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A multicenter, placebo-controlled study of twice daily triamcinolone acetonide (800 µg per day) for the treatment of patients with mild-to-moderate asthma

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Background: National and international guidelines recommend the use of inhaled antiinflammatory medications in patients with all but the mildest forms of asthma. Twice daily dosing may increase compliance with therapy. **Objective:** We sought to evaluate the safety and efficacy of 400 µg twice daily triamcinolone acetonide (TAA) compared with placebo in adult patients with mild-to-moderate asthma who were poorly controlled by β_2 -agonist therapy. **Methods:** We performed a multicenter, randomized, double-blind, placebo-controlled study, including a screening visit, a 7- to 21-day pretreatment baseline phase, and a 6-week double-blind treatment phase. Efficacy was measured by weekly spirometry and daily diary recordings of peak flow rates, asthma symptom scores, and albuterol use. Eligible patients used albuterol four or more times per day, had total asthma symptom scores of 15 or greater (possible total, 60) over 5 of 7 baseline days, and had FEV₁ measurements of 60% of predicted value or greater. **Results:** One hundred twenty-one patients were randomized to treatment. TAA was superior to placebo for all efficacy measures, with significant improvements in asthma symp-

toms, albuterol use, morning and evening peak flow rates, and forced vital capacity evident at Treatment Week 1. Significant improvements in other pulmonary function measurements were observed after 2 or more weeks. All efficacy variables improved progressively throughout the study. **Conclusions:** Twice daily TAA (400 µg) decreased asthma symptoms and improved lung function in patients with mild-to-moderate asthma compared with placebo. Therapeutic benefit was evident within 1 week and increased throughout treatment. (*J Allergy Clin Immunol* 1998;101:433-8.)

Key words: Triamcinolone, asthma, inhaled corticosteroid

The basis for treatment of asthma is the suppression and reversal of the underlying inflammatory process.¹ It is now known that the cellular changes and airway remodeling that characterize asthmatic inflammation are present even in newly diagnosed patients and patients with mild asthma.²⁻⁴ Inhaled corticosteroids are well established as the most effective antiinflammatory agents for the long-term management of patients with moderate-to-severe asthma.⁵⁻⁸ These agents impact on many phases of the bronchial inflammatory response, including the reduction of cytokine production and reduction in numbers of T-lymphocytes, eosinophils, and mast cells in bronchial tissue.^{7,8}

Recent evidence suggests that long-lasting clinical improvements could be achieved with the use of inhaled corticosteroids by patients with mild asthma.^{9,10} Therefore a critical issue is compliance with antiinflammatory therapy. However, compliance varies greatly among patients taking inhaled medications three to four times

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Abbreviations used

FEF _{25%-75%} :	Forced expiratory flow 25% to 75% of expired volume
FVC:	Forced vital capacity
PEFR:	Peak expiratory flow rate
TAA:	Triamcinolone acetonide

daily.¹¹⁻¹⁶ For this reason, decreasing the frequency of inhaled corticosteroid treatment to twice daily may be of critical importance in treating patients with mild-to-moderate asthma.

This article describes a controlled clinical trial of triamcinolone acetonide (TAA) (400 µg) given twice daily for the treatment of mild-to-moderate asthma. The clinical efficacy of 200 µg TAA given four times daily to steroid-dependent¹⁸ and nonsteroid-dependent¹⁹ patients with moderate-to-severe asthma is well documented. However, limited data are available on the use of this agent when administered twice daily²⁰ or when used to treat patients with mild-to-moderate asthma. The use of TAA in patients with milder asthma is of interest in light of the current asthma management guidelines, which encourage consideration of inhaled corticosteroids to treat appropriate patients earlier in the course of the disease (i.e., patients with asthma of mild-to-moderate severity).^{1,6}

