) and post-salmeterol FEV₁

(1 hour after administration of 42 µg

of salmeterol xinafoate); (2) AM and PM

PEF (Airwatch; ENACT Health Man-

agement Systems, Mountain View,

Calif); (3) salmeterol-protected metha-

choline response (methacholine PC₂₀)

measured 1 hour after a 42 µg dose of

salmeterol xinafoate; (4) asthma day

and night symptom scores, the scores of

5 symptoms—shortness of breath,

chest tightness, wheezing, cough, and

phlegm/mucus—each measured on a

scale from 0 (no symptoms) to 3 (se-

vere symptoms) and recorded on daily

diary cards; (5) asthma quality-of-life

scores, which were derived from a 32-

item questionnaire with each item

scored from 1, no limitations, to 7, to-

tally limited. An overall asthma quality-
of-life score was calculated by averag-

ing the responses to all 32 items, and a

separate average quality of life score for

each of 4 individual domains was cal-

culated17; and (6) rescue albuterol use

recorded on daily diary cards. Values

for each of these secondary outcome

measures were compared within each
group and between groups for the 3

phases of the study. All study-related

tests (eg, FEV₁) were administered by

ACRN-certified personnel using net-

work standardized equipment and pro-

cedures.18 Study outcomes were re-

viewed by the ACRN data and safety

monitoring board.

Statistical Analyses

The study was designed to have 80%
power to detect a difference between
the expected asthma treatment failure per-

centages of 5% in the salmeterol-plus

group and 20% in the salmeterol-

minus group from the time the triam-

cinolone dosage was reduced (triam-

cinolone reduction phase) to the end of

the study (Figure 1), allowing for a 10%

withdrawal rate and testing at a 2.9% sig-

ificance level (adjusted from 5% to

account for an interim analysis at the trial

midpoint based on the Pocock group

sequential method19). To achieve this sta-

tistical objective, 65 patients were

required in each of the salmeterol groups.

The primary outcome was the percent-

age failing treatment according to

Kaplan-Meier estimates using the log-

rank test for comparison between

groups. Estimates are also provided from

the Kaplan-Meier curve of the percent-

age failing at the end of the triamcino-

lone reduction and elimination phases.

To compare the salmeterol-plus with the

salmeterol-minus treatment arms dur-

ing each phase of the trial, the time-to-

treatment failure was analyzed in an

intent-to-treat manner by a Cox regres-

sion model with time-dependent covar-

iates.20 The treatment group in the reduc-

tion and elimination phases was modeled

as a time-dependent covariate, thus

allowing a separate estimate of relative

risk among treatment groups within each

phase. The change over each of the 3

phases was tested within and between

the salmeterol groups for secondary out-

comes. Secondary outcomes with a sym-

metric distribution were assessed with

longitudinal data analyses based on fit-

ting a mean for each treatment group

each time point. Model-based esti-

mates of the change were used for all

tests. Outcomes with a nonsymmetric or

discrete distribution were analyzed by

nonparametric rank tests. The change

was calculated and compared within

each group with a Wilcoxon sign-rank

test and between groups with a Wil-

coxon-Mann Whitney test. All second-

ary outcomes were analyzed using both

intent-to-treat and last value carried-

forward methods (ie, the last value prior
to treatment failure was carried for-

ward at all future time points); similar

results were obtained using both meth-

ods. The 2 approaches to the secondary

analyses should provide the relative

extremes of the possible results. Since

treatment failures were treated with

increasing dosages of inhaled triamcino-

lone, oral corticosteroids, or both, trends

in various secondary outcome mea-

sures are depicted with the use of carried-

forward analysis to avoid confounding

by this treatment intervention.

RESULTS

Enrollment, Retention, and

Adherence

A total of 422 patients were eligible to
take the common 6-week run-in pe-

riod for the SOCS13 and SLIC compan-

ion studies (Figure 1). Of these, 361

completed the triamcinolone run-in pe-

riod. The 164 patients who achieved

good asthma control, according to pre-
established criteria, entered the SOCS

trial; and the 175 who did not, entered

the SLIC trial. Twenty-two patients did

not qualify for either protocol or with-
drew consent. Of the patients assigned
to the SLIC study, 144 (82.3%) qualified by FEV1 criterion only, 24 (13.7%) by both FEV1 and PEF variability criteria, and 7 (4%) by PEF variability criterion alone. The characteristics of the patients in each of the 3 groups in the SLIC study prior to the second randomization are listed in Table 1; comparisons of characteristics among the treatment groups revealed no significant differences (all P values >.05).

