Salmeterol was not as effective as triamcinolone for persistent asthma

Lazarus SC, Boushey HA, Fahy JV, et al., for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. **Long-acting β_2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. A randomized controlled trial.** JAMA. 2001 May 23/30;285:2583-93.

QUESTION

In patients with persistent asthma, is salmeterol monotherapy as effective as triamcinolone for managing asthma?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, {clinicians, outcome assessors}†, and statisticians),* placebo-controlled trial with 16-week follow-up.

SETTING

6 university-based ambulatory care centers in the United States.

PATIENTS

164 patients (mean age 31 y, 65% women, 70% white) who were 12 to 65 years of age and nonsmoking; had no respiratory tract infection or asthma exacerbation within 6 weeks of the run-in period; had no serious illness other than asthma; did not use medications other than inhaled corticosteroids, oral contraceptives, or nasal beclomethasone; and met run-in period criteria. Patients whose asthma was not well controlled were excluded. 152 patients (93%) completed follow-up.

INTERVENTION

After the 6-week run-in period during which all patients received a metered-dose inhaler (MDI) of triamcinolone acetonide, 400 µg (4 puffs) twice daily, patients were allocated to 1 of 3 groups: 54 were allocated to the same dosage schedule of triamcinolone used in the run-in period; 54 were allocated to an MDI of salmeterol xinafoate, 42 µg (2 puffs) twice daily; and 56 were allocated to an MDI of placebo (2 puffs) twice daily. Albuterol inhalers were given to patients for rescue treatment use.

MAIN OUTCOME MEASURES

Change in morning peak expiratory flow (PEF). Secondary outcomes were treatment failure and asthma exacerbations.

MAIN RESULTS

Analysis was by intention to treat. The salmeterol, triamcinolone, and placebo groups did not differ for change in morning PEF ($P \geq 0.09$ for all comparisons). Treatment failure rate and asthma exacerbations were higher in the salmeterol group than in the triamcinolone group (Table).

CONCLUSION

Patients with persistent asthma controlled with triamcinolone could not be switched to salmeterol monotherapy without risk for treatment failure and asthma exacerbations.

Sources of funding: National Heart, Lung, and Blood Institute. Medications and equipment provided by Aradigm Corp.; Enact Health Management Systems; GlaxoWellcome Inc.; Hoechst Marion Roussel Inc.; Rhône-Poulenc Rorer Pharmaceuticals Inc.; Sievers Instruments Inc.

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*See Glossary.

†Information provided by author.

Salmeterol vs triamcinolone at 16 weeks for persistent asthma‡

Outcomes	Salmeterol	Triamcinolone	RRI (95% CI)	NNH (CI)
Treatment failure	24%	5.6%	333% (43 to 1267)	6 (4 to 19)
Asthma exacerbations	20%	7.4%	175% (0 to 683)	8 (4 to 648)

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

The addition of long-acting β_2-agonists to inhaled corticosteroids has been shown to improve control in patients with persistent asthma, and complementary effects with corticosteroid receptors and β_2-adrenoceptors have been reported. However, once control is obtained, the timing of reduction or total withdrawal of inhaled corticosteroids is unclear, and inconsistent findings have been reported to date. The merits of monotherapy of inhaled corticosteroids compared with those of long-acting β_2-agonists have required further evaluation, particularly as β_2-agonists have been recognized as long-term controllers with possible subtle anti-inflammatory effects (1).

A common sampling frame of patients with asthma provided recruits for 2 studies to address these issues. The first, by Lazarus and colleagues, showed that in patients whose asthma was considered to be well-controlled with low-dose inhaled corticosteroids, switching to monotherapy with long-acting β_2-agonists was inferior to continuation of the inhaled corticosteroids for several outcomes, including asthma exacerbation, treatment failure, and airway inflammation. Morning peak expiratory flow and asthma symptom scores were not affected in the salmeterol group and thus cannot be used to predict treatment failure or asthma exacerbation. This lack of effect may have clinical implications because salmeterol may treat symptoms and limit changes in lung function but not prevent exacerbations.

The second study by Lemanske and colleagues included patients whose asthma was not well controlled with low-dose inhaled corticosteroids. Long-acting β_2-agonists were added to the therapy regimen, and the effects of stepwise removal of inhaled corticosteroids were examined. This study showed that halving inhaled corticosteroid doses resulted in at least a doubling of the risk for treatment failure, although the difference between the salmeterol-plus-triamcinolone and salmeterol-minus-

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Stopping triamcinolone led to treatment failures in patients with persistent asthma who were receiving salmeterol and triamcinolone

Lemanske RF, Sorkness CA, Mauger EA, et al., for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. **Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol. A randomized controlled trial.** JAMA. 2001 May 23/30;285:2594-2603.

