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
Joseph D. Spahn, MD
Stanley J. Szefler, MD
for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute

I N PATIENTS WITH PERSISTENT ASTHMA inadequately controlled by treatment with a low dose of inhaled corticosteroids (ICSs), the addition of a long-acting β₂-agonist provides an incremental improvement in asthma control exceeding that achieved by increasing dosages of ICS. We anticipated that once this improvement occurred, many patients would question whether their dosage of ICS could be reduced or even eliminated. Evidence both supporting and refuting...
ing\textsuperscript{7,9} the concept that continual long-acting \( \beta_2 \)-agonist therapy treats symptoms but not the underlying disease\textsuperscript{6} has generated controversy. Although some studies\textsuperscript{5,10} 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 \( \pm \) 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 \( \beta_2 \)-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\textsuperscript{11} who met recommended criteria for treatment with ICSs\textsuperscript{12} 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.\textsuperscript{13} 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 (FEV\(_1\)) of 80% of the

**Figure 1. Flow Diagram of the Salmeterol \( \pm \) Inhaled Corticosteroids (SLIC) Trial**

- 422 Patients Enrolled
- Triamcinolone Run-in Period (6 wk)
- 422 Patients Received Triamcinolone 400 \( \mu \)g Twice Daily
- 61 Did Not Complete Run-in
- 361 Completed Run-in
- 22 Excluded
  - 1 Pregnancy
  - 2 Asthma Exacerbation
  - 3 Withdraw Consent
  - 16 Ineligible
- 339 Eligible for Randomization
- 164 Entered SOCS Trial (FEV\(_1\) \( \leq 80\%) Predicted, PEF Variability \( \leq \) 20%)
- 175 Randomized (FEV\(_1\) \( \leq 80\%) Predicted, or if FEV\(_1\) > 80\% Predicted, PEF Variability >20%)
- Salmeterol Introduction Phase (2 wk)
  - 21 Assigned to Receive Triamcinolone 400 \( \mu \)g Twice Daily Plus Placebo Salmeterol
  - 6 Excluded
  - 1 Treatment Failure
  - 1 Withdraw Consent
- Triamcinolone Reduction Phase (8 wk)
  - 148 Randomized
  - Placebo-Minus
    - 19 Assigned to Receive Triamcinolone 200 \( \mu \)g Twice Daily Plus Placebo Salmeterol
    - 1 Withdrew
  - Salmeterol-Plus
    - 74 Assigned to Receive Triamcinolone 400 \( \mu \)g Twice Daily Plus Salmeterol 42 \( \mu \)g Twice Daily
    - 3 Withdrew
  - Salmeterol-Minus
    - 74 Assigned to Receive Triamcinolone 400 \( \mu \)g Twice Daily Plus Placebo Salmeterol 42 \( \mu \)g Twice Daily
    - 3 Withdrew
- Triamcinolone Elimination Phase (8 wk)
  - 18 Assigned to Receive Placebo Triamcinolone and Placebo Salmeterol
    - 1 Withdrew
  - 71 Assigned to Continue Triamcinolone 400 \( \mu \)g Twice Daily Plus Salmeterol 42 \( \mu \)g Twice Daily
    - 2 Withdrew
  - 71 Assigned to Receive Placebo Triamcinolone Plus Salmeterol 42 \( \mu \)g Twice Daily
    - 5 Withdrew
- 17 Completed Trial
- 69 Completed Trial
- 66 Completed Trial

FEV\(_1\), indicates forced expiratory volume in 1 second; PEF, peak expiratory flow; SOCS, Salmeterol or Corticosteroids trial.
**Box. Definition of Treatment Failure**

Treatment failure status was defined as the occurrence of ≥1 of the following:

1. Decrease in postbronchodilator forced expiratory volume in 1 second (FEV₁) ≥20% below value recorded at the end of the 6-week triamcinolone acetonide run-in period (all values obtained after administration of salmeterol xinafoate)
2. Prebronchodilator FEV₁ values on 2 successive visits ≥20% below values obtained at the end of the 6-week triamcinolone run-in period
3. Decrease in postbronchodilator (up to at least 6 puffs of rescue albuterol within 1 hour [2-4 puffs every 20 minutes]) AM peak expiratory flow (PEF) ≥20% below the mean value of the AM prebronchodilator PEF recorded for the last 2 weeks of the triamcinolone run-in period
4. Prebronchodilator PEF ≤65% of mean value of AM prebronchodilator PEF recorded for the last 2 weeks of the triamcinolone run-in period on any of 2 of 3 consecutive scheduled measurements
5. Increase in as needed rescue albuterol use of 8 puffs per 24 hours over the average daily use during the last 2 weeks of the triamcinolone run-in period for 48 hours or ≥16 puffs per 24 hours for 48 hours
6. Need for emergency department treatment that is related to or complicated by asthma and that results in corticosteroid treatment or hospitalization for an acute asthma exacerbation
7. Any use of oral or parenteral corticosteroids related to the treatment of the patient’s asthma
8. Physician clinical judgment for safety reasons

*Greater deteriorations in asthma control (PEF value ≤65% of baseline [mean value of AM prebronchodilator values over a 2 week period] after the first 60 minutes of rescue albuterol use, or an increase in rescue albuterol use ≥8 puffs/24 hours over baseline use or ≥16 puffs/24 hours for 48 hours) were considered asthma exacerbations and were treated by a predetermined set of rescue algorithms that included oral or parenteral corticosteroid administration. All asthma exacerbations were also considered treatment failures.

Predicted value or less and a 12% or greater increase after treatment with aerosolized albuterol. For patients already receiving ICSs, 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 beclomethasone, 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. After a 6-week run-in period with open-label triamcinolone acetonide 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 ICS 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-
agea together, labeled with a unique
number, and distributed to the clinical
centers. The contents of the drug pack-
ages were known only to adminis-
trative personnel at the data coor-
dinating 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
day by open-label inhaler and con-
tinued coded inhalers of triamcinol-
one, 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 sal-
meterol 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-
one 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
intentional 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
at 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 secondary
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.

RESULTS
Enrollment, Retention,
and Adherence
A total of 422 patients were eligible to
enter 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
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ICS REDUCTION/ELIMINATION AFTER ADDING SALMETEROL

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></td>
</tr>
<tr>
<td>Black</td>
<td>5 (26.3)</td>
<td>15 (20.3)</td>
<td>17 (23.0)</td>
<td>.92</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 0.55)</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>Evenings§</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>PC_{20}, 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 (0.09 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 twice daily during the triamcinolone reduction phase (8 weeks) followed by placebo salmeterol and placebo triamcinolone during the triamcinolone elimination 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 reduction phase (8 weeks) followed by 42 µg of salmeterol and placebo triamcinolone twice daily during the triamcinolone elimination phase (8 weeks); PEF, peak expiratory flow; IQR, interquartile range; FEV1, forced expiratory volume in 1 second; QOL, quality of life; and PC_{20}, provocative concentration of methacholine that reduces FEV1 by 20%.

†Average over 2 weeks of salmeterol introduction phase.

‡Averaged over 2 weeks of salmeterol introduction phase.

§Averaged at the end of the salmeterol introduction phase.

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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 2. Reasons for Treatment Failure by Treatment Group 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 &lt; 80% baseline</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Pre-salmeterol FEV1 &lt; 80% baseline</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Postbronchodilator AM PEF &lt; 80% baseline</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prebronchodilator PEF &lt; 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>1</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>17</td>
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<td>Clinical safety judgment</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
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* 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 placebo triamcinolone during the triamcinolone elimination 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 placebo triamcinolone during the triamcinolone elimination phase (8 weeks); salmeterol-minus, patients who received 42 µg of salmeterol and 400 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 (8 weeks).

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

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>No. at Risk</th>
<th>Salmeterol-Minus</th>
<th>Salmeterol-Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction Phase</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>Elimination Phase</td>
<td>70</td>
<td>76</td>
</tr>
</tbody>
</table>

P < .001 for the comparison of time-to-treatment failure between the 2 salmeterol treatment groups based on the log-rank test. Patients who continued to be at risk for treatment failure as the trial proceeded are indicated at the bottom of the graph.

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asthma symptom scores and daily use of rescue albuterol decreased, pre-
salmeterol FEV₁ values increased, and asthma quality-of-life scores im-
proved 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 sal-
meterol-plus group. When changes during the salmeterol introduction phase were compared between the 2 salme-
terol groups, no significant differences were noted. No change in any sec-
ondary outcome measure was observed in the placebo-minus group.