During the salmeterol introduction phase, 21 patients (12%) were assigned to the placebo-minus group and 154 (88%) to the combined salmeterol group. At the beginning of the triamcinolone reduction phase, 19 patients remained in the placebo-minus group. Of the 154 patients assigned to receive salmeterol, 148 completed the salmeterol introduction phase, and 74 were then randomly assigned to the salmeterol-plus and salmeterol-minus groups (Figure 1). During the triamcinolone reduction and elimination phases, 13 patients (8.8%) in the salmeterol groups withdrew for personal reasons, none citing dissatisfaction with asthma control. Frequency of withdrawal was not significantly different among groups. The fraction of weeks in which patients were adherent to protocol-defined treatment for more than 70% of the days was 3351/3673 (91.2%), with no significant differences among groups.

**Primary Outcome Measure**

Of the 167 patients who completed the salmeterol introduction phase, 50 (29.9%) went on to meet one or more of the preestablished criteria for treatment failure (Box and Table 2). Failure to achieve before and after salmeterol FEV1 values of 80% or greater of the reference baseline uniquely accounted for 20 (40%) of treatment failures; there were only 2 treatment failures (4.0%) for which clinical safety judgment was the sole reason (Table 2). Seventeen patients (34.0%) with treatment failure (1

---

**Table 1. Characteristics of Patients in the Salmeterol ± Inhaled Corticosteroids (SLIC) Study at the End of the Salmeterol Introduction Phase**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo-Minus (n = 19)</th>
<th>Salmeterol-Plus (n = 74)</th>
<th>Salmeterol-Minus (n = 74)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>8 (42.1)</td>
<td>39 (52.7)</td>
<td>35 (47.3)</td>
<td>.62</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>35.58 (14.39)</td>
<td>35.70 (12.25)</td>
<td>34.23 (10.80)</td>
<td>.44</td>
</tr>
<tr>
<td>Patients aged &lt;18 y, No. (%)</td>
<td>4 (21.1)</td>
<td>5 (6.8)</td>
<td>4 (5.4)</td>
<td>.99</td>
</tr>
<tr>
<td>Race or ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (63.2)</td>
<td>50 (67.6)</td>
<td>45 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>0 (0)</td>
<td>3 (4.1)</td>
<td>4 (5.4)</td>
<td>.92</td>
</tr>
<tr>
<td>Black</td>
<td>5 (26.3)</td>
<td>15 (20.3)</td>
<td>17 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (10.5)</td>
<td>5 (6.8)</td>
<td>6 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Other races</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>PEF, mean (SD), L/min‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM PEF</td>
<td>398.4 (110.3)</td>
<td>445.6 (124.2)</td>
<td>425.3 (125.3)</td>
<td>.32</td>
</tr>
<tr>
<td>PM PEF</td>
<td>413.3 (88.3)</td>
<td>450.5 (121.0)</td>
<td>430.8 (123.3)</td>
<td>.33</td>
</tr>
<tr>
<td>PEF variability, mean (SD)§</td>
<td>0.17 (0.08)</td>
<td>0.11 (0.05)</td>
<td>0.11 (0.06)</td>
<td>.76</td>
</tr>
<tr>
<td>Daily asthma symptom score, median (IQR)‡</td>
<td>0.16 (0.02 to 0.35)</td>
<td>0.14 (0.04 to 0.39)</td>
<td>0.19 (0.03 to 0.35)</td>
<td>.65</td>
</tr>
<tr>
<td>Rescue albuterol use, median (IQR), puffs‡</td>
<td>0.00 (0.00 to 0.77)</td>
<td>0.00 (0.00 to 0.14)</td>
<td>0.00 (0.00 to 0.15)</td>
<td>.74</td>
</tr>
<tr>
<td>Morning‡</td>
<td>1.38 (0.43 to 3.50)</td>
<td>0.46 (0.00 to 2.15)</td>
<td>0.48 (0.00 to 2.36)</td>
<td>.49</td>
</tr>
<tr>
<td>Daily average‡</td>
<td>0.89 (0.43 to 1.93)</td>
<td>0.39 (0.00 to 1.25)</td>
<td>0.35 (0.00 to 1.38)</td>
<td>.63</td>
</tr>
<tr>
<td>FEV1, mean (SD), L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-salmeterol§</td>
<td>2.31 (0.61)</td>
<td>2.54 (0.57)</td>
<td>2.53 (0.63)</td>
<td>.87</td>
</tr>
<tr>
<td>Post-salmeterol§</td>
<td>2.70 (0.68)</td>
<td>2.76 (0.61)</td>
<td>2.69 (0.67)</td>
<td>.50</td>
</tr>
<tr>
<td>Improvement, mean (SD), %§</td>
<td>17.66 (13.02)</td>
<td>9.25 (12.05)</td>
<td>6.91 (7.72)</td>
<td>.16</td>
</tr>
<tr>
<td>Pre-salmeterol FEV1, % predicted, mean (SD)§</td>
<td>72.47 (12.50)</td>
<td>73.81 (10.43)</td>
<td>73.78 (11.24)</td>
<td>.99</td>
</tr>
<tr>
<td>Post-salmeterol FEV1, % predicted, mean (SD)§</td>
<td>84.63 (13.06)</td>
<td>79.91 (10.93)</td>
<td>78.42 (10.91)</td>
<td>.41</td>
</tr>
<tr>
<td>PC20, geometric mean (IQR), mg/mL§</td>
<td>2.08 (~0.35 to 2.32)</td>
<td>0.90 (~1.25 to 1.02)</td>
<td>0.82 (~1.81 to 0.86)</td>
<td>.57</td>
</tr>
<tr>
<td>Exhaled nitric oxide, median (IQR), ppb§</td>
<td>28.00 (20.60 to 29.10)</td>
<td>16.70 (11.40 to 24.70)</td>
<td>16.00 (11.40 to 23.40)</td>
<td>.99</td>
</tr>
<tr>
<td>Asthma QOL overall score, median (IQR)§</td>
<td>2.50 (2.09 to 3.16)</td>
<td>2.05 (1.44 to 2.75)</td>
<td>1.81 (1.50 to 2.47)</td>
<td>.35</td>
</tr>
</tbody>
</table>