QUESTION

In patients with persistent asthma controlled with salmeterol and triamcinolone (TMC), can TMC therapy be reduced or eliminated without increasing treatment failure rates?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, {clinicians, outcome assessors}†, and statisticians),* placebo-controlled trial with 18-week follow-up.

SETTING

6 university-based ambulatory care centers in the United States.

PATIENTS

175 patients who were 12 to 65 years of age and nonsmoking; did not use medications other than inhaled corticosteroids, oral contraceptives, or nasal beclomethasone; had no respiratory tract infection or asthma exacerbation within 6 weeks of the run-in period; had no serious illness other than asthma; met run-in period criteria; and had asthma considered not well controlled after the run-in period ($FEV_1 \leq 80\%$ of predicted value or, if > 80% of predicted value, had an average peak expiratory flow variability > 20%). 167 patients (mean age 35 y, 51% women, 64% white) completed the 2-week salmeterol introduction phase. 152 patients (87%) completed follow-up.

INTERVENTION

For the first 2 weeks, all patients continued to receive a metered-dose inhaler (MDI) of TMC acetonide, 400 µg (4 puffs) twice daily (as was administered during the 6-wk run-in period). 13 of every 15 patients were also allocated to receive an MDI of salmeterol xinafoate, 42 µg (2 puffs) twice daily, while the remaining patients received an MDI of placebo salmeterol (placebo group). At the end of 2 weeks, 50% of the patients receiving TMC and salmeterol and not meeting criteria for treatment failure (i.e., whose asthma was controlled) were allocated to remain at their dosage (salmeterol-plus-TMC group); the remaining 50% of the patients received a 50% dose reduction of TMC for 8 weeks, followed by TMC elimination (salmeterol-minus-TMC group) for another 8 weeks. Patients in the placebo (of salmeterol) group received the same reductions of TMC during this period if they did not meet treatment failure criteria.

MAIN OUTCOME MEASURE

Time to treatment failure.

MAIN RESULTS

Analysis was by intention to treat. Treatment failure was not statistically different between groups when TMC was reduced by 50% (Table). However, treatment failure was statistically higher in the salmeterol-minus-TMC group during the elimination phase (Table).

CONCLUSION

In patients with persistent asthma that is not well controlled with triamcinolone (TMC) alone, but is controlled after adding salmeterol, TMC doses can subsequently be reduced but should not be eliminated.

Sources of funding: National Heart, Lung, and Blood Institute. Medications and equipment provided by Aradigm Corp.; Enact Health Management Systems; GlaxoWellcome Inc.; Hoechst Marion Roussel Inc.; Rhône-Poulenc Rorer Pharmaceuticals Inc.; Sievers Instruments Inc.

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*See Glossary.

†Information provided by author.

Salmeterol (Sal) with reduced and eliminated triamcinolone (TMC) doses (Sal–) vs Sal with unaltered TMC doses (Sal+) for treatment failure rates in persistent asthma that is controlled with Sal and TMC‡

Study phase	Failure rate		RRI (95% CI)	NNH (CI)
	Sal–	Sal+		
Reduced TMC	8.3%	2.8%	120% (–50 to 820)	Not significant
Eliminated TMC	46.3%	13.7%	330% (100 to 820)	4 (3 to 6)

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from log-rank data in article.

COMMENTARY *(continued from page 14)*

triamcinolone groups was not statistically significant (2.8% vs 8.3%, after 8 wk). An increase in treatment failure occurred after 8 weeks of complete inhaled corticosteroid elimination. Lemanske and colleagues state that inhaled corticosteroids had been "safely reduced" and that the clinical significance of the increased treatment failures was doubtful. An alternative interpretation would be that a more modest reduction in inhaled corticosteroids may be a safer option. Because this trial only evaluated halving the inhaled corticosteroid dose for 8 weeks, the longer-term bronchoprotective effects against viral infections and various other provocative agents are unclear. Clearly, some reduction of the inhaled corticosteroid dose during periods of relatively good asthma control should be considered, but such reduction should be done with caution.

The prescribing uptake of long-acting β_2-agonists by clinicians in many countries has been substantial. Given the prevalence of asthma and other airway diseases, the cost implications are also considerable. These 2 studies show more favorable clinical outcomes and suppression of markers of inflammation with inhaled corticosteroids than with long-acting β_2-agonist monotherapy. These studies are also consistent with current guideline recommendations that inhaled corticosteroids should be used to control airway inflammation, that the addition of long-acting β_2-agonists has a role in managing persistent symptoms, and that cautious reduction of inhaled corticosteroid dose should be considered during periods of good asthma control.

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Reference

1. **Holgate ST.** JAMA. 2001;285:2637-9.