METHODS

Subjects

Patients who enrolled in the study were 19 years of age or older, nonsmokers with or without a past smoking history of less than 10 years, and had at least a 2-year history of mild-to-moderate perennial asthma as defined by the National Heart, Lung and Blood Institute Guidelines. At the screening visit, eligible patients required an aerosolized β_2 -agonist treatment three or more times per week, used no more than one additional antiasthma medication (e.g., oral β_2 -agonist, inhaled corticosteroids, theophylline, or cromolyn sodium) to control symptoms, and had an FEV₁ of 70% of predicted value or greater. After a 7- to 21-day baseline period, an FEV₁ of 60% of predicted value or greater was required, and an increase in FEV₁ of 15% or greater was required after inhaled albuterol. Each enrolled patient gave written informed consent.

Excluded from the study were pregnant or lactating women and women not using a reliable contraceptive method; patients who had a significant medical condition, a history of sensitivity or nonresponse to inhaled corticosteroids, an upper respiratory tract infection, or acute exacerbation of asthma within 30 days of the screening visit; and patients who, on the basis of previous history, were expected to experience seasonal fluctuations in asthma during the study. Also excluded were patients who had received systemic corticosteroids or initiated immunotherapy within 6 months of the screening visit, had taken any investigational drug within 30 days of the screening visit, or were taking any medication that could interfere with study results.

TABLE I. Patient demographics

Characteristic	TAA group	Placebo group
No. of patients	60	61
Age (yrs)		
Mean	34.7	33.6
Range	19-63	20-58
Sex (%)		
M	20 (33)	29 (47)
F	40 (67)	32 (53)
History of asthma (yrs)		
Mean	22.0	18.1
SEM	1.78	1.44
Patients receiving previous asthma therapy (%)		
Inhaled corticosteroids	33 (55.0)	33 (54.1)
Cromolyn sodium	2 (3.3)	2 (3.3)
β -agonists	60 (100)	61 (100)
Theophylline	8 (13.3)	2 (3.3)
Immunotherapy	2 (3.3)	2 (3.3)

Study medications

During the double-blind treatment phase of the study, patients were randomly assigned to receive four inhalations of either 100 µg TAA per actuation (Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pa.) or placebo twice daily for 6 weeks.

During the study, patients were permitted to take medications for rhinitis (nasal steroids, decongestants, and intranasal cromolyn sodium). Patients were also allowed to use rescue inhaled albuterol and continue maintenance immunotherapy. Use of any concomitant medications that could affect the severity of asthma or interfere with the interpretation of the study results was not permitted.

Study Design

This double-blind, placebo-controlled study was conducted at six study centers in the United States. The protocol and informed consent forms were reviewed and approved by an institutional review board at each center.

The study consisted of three phases. Phase 1 was a screening visit to determine eligibility for enrollment; phase 2 was a 7- to 21-day baseline phase to determine albuterol use of four or more inhalations per day on 5 of the last 7 days and total symptom score of 15 or greater for those 5 days; and phase 3 was a 6-week, double-blind treatment phase with patients randomized to use either TAA or placebo.

During the screening visit (visit 1), a medical history was taken, a physical examination was performed, and specimens were collected for blood chemistry, hematology, and urinalysis. Pulmonary function was assessed by spirometry at least 6 hours after the last use of a β_2 -agonist. Three spirometric attempts were performed at each time point, and the maneuver with the best FEV₁ was recorded. Eligible patients who achieved an FEV₁ measurement of at least 70% of predicted value continued into the 7- to 21-day baseline phase. At the screening visit, patients discontinued use of all asthma medications except albuterol. Patients recorded frequency of albuterol use and morning and evening peak flow rates in a daily diary. Patients recorded their asthma symptoms twice daily using a symptom