* PLACEBO-MINUS indicates patients who received placebo salmeterol and 400 µg of triamcinolone twice daily during the salmeterol introduction phase (2 weeks) followed by placebo salmeterol and 200 µg of triamcinolone once daily during the triamcinolone reduction phase (8 weeks); Salmeterol-minus, patients who received 42 µg of salmeterol and 200 µg of triamcinolone twice daily during the salmeterol introduction phase (2 weeks) followed by 42 µg of salmeterol and 200 µg of triamcinolone twice daily during the triamcinolone reduction phase (8 weeks); Salmeterol-plus, patients who received 42 µg of salmeterol and 400 µg of triamcinolone twice daily during the salmeterol introduction phase (2 weeks) followed by 42 µg of salmeterol and 200 µg of triamcinolone twice daily during the triamcinolone reduction phase (8 weeks) followed by placebo salmeterol and placebo triamcinolone twice daily during the triamcinolone elimination phase (2 weeks).

† Averaged over 2 weeks of salmeterol introduction phase.

§ Averaged at the end of the salmeterol introduction phase.

©2001 American Medical Association. All rights reserved.
in the placebo-minus group; 4, salmeterol-plus group; and 12, salmeterol-minus group) developed asthma exacerbations (defined in Box). Two patients (4%) in the salmeterol-minus group with treatment failure required brief hospitalization to optimize their asthma control; both episodes occurred during the triamcinolone elimination phase.

