Long-Acting β₂-Agonist Monotherapy vs Continued Therapy With Inhaled Corticosteroids in Patients With Persistent Asthma: A Randomized Controlled Trial

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Context
Long-acting β₂-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 β₂-agonist, as replacement therapy in patients whose asthma is well controlled by low-dose triamcinolone acetone, 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 µg twice per day).

Interventions
Patients were randomly assigned to continue triamcinolone therapy (400 µg twice per day; n=54) or switch to salmeterol (42 µg 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 use, asthma-specific quality-of-life scores, treatment failure, asthma exacerbation, bronchial reactivity, and markers of airway inflammation, compared among the 3 treatment groups.

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.

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asthma is well controlled by low-to-moderate doses of an ICS, must the ICS be continued, or might monotherapy with a long-acting $\beta_2$-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 $\beta_2$-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 Society who met recommended criteria for treatment with an ICS were recruited. Four hundred twenty-two patients who met the inclu-

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**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: FEV$_1 \geq 80\%$ of predicted value; and Documentation of $\geq 12\%$ increase in FEV$_1$ after aerosolized albuterol treatment
3. For patients already receiving an ICS: FEV$_1 \geq 40\%$ of predicted value
   - If FEV$_1$ is 40%-80% of predicted value, patient must demonstrate $\geq 12\%$ increase in FEV$_1$ after aerosolized albuterol treatment
   - If FEV$_1$ is $>80\%$ of predicted value, patient must demonstrate a 20% reduction in FEV$_1$ in response to a concentration of inhaled methacholine $\leq 8$ mg/mL (PC$_{20}$ FEV$_1 \leq 8$ mg/mL)
3. Nonsmoker (total lifetime smoking history $\leq$ 10 pack-years; no smoking for at least 1 year)
4. No regular use of other medications except oral contraceptives and nasal beclomethasone
5. No respiratory tract infection or asthma exacerbation within 6 weeks of run-in period
6. No serious medical illness other than asthma

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

1. FEV$_1 > 80\%$ of predicted value; and
2. Average peak expiratory flow (PEF) variability $\leq 20\%$, calculated as $\left[\frac{(PM PEF - AM PEF)(PM PEF + AM PEF)}{2}\right] \times 100$, 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

Equally controlled by low-to-moderate dosages of an inhaled corticosteroid (ICS) because addition of salmeterol xinafoate or formoterol fumarate, 2 long-acting $\beta_2$-agonists, was shown to be more effective than increasing the dose of the ICS. 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 $\beta_2$-agonists as monotherapy, however, is unclear, since most studies of salmeterol have included a significant proportion of patients taking other controller medications, including ICSs. A recent study suggests that salmeterol may be equivalent to low-dose beclomethasone dipropionate in corticosteroid-naive patients with persistent asthma.
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 acetonide. 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 ± 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 (PC20), the provocative concentration of methacholine required to decrease forced expiratory volume in 1 second [FEV1] 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 each visit.22

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 FEV1, asthma symptom scores, rescue albuterol use, quality-of-life scores, and PC20. 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 acetonide, 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. 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. 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.
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 inflammatory 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 period, 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 µg twice per day of open-label triamcinolone (TABLE 2).

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Table 1. Patient Characteristics at Randomization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 56)</th>
<th>Salmeterol (n = 54)</th>
<th>Triamcinolone (n = 54)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>18 (32.1)</td>
<td>21 (38.9)</td>
<td>18 (33.3)</td>
<td>.77</td>
</tr>
<tr>
<td>Age at randomization, mean (SD), y</td>
<td>31.19 (10.62)</td>
<td>31.62 (10.77)</td>
<td>31.32 (10.95)</td>
<td>.99</td>
</tr>
<tr>
<td>Patients aged &lt;18 y, No. (%)</td>
<td>5 (8.9)</td>
<td>5 (9.3)</td>
<td>6 (11.1)</td>
<td>.95</td>
</tr>
<tr>
<td>Race or ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (67.9)</td>
<td>41 (75.9)</td>
<td>36 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>4 (7.1)</td>
<td>2 (3.7)</td>
<td>3 (5.6)</td>
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<tr>
<td>Black</td>
<td>9 (16.1)</td>
<td>7 (12.9)</td>
<td>8 (14.8)</td>
<td>.55</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (8.9)</td>
<td>3 (5.6)</td>
<td>5 (9.3)</td>
<td></td>
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<tr>
<td>Other</td>
<td>0</td>
<td>1 (1.9)</td>
<td>2 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Previous inhaled corticosteroid use, No. (%)</td>
<td>52 (92.9)</td>
<td>53 (98.2)</td>
<td>54 (100)</td>
<td>.13</td>
</tr>
</tbody>
</table>
| Previous inhaled corticosteroid use, mean (SD), μg/d

PM PEF, L/min 452.9 (96.3) 453.4 (112.6) 473.3 (110.7) .54
PM PEF variability, mean (SD)

0.108 (0.041) 0.100 (0.048) 0.108 (0.054) .55
Daily asthma symptom score, median (IQR)

0.159 (0.054-0.411) 0.223 (0.064-0.431) 0.253 (0.080-0.463) .42
Rescue albuterol use, median (IQR), puffs/dd

0.445 (0.000-2.307) 1.129 (0.067-2.313) 0.75 (0.200-2.476) .50
FEV1, mean (SD), L

3.066 (0.623) 3.105 (0.786) 3.213 (0.646) .51
FEV1 % predicted, mean (SD)

93.25 (8.29) 92.54 (8.65) 95.67 (10.35) .18
PC20, geometric mean (IQR), mg/mL

0.767 (0.277-1.670) 0.885 (0.299-1.970) 0.966 (0.395-2.050) .50
Sputum eosinophils, median (IQR), %

0.7 (0.2-2.0) 0.6 (0.0-1.8) 0.6 (0.0-1.8) .83
Exhaled nitric oxide, median (IQR), ppb

14.3 (11.4-24.5) 14.1 (8.8-29.7) 15.7 (11.3-28.4) .94

*PEF 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%).

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

Asthma exacerbations were experienced by 16 patients (29%) in the placebo group, 11 (20%) in the salmeterol group, and 4 (8%) 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 (8%) in the triamcinolone group.
(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 ≤ .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 β2-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] ppb) all increased.
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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 received 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).

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

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>AM PEF, L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo vs Salmeterol</td>
<td>Placebo vs Triamcinolone</td>
</tr>
<tr>
<td>End of run-in (wk 6)</td>
<td>449.2 (16.8)</td>
</tr>
<tr>
<td>End of randomized treatment (wk 22)</td>
<td>430.8 (14.3)</td>
</tr>
<tr>
<td>End of run-out (wk 28)</td>
<td>429.6 (15.5)</td>
</tr>
</tbody>
</table>

| 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] | 21.3 [-11.3 to 53.9] | 14.2 [-17.5 to 46.0] |

*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, FEV$_1$, and PC$_{20}$, 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 FEV$_1$, 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 FEV$_1$ ($P = .015$ by ITT), and PC$_{20}$ ($P = .003$ 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, FEV$_1$, and PC$_{20}$ 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 $\beta_2$-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 $\beta_2$-agonists only as additive therapy,$^3$ but this recommendation was
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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.59

The effect of long-acting β2-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 β2-agonists may mask worsening airway inflammation and delay awareness of worsening asthma.60 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 ICS60 or with the long-acting β2-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 failure 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.

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