TABLE II. Pulmonary function measurements at clinic visits

Treatment group	Baseline (mean $\pm$ SEM)	Week 2 (mean $\pm$ SEM)	Week 4 (mean $\pm$ SEM)	Week 6 (mean $\pm$ SEM)
FEV ₁ (L)				
Placebo	2.69 $\pm$ 0.08	2.85 $\pm$ 0.11	2.93 $\pm$ 0.11	2.80 $\pm$ 0.11
TAA	2.59 $\pm$ 0.09	2.99 $\pm$ 0.12†	3.04 $\pm$ 0.11*	3.07 $\pm$ 0.11‡
FEF _{25%-75%} (L/sec)				
Placebo	1.97 $\pm$ 0.09	2.24 $\pm$ 0.15	2.25 $\pm$ 0.13	2.08 $\pm$ 0.14
TAA	2.04 $\pm$ 0.12	2.53 $\pm$ 0.14*	2.60 $\pm$ 0.15*	2.68 $\pm$ 0.15‡
FVC (L)				
Placebo	3.84 $\pm$ 0.13	4.01 $\pm$ 0.14	4.11 $\pm$ 0.14	4.04 $\pm$ 0.14
TAA	3.59 $\pm$ 0.13	3.98 $\pm$ 0.15*	4.05 $\pm$ 0.14*	4.05 $\pm$ 0.14†

Probability (*p*) values indicate significant differences between the two groups in changes in lung function from baseline values.

**p* $\leq$ 0.05.

†*p* $\leq$ 0.01.

‡*p* $\leq$ 0.001.

scale reported by Tinkelman et al.²⁰ On awakening (nighttime symptoms) and at bedtime (daytime symptoms), patients scored each symptom on a scale from 0 to 6 (0 = no symptoms, 1 = symptoms present but no interference with daily activities or sleep, 2 = symptoms occasionally interfere with activities or sleep, 3 = symptoms frequently interfere with activities or sleep, 4 = symptoms constantly interfere with activities or sleep, 5 = symptoms prevent activities or sleep, and 6 = incapacitating symptoms requiring physician intervention). The total daily asthma symptom score represented a summation of nighttime and daytime symptoms (range, 0 to 12).

At the end of the baseline phase (visit 2), patients were evaluated for entry into the 6-week double-blind treatment phase. Eligible patients met the following criteria: (1) albuterol use of four or more puffs per day on 5 of the last 7 baseline days, (2) combined total daily symptoms score of 15 or greater over those 5 days, and (3) an FEV₁ of 60% of predicted value or greater, with a demonstrated increase of 15% or greater after albuterol administration. Medications and diary cards were dispensed to eligible patients according to a randomized schedule. They were instructed on proper administration of study drug and use of a peak flow meter. Instructions were repeated at subsequent visits to encourage compliance and ensure consistent peak flow measurements and drug delivery.

During the 6-week double-blind phase, patients recorded in a daily diary their albuterol and study medication use, nighttime and daytime asthma symptoms, morning and evening peak flow rates, concomitant medications, and adverse events. At the end of each week of treatment (visits 3 to 8), patients were evaluated by spirometry (at least 6 hours after the last use of albuterol) within 1 hour of the time at which the baseline visit occurred and underwent a limited physical examination. Diary cards were reviewed, and patients were interviewed regarding adverse events and use of concomitant medications. Although study canisters were not weighed, patient drug diaries were checked on each visit for compliance, and patients were terminated from the study for noncompliance at the discretion of the investigator. At the end of the study (visit 8), each patient had a complete physical examination and specimens were collected for blood chemistry, hematology, and urinalysis.

Variables selected as primary and secondary measures included data derived from patient diaries as well as from clinic visits. For *diary variables*, "baseline" was the mean measurement/score for the week before the start of the double-blind treatment phase, and "endpoint" was the mean score for data

from the last sequential week of treatment during the double-blind treatment phase (the week before Visit 8). For *clinical variables* (pulmonary function tests), "baseline" was the measurement taken on visit 2, immediately before the start of the double-blind phase, and "endpoint" was the last measurement taken during the double-blind phase (at the last evaluable visit for each patient).