Nine patients in the placebo-minus group experienced treatment failure during the reduction and elimination phases of the study (47.4%; 95% confidence interval [CI], 24.5%-70.3%). 9 patients in the salmeterol-plus group (12.2%; 95% CI, 4.6%-19.8%), and 32 patients in the salmeterol-minus group (43.2%; 95% CI, 31.7%-54.7%). Analysis of the percentage of patients experiencing treatment failure during the triamcinolone reduction and elimination phases vs the time-to-treatment failure for the 2 primary comparison groups showed a significant difference between the groups (P<.001, log-rank test) (FIGURE 2). However, independent analysis of treatment failure for the triamcinolone reduction and elimination phases showed differences in terms of the phase of the study in which the majority of failures occurred. For the reduction phase, the proportion of treatment failures was 2.8% (95% CI, 0%-7%) in the salmeterol-plus group and 8.3% (95% CI, 2%-15%) in the salmeterol-minus group. At the end of the elimination phase, however, the difference in the proportion of treatment failures in the 2 groups substantially increased, with values of 13.7% (95% CI, 5%-22%) for the salmeterol-plus group and 46.3% (95% CI, 34%-59%) for the salmeterol-minus group. The relative risk of treatment failure for patients in the salmeterol-minus group compared with the salmeterol-plus group was 2.2 (95% CI, 0.5-9.2) during the triamcinolone reduction phase (P = .27; Cox regression model); and during the elimination phase, the relative risk of treatment failure in the salmeterol-minus group increased further to 4.3 (95% CI, 2.0-9.2), and was significantly greater than in the salmeterol-plus group (P<.001).

**Figure 2.** Kaplan-Meier Survival Curves for the Salmeterol Treatment Groups During the Triamcinolone Reduction and Elimination Phases

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Placebo-Minus (n = 19)</th>
<th>Salmeterol-Plus (n = 74)</th>
<th>Salmeterol-Minus (n = 74)</th>
<th>Total† (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-salmeterol FEV1 ≤ 80% baseline</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Pre-salmeterol FEV1 ≤ 80% baseline</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Postbronchodilator AM PEF ≤ 80% baseline</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prebronchodilator PEF ≤ 65% baseline</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rescue albuterol use ≥ 8 puffs over baseline</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rescue albuterol use ≥ 16 puffs</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Emergency treatment</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Clinical safety judgment</td>
<td>3</td>
<td>4</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Clinical safety judgment only</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Placebo-minus indicates patients who received placebo salmeterol and 400 µg of triamcinolone twice daily during the salmeterol introduction phase (2 weeks) followed by placebo salmeterol and 200 µg of triamcinolone twice daily during the triamcinolone reduction phase (8 weeks); salmeterol-plus, patients who received 42 µg of salmeterol and 400 µg of triamcinolone twice daily through all 3 phases of the study after the triamcinolone run-in period; salmeterol-minus, patients who received 42 µg of salmeterol and 400 µg of triamcinolone twice daily during the salmeterol introduction phase (2 weeks) followed by 42 µg of salmeterol and 200 µg of triamcinolone twice daily during the triamcinolone elimination phase (8 weeks); FEV1, forced expiratory volume in 1 second; and PEF, peak expiratory flow. Baseline refers to values at the end of the triamcinolone run-in period.

†Patients may have met more than 1 criterion for treatment failure.

©2001 American Medical Association. All rights reserved.
asthma symptom scores and daily use of rescue albuterol decreased, pre-salmeterol FEV₁ values increased, and asthma quality-of-life scores improved overall and for each domain (Table 3 and Figure 3).

In contrast to these improvements in asthma control, the salmeterol-protected methacholine response PC₂₀ significantly decreased. Although the post-salmeterol FEV₁ values decreased in both salmeterol groups, the change was significant only for the salmeterol-plus group. When changes during the salmeterol introduction phase were compared between the 2 salmeterol groups, no significant differences were noted. No change in any secondary outcome measure was observed in the placebo-minus group.

**Tramcinolone Reduction Phase.** During the tramcinolone reduction phase, 2 statistically significant interval changes occurred. First, the daily symptom score increased in the salmeterol-minus group (P=.03; increase of 0.01 on a 3-point scale), the clinical relevance of which is questionable. Second, the salmeterol-protected methacholine response PC₂₀ significantly increased within the salmeterol-plus group (Table 3; Figure 3D). However, there was no significant difference between the interval change for methacholine response (P=.11) or for any other outcome among the salmeterol groups.