Triamcinolone Reduction Phase. During the triamcinolone reduction phase, 2 statistically significant interval changes occurred. First, the daily symp-
tom score increased in the salmeterol-minus group (P = .03; increase of 0.21 on a 3-point scale), the clinical relevance of which is questionable. Second, the salme-
terol-protected methacholine response PC₂₀ significantly increased

within the salmeterol-plus group (Table 3; Figure 3D). However, there was no sig-
nificant difference between the interval change for methacholine response
(P = .11) or for any other outcome among the salmeterol groups.

Triamcinolone Elimination Phase. During the triamcinolone elimination phase, outcomes in the salmeterol-
minus group significantly deteriorated. Daily asthma symptom scores and daily rescue albuterol use increased, and before and after salmeterol FEV₁ values and quality of life scores (overall and for each individual domain) decreased. In con-
trast, no significant deterioration occurred in any outcome measure in the salmeterol-plus group (Figure 3 and Table 3). Significant differences in between-group interval change compari-
sions were noted for daily symptom scores (P < .01), daily rescue albuterol use
(P < .01), and quality-of-life scores (overall and for each domain; P < .01).

Sequential Effects. To determine what the overall anticipated effect would be in clinical practice following (1) the addition of salmeterol to triami-
cinolone therapy and (2) either a re-
duction in or elimination of or no
change in triamcinolone dosages, we
compared the interval change for 4 out-
come measures from the start of the sal-
meterol introduction phase to 2 later time points: (1) the end of the triam-
cinolone elimination phase, and (2) the end of the elimination phase (Figure 3).

For the first interval comparison, asthma symptom scores improved for

<table>
<thead>
<tr>
<th>Table 3. Interval Change in Secondary Outcome Measures (Last Value Carried Forward Analysis)†</th>
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</thead>
<tbody>
<tr>
<td>Outcome Measure</td>
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<tr>
<td>AM PEF, mean (SE), L/min</td>
</tr>
<tr>
<td>Daily asthma symptom score, median (IQR)</td>
</tr>
<tr>
<td>Daily rescue albuterol use, median (IQR), puffs/d</td>
</tr>
<tr>
<td>Pre-salmeterol FEV₁, mean (SE), L</td>
</tr>
<tr>
<td>Post-salmeterol FEV₁, mean (SE), L</td>
</tr>
<tr>
<td>Salmeterol-protected methacholine response, mean (SE), mg/mL</td>
</tr>
<tr>
<td>Asthma Quality of Life Score, median (IQR)§</td>
</tr>
<tr>
<td>Activity</td>
</tr>
<tr>
<td>Emotion</td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>Symptom</td>
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<tr>
<td>Overall</td>
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</table>

* Salmeterol-plus indicates 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 reduction phase (8 weeks); PEF, peak expiratory flow; IQR, interquartile range; and FEV₁, forced expiratory volume in 1 second. Interquartile range represents the first and the third quartiles.
† Within-group change from the end to the beginning of that treatment interval.
‡ Responses were measured 1 hour after administering salmeterol and represents the doubling dosage interval change.
§Recorded on a 7-point scale from 1 (no limitations) to 7 (totally limited).
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,⁰¹ the demonstration of the safety of regularly scheduled use of inhaled albuterol,⁰⁸ 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.⁰²⁰⁴ 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.⁰¹⁰² 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 al⁰¹ and Juniper et al.⁰² 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.⁰¹⁰⁵ 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
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.24-26 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 were 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 increased26-29 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 Pharmacy, 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 Draelzen 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 Krafft and Martin) and Pediatrics (Drs Sparh and Sefler) National Jewish Medical and Research Center, Denver, Colo.

Author Contributions: Study concept and design: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Draelen, Chinchilli, Craig, Fish, Ford, Israel, Krafft, Martin, Nachman, Peters, Sparh, and Sefler.

Analysis and interpretation of data: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Draelen, Chinchilli, Craig, Fish, Ford, Israel, Krafft, Martin, Nachman, Peters, Sparh, and Sefler.

Drafting of the manuscript: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Draelen, Chinchilli, Craig, and Israel.

Critical revision of the manuscript for important intellectual content: Lemanske, Sorkness, Mauger, Lazarus, Boushey, Fahy, Draelen, Chinchilli, Fish, Ford, Israel, Krafft, Martin, Nachman, Peters, Sparh, and Sefler.

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

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