The primary efficacy variables were the mean changes, from baseline to endpoint, in FEV₁ measurements (percent change) and in the 24-hour use of albuterol (puffs per day). The primary analysis was the comparison of active treatment with placebo. Secondary efficacy variables were the mean changes, from baseline to endpoint, in asthma symptom scores and in morning and evening peak expiratory flow rates (PEFRs), as well as mean percent changes, from baseline to endpoint, for other pulmonary function variables measured by spirometry during weekly clinic visits. These included forced vital capacity (FVC), PEFR, forced expiratory flow after 25% to 75% of volume is expelled (FEF_{25%-75%}), and the FEV₁/FVC ratio.

Statistical analysis

Descriptive statistics, including means and standard error of the means or percentages, were calculated as appropriate. The significance of a center-by-treatment interaction was investigated with a two-way analysis of variance model with center, treatment, and treatment-by-center interaction effects at a level of 10% for the primary efficacy variables. Comparison of the active and placebo groups was done with a two-tailed, two-way analysis of variance model, with center and treatment as main effects and no interaction term. The critical level of significance was a *p* value of 0.05, with a power of 90% to detect a treatment difference of 10% in mean percent change in FEV₁ from baseline (with a standard deviation of 12%) and a treatment difference of three puffs per day in mean albuterol use (with a standard deviation of 3.2 puffs). Because of the lack of normality in the percent changes from baseline in the pulmonary functions, a nonparametric procedure, the Cochran-Mantel-Haenszel test with modified ridit scores stratified by center, was also performed.

RESULTS

The demographic features of the 121 patients enrolled in this study were comparable between the two treatment groups (Table I). The duration of asthma and the

Change from baseline
(mean nighttime symptom scores)

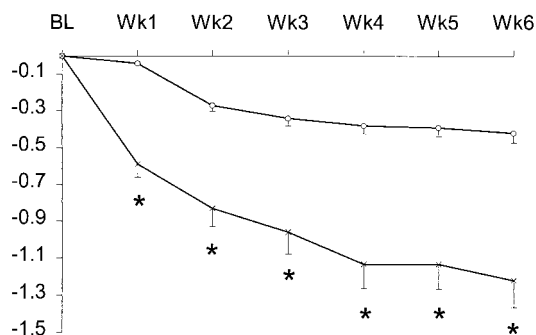


FIG. 1. Changes from baseline to endpoint for weekly means of nighttime asthma symptom scores for two treatment groups (open circles, placebo; x, TAA). Nighttime symptom scores were recorded in the morning (scale: 0 = no symptoms to 6 = very severe, incapacitating symptoms). Baseline scores were similar between groups (TAA: 2.5, placebo: 2.2). Between-group differences were statistically significant, in favor of TAA group, at all time points. * $p < 0.0001$.

use of antiasthmatic medications were similar between the two treatment groups. All patients used a short-acting inhaled β_2 -agonist, and 33 patients in each group (55% receiving TAA and 54% receiving placebo) were using an inhaled corticosteroid as maintenance therapy (Table I).

Baseline means of frequency of albuterol use, morning and evening PEFs, and symptom scores were similar between the two treatment groups (see Figure legends). There were no significant between-group differences in baseline means of spirometric measurements (Table II). An analysis of variance showed no significant interaction between treatment and center for the endpoint analyses, and thus the data was pooled across the centers.

A total of 107 (88%) of the 121 treated patients completed the entire study. In the placebo group, 11 patients withdrew from the study (eight for exacerbations of asthma and/or ineffectiveness of the study drug, one for withdrawn consent, one for bronchitis, and one because of relocation). In the TAA group, three patients withdrew from the study (two for sinusitis and one for protocol deviation). There were no significant differences between the two treatment groups for drop-out rates.