**Table 3. Interval Change in Secondary Outcome Measures (Last Value Carried Forward Analysis)**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Salmeterol-Plus</th>
<th>Salmeterol-Minus</th>
<th>Triamcinolone Reduction Phase†</th>
<th>Triamcinolone Reduction Phase†</th>
<th>Triamcinolone Elimination Phase†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM PEF, mean (SE), L/min</td>
<td>44.7 (5.8)</td>
<td>40.8 (5.8)</td>
<td>1.8 (10.7)</td>
<td>−6.8 (10.6)</td>
<td>−3.9 (9.0)</td>
</tr>
<tr>
<td>Daily asthma symptom score, median (IQR)§</td>
<td>−0.05 (−0.22 to 0)</td>
<td>−0.05 (−0.18 to 0)</td>
<td>0.00 (−0.10 to 0.11)</td>
<td>−0.02 (−0.06 to 0.12)</td>
<td>−0.06 (−0.06 to 0.31)</td>
</tr>
<tr>
<td>Daily rescue albuterol use, median (IQR), puffs/d</td>
<td>−0.29 (−1.00 to 0)</td>
<td>−0.42 (−1.21 to 0)</td>
<td>0.00 (−0.40 to 0.17)</td>
<td>−0.14 (−0.05 to 0.17)</td>
<td>0.14 (0 to 0.86)</td>
</tr>
<tr>
<td>Pre-salmeterol FEV₁, mean (SE), L</td>
<td>0.09 (0.04)</td>
<td>0.10 (0.04)</td>
<td>0.03 (0.05)</td>
<td>−0.03 (0.05)</td>
<td>−0.08 (0.06)</td>
</tr>
<tr>
<td>Post-salmeterol FEV₁, mean (SE), L</td>
<td>−0.06 (0.02)</td>
<td>−0.04 (0.02)</td>
<td>0.01 (0.03)</td>
<td>−0.02 (0.03)</td>
<td>−0.04 (0.04)</td>
</tr>
<tr>
<td>Salmeterol-protected methacholine response, mean (SE), mg/mL</td>
<td>−0.95 (0.14)</td>
<td>−0.90 (0.14)</td>
<td>0.42 (0.18)</td>
<td>−0.01 (0.18)</td>
<td>−0.12 (0.18)</td>
</tr>
</tbody>
</table>

| Asthma Quality of Life Score, median (IQR)§            | −0.18 (−0.45 to 0.09) | −0.27 (−0.60 to 0.00) | −0.09 (−0.39 to 0.18)         | −0.09 (−0.31 to 0.36)         | 0 (−0.27 to 0.18)               |
| Activity                                              | −0.40 (−0.60 to 0)    | −0.40 (−0.80 to 0)   | 0 (−0.40 to 0.40)            | −0.40 (−0.60 to 0.40)         | 0 (−0.60 to 0.40)               |
| Emotion                                               | −0.50 (−0.75 to 0)    | −0.38 (−1.0 to 0)    | 0 (−0.50 to 0.25)            | −0.25 (−0.25 to 0.25)         | −0.50 (−0.50 to 0.25)           |
| Environment                                            | −0.33 (−0.75 to 0.08) | −0.45 (−0.75 to 0)   | −0.17 (−0.33 to 0.17)        | −0.25 (−0.25 to 0.33)         | −0.25 (−0.25 to 0.33)           |
| Symptom                                               | −0.31 (−0.53 to 0.03) | −0.39 (−0.63 to 0)   | −0.09 (−0.34 to 0.18)        | −0.02 (−0.28 to 0.22)         | −0.02 (−0.28 to 0.22)           |
| Overall                                               | 0.28 (0 to 1.1)       | 0.28 (0 to 0.87)     | 0.25 (0 to 0.75)             | 0.25 (0 to 0.75)              | 0.25 (−0.08 to 1.1)             |

**Sequential Effects.** To determine what the overall anticipated effect would be in clinical practice following (1) the addition of salmeterol to tramcinolone therapy and (2) either a reduction in or elimination of or no change in tramcinolone dosages, we compared the interval change for 4 outcome measures from the start of the salmeterol introduction phase to 2 later time points: (1) the end of the tramcinolone elimination phase, and (2) the end of the elimination phase (Figure 3). For the first interval comparison, asthma symptom scores improved for...
the salmeterol-plus (P<.01) and salmeterol-minus (P=.04) groups and average daily rescue albuterol use for both salmeterol groups decreased (P<.001). For pre-salmeterol FEV1 values, only the salmeterol-plus group demonstrated significant improvement (P = .02). Salmeterol-protected methacholine response PC20 decreased significantly in both the salmeterol-plus (P = .01) and salmeterol-minus (P<.001) groups.

For the second interval comparison, the salmeterol-plus group demonstrated significant improvement in AM PEF values, daily asthma symptom scores, daily rescue albuterol use, and overall quality-of-life scores (P<.01, all comparisons); salmeterol-protected methacholine response PC20 decreased (P<.01). No improvement in any outcome measure was noted for the salmeterol-minus group. Salmeterol-protected methacholine response PC20 decreased (P<.001) with a trend for a significant decrease in pre-salmeterol FEV1 during this interval (P=.07).

**COMMENT**

The idea that treatment with salmeterol could allow a reduction in ICS dosages in patients with persistent asthma was based on the availability of long-acting β2-agonists for the treatment of asthma,21 the demonstration of the safety of regularly scheduled use of inhaled albuterol,18 and the results of controlled clinical trials demonstrating that the addition of long-acting β2-agonists to a fixed dosage of ICS improves asthma control more than increasing dosages of ICS.1,2,4 To provide information for clinical decision making, we designed a clinical trial to determine whether the dosages of ICS can be reduced and subsequently eliminated in patients treated with low to moderate dosages of ICS whose asthma control had improved with the addition of salmeterol treatment. Our data indicate that in patients treated with add-on salmeterol, the ICS dosage required to achieve asthma control can be safely reduced, but total elimination of ICS results in an unacceptably high rate of treatment failure.

The SLIC protocol included 3 phases to evaluate whether salmeterol use could allow ICS reduction, elimination, or both. The salmeterol introduction phase was designed to parallel as closely as possible 2 previously published clinical trials.1,2 Although the SLIC study population was somewhat younger, baseline pulmonary function values (mean [SD] FEV1, % predicted 70.4 [8.4]) and ICS doses were comparable. The significant improvements in pulmonary function and asthma quality of life that we observed during the salmeterol introduction phase of the trial (Table 3) were comparable to those observed in the patients evaluated by Woolcock et al1 and Juniper et al.22 Our replication of these findings in the first phase of the SLIC trial provided the foundation for our test of the hypothesis that the introduction of salmeterol could enable reduction and elimination of ICS.

Prior to the SLIC trial, no definitive guidelines for the reduction or elimination of ICS following the addition of salmeterol therapy existed. For the triamcinolone reduction phase, we reasoned that a 1-step 50% reduction in ICS dosage would be clinically relevant. We chose an interval of 8 weeks during which time we could analyze the effects of ICS dosage reduction and elimination based on reported findings that asthma exacerbation rates plateau within this period when such treatment interventions are initiated.15,16 Our data demonstrate that, after the introduction of salmeterol to patients receiving ICS therapy, reductions of ICS dosages by 50% were possible in the majority (>90%) of patients. During the triamcinolone reduction phase, the

**Figure 3. Secondary Outcome Measures**

During the triamcinolone run-in period (study weeks 1-6), all patients received 400 µg twice daily of triamcinolone. During the triamcinolone introduction phase (study weeks 7-8), patients in the salmeterol groups received 42 µg of salmeterol twice daily and 400 µg twice daily of triamcinolone. During the triamcinolone reduction (study weeks 9-16) and elimination (study weeks 17-24) phases, patients received the same dosage of salmeterol, but those in the salmeterol-minus group received 200 µg twice daily of triamcinolone for 8 weeks followed by placebo triamcinolone for 8 weeks. Panels C and D present means based on model estimates.

©2001 American Medical Association. All rights reserved. (Reprinted) JAMA, May 23/30, 2001—Vol 285, No. 20 2601
treatment failure rates in both salmeterol groups were low and not significantly different, even though they differed 2.2-fold. Our study did not have the power to detect a risk ratio of this magnitude when the absolute risks (8.3%, salmeterol-minus; 2.8%, salmeterol-plus groups) are this small. We doubt that these modest differences are clinically significant. On the basis of these results and the lack of clinically relevant adverse differences for any of the secondary outcome measures during this phase of the study, we propose that most patients can tolerate a 50% reduction in their ICS dosage while continuing salmeterol therapy.

In contrast, total elimination of triamcinolone therapy resulted in significant deterioration in asthma control. Specifically, during the triamcinolone elimination phase, the treatment failure rate in the group using salmeterol monotherapy was 4.3-fold greater than in the group using combination therapy. Indeed, the treatment failure rate was nearly 50%, a rate similar to that in the placebo-minus group, which is clearly unacceptably high. Moreover, we noted significant deterioration in a number of secondary outcome measures only during the elimination phase of the trial and only in those patients who were receiving monotherapy with salmeterol. To our knowledge, we are the first to observe a difference between patients receiving and not receiving ICS in terms of decreases in baseline FEV₁ values following chronic salmeterol administration.23-24 Our data confirm previous reports of the loss of bronchoprotection to methacholine-induced bronchoconstriction following chronic salmeterol administration.25 Although this loss tended to be greater in those patients in whom ICS therapy was eliminated, the differences were not significant.

The methods in our study differ from those in published articles on the effectiveness of salmeterol as an ICS-sparing agent.5,10 We believe the simplicity of the study design makes it a relevant model for patient care for a number of reasons. First, the SLIC trial followed what would commonly occur in clinical practice: salmeterol treatment was added, asthma control was improved, and then the triamcinolone dosage was reduced and eliminated, sequentially. Second, triamcinolone reduction and elimination was uniformly structured among the treatment groups, and evaluation of the effects of these step-downs in therapy occurred over 8 weeks, a clinically relevant and practical time interval. Third, we chose a set of criteria that would be considered by most clinicians to represent a clinically significant loss of asthma control. The safety and validity of this set of criteria were established previously in an ACRN-conducted clinical trial.16 We conclude that the addition of salmeterol therapy to ICS therapy has not only the potential to improve overall asthma control in patients with persistent asthma but it may permit ICS dosage reductions of at least 50% as well. Since it is likely that the potential for ICSs to produce adverse effects increases as dosages are increased,26-29 the effectiveness of salmeterol in permitting this degree of ICS dosage reduction is a clinically important feature of its pharmacologic profile. We recognize that our data, in the setting of a clinical trial, may not be directly transferable to clinical practice, but the simple message that the addition of salmeterol will aid in ICS dosage reduction but not elimination should be readily applicable to practice settings. Several studies have suggested complementary interactions between β₂-agonists and corticosteroids in that corticosteroids increase β₂-receptor synthesis and decrease β₂-receptor desensitization,30 while β₂-agonists prime the glucocorticoid receptor for corticosteroid-dependent activation.31 However, although these synergistic interactions may facilitate clinically relevant reductions in ICS dosing in many patients, our results indicate that total elimination of ICS therapy in patients receiving salmeterol is not safe and therefore cannot be recommended.

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

Author Contributions: Study concept and design: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Drazen, Chinchilli, Craig, Fish, Ford, Israel, Kraft, Martin, Nachman, Peters, Spahn, and Szelfer. Acquisition of data: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Drazen, Chinchilli, Craig, Fish, Ford, Israel, Kraft, Martin, Nachman, Peters, Spahn, and Szelfer. Analysis and interpretation of data: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Drazen, Chinchilli, Craig, Fish, Ford, Israel, Kraft, Martin, Nachman, Peters, Spahn, and Szelfer.

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

Statistical expertise: Lemanske, Mauger, Lazarus, and Chinchilli.

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

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

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

Financial Disclosures: Lemanske: Abbott (patent pending), Astra-Zeneca (honorary), Aventis (honorary), GlaxoSmithKline (consultant and honorary), and Merck (consultant and honorary). Sorkness: Astra-Zeneca (consultant and honorary), GlaxoSmithKline (consultant and honorary), and Merck (consultant and honorary). Lazarus: Abbott (research funding and honorary), Astra (honorary), Aventis (consultant), Boehringer Ingelheim (research funding), Fujisawa (consultant), Genentech (research funding), GlaxoSmithKline (consultant), Immunex (consultant), Merck (consultant), Merck Frost (honorary), Novartis (consultant), Pfizer (research funding), Pharmacia-Upjohn (research funding), and Zeneca Pharmaceuticals (research funding and honorary). 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 honorary), Boehringer Ingelheim (research funding), Fujisawa (consultant), Genelabs Inc (research funding), Genentech (consultant), GlaxoSmithKline (research funding), Merck (honorary), Novartis (research funding), Rhone-Poulenc Rorer (consultant), Roche BioSciences (Syntex) (consultant), and Texas Biotechnology (consultant). 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 under-
ICS REDUCTION/ELIMINATION AFTER ADDING SALMETEROL

REFERENCES


11. American Thoracic Society. Standards for the di-
agnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis. 1987;136:235-244.


©2001 American Medical Association. All rights reserved.