Pulmonary function at clinic visits

Patients in the TAA group showed greater improvements in pulmonary function tests as compared with patients in the placebo group (Table II), and between-group differences reached statistical significance ($p < 0.05$), favoring the TAA group by or before treatment week 2 for FEV₁, FEF_{25-75%}, and FVC. These improvements were sustained throughout the study, with the greatest differences at the end of the study. At the last clinic visit (week 6), patients in the TAA group achieved

Change in am PEFr
from baseline (mL/min)

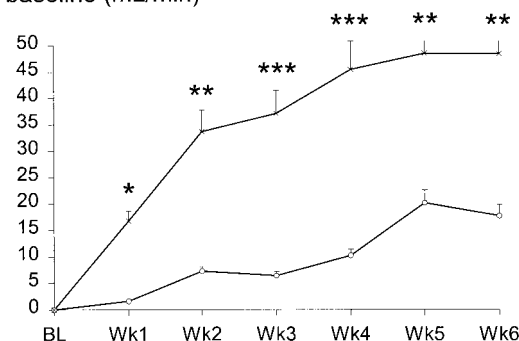


FIG. 2. Changes from baseline to endpoint for weekly means of morning PEFrs for two treatment groups (open circles, placebo; x, TAA). Baseline PEFrs were similar between groups (TAA: 361.3 ml/min, placebo: 368.5 ml/min). Between-group differences were statistically significant, in favor of TAA group, at all time points. * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

an 18% improvement (from 2.6 to 3.1 L) in mean FEV₁ measurements as compared with a 3% improvement (from 2.7 to 2.8 L) in the placebo group ($p = 0.0001$).

Asthma symptoms and PEFs

Patients treated with triamcinolone acetonide recorded lower asthma symptom scores (shown in Fig. 1 for nighttime asthma) than patients in the placebo group. Statistically significant differences between the two groups were evident by the end of the first week of treatment ($p < 0.0001$ for mean nighttime, daytime, and 24-hour asthma symptom scores) and were maintained throughout the trial ($p < 0.0001$) for all three scores. Relative to baseline, the reductions in daytime and nighttime asthma symptom scores at treatment week 6 were between 43% and 50% for TAA as compared with reductions of 16% to 18% for placebo.

Similarly, improvements from baseline in morning and evening PEFs were significant after 1 week of therapy for patients in the TAA group as compared with those in the placebo group ($p = 0.03$ for mean morning PEFr, Fig. 2; $p = 0.004$ for mean evening PEFr). PEFs in the TAA group were higher than those in the placebo group throughout the treatment phase ($p < 0.05$). Endpoint analyses (week 6) showed that morning PEFs increased from baseline by 46 ml/min (from 361.3 to 407.2 ml/min) for patients in the TAA group as compared with an increase of 7 ml/min (from 368.5 to 375.2 ml/min) for those in the placebo group ($p = 0.0003$). Compared with baseline, mean evening PEFs at week 6 increased more for the TAA group (38 ml/min; from 389.4 to 427.4 ml/min) versus the placebo group (4 ml/min; from 400.1 to 404.3 ml/min) ($p = 0.001$).

Albuterol use

Patients in the TAA group had significantly greater reductions in their daily use of albuterol as compared with patients in the placebo group ($p < 0.0001$) during

weeks 1 to 6 of treatment (Fig. 3). At week 6, patients in the TAA group had decreased their mean daily dosage of albuterol by more than three puffs per day (from 6.9 to 3.5 puffs/day) as compared with a reduction of less than one puff per day (from 6.1 to 5.5 puffs/day) in the placebo group ($p < 0.0001$).

Safety

In general, patients in both groups tolerated their study drugs well. No deaths or serious adverse events were reported. The incidence of asthma exacerbations was greater for patients in the placebo group (20%) than in the TAA group (5%), and the incidence of pharyngitis, including red or sore throat, was greater for patients in the TAA group (25%) than in the placebo group (10%). These differences did not reach statistical significance. No clinically significant changes occurred in physical findings, vital signs, or clinical laboratory test results for patients in either treatment group.

DISCUSSION

Results from this study demonstrated that 400 μ g of TAA administered twice daily was superior to placebo in treating patients with mild and moderate asthma who were poorly controlled by β_2 -agonist medications. This was established by statistically significant reductions in the use of albuterol and in asthma symptom scores, as well as significant improvements in pulmonary function test results in patients treated with TAA.

The benefits of the TAA regimen were apparent as early as 1 week after treatment began for albuterol use, asthma symptom scores, and FVC ($p = 0.015$). Statistically significant improvements in FEV₁ and FEF_{25%-75%} occurred after 2 weeks or more of therapy. Patients continued to improved progressively throughout the study, as indicated by the increasing magnitude of difference between the two groups for all efficacy variables, with the largest differences occurring at the end of the study.

In general, twice daily treatment with TAA was well tolerated, with a frequency of adverse events similar to that of the placebo group. The mouth and throat symptoms reported by more patients in the TAA group may have been due to the topical effects of corticosteroids, an effect that is similarly reported by patients using other currently available inhaled corticosteroids.²¹⁻²³

This study affects two aspects of asthma management that are currently the subjects of considerable discussion: (1) the need for earlier use of antiinflammatory agents to treat patients with all but the mildest asthma and (2) variable patient compliance with treatment regimens. Until recently, inhaled corticosteroid medications were reserved for use in patients with moderate-to-severe asthma. Current practice guidelines,^{1, 5, 6} however, encourage the use of inhaled corticosteroids earlier in the course of the disease and in patients with mild persistent asthma, defined as those with normal or minimally decreased lung function who require frequent

Change from baseline
(mean albuterol puffs/day)

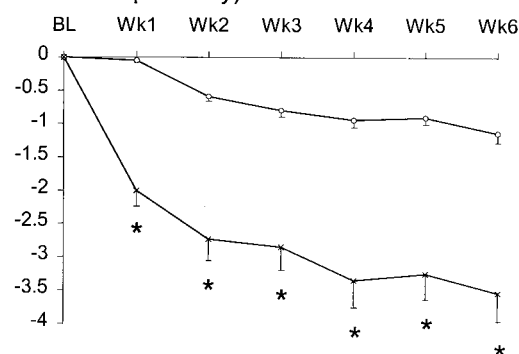


FIG. 3. Change in mean daily use of albuterol (puffs) from baseline to endpoint for two treatment groups (open circles, placebo; x, TAA). Use of albuterol at baseline was similar between groups (TAA: 6.8 puffs/day, placebo: 6.1 puffs/day). Between-group differences were statistically significant, in favor of TAA group, at all time points. * $p < 0.0001$.

administration of β_2 -agonists for episodic bronchospasm.

This study demonstrates that patients with mild-to-moderate asthma can be effectively and safely treated with twice daily dosing of the inhaled corticosteroid TAA. Although urgent care visits were not assessed in this study, the patients treated with TAA were able to significantly reduce their need for β_2 -agonist medications, while decreasing daily and nocturnal symptoms and improving lung function.

These findings are in agreement with other studies showing clinical improvements in patients with mild asthma treated with inhaled corticosteroids. Haahtela and colleagues^{9, 10} published two separate reports detailing the benefits of such treatment in this population of patients. These authors reported that patients with asthma who began therapy early in the disease process achieved greater improvements in lung function than did patients who waited until their disease progressed. Moreover, the clinical benefits observed appeared to reflect changes in the patients' inflammatory status as assessed by lung biopsy. Biopsy samples showed an increase in the ciliated-to-goblet cell ratio and a decrease in the number of postcapillary venules after 3 months of inhaled corticosteroid therapy as compared with therapy consisting only of β_2 -agonist treatments.²⁴ These findings linking the clinical benefits of inhaled corticosteroids with their cellular effects in the lungs have prompted many to consider use of these agents earlier in the asthmatic inflammatory process.^{1, 5, 6, 25}

If antiinflammatory agents are to be initiated early in the disease process, the success of this strategy depends on patient compliance. Considerable variation in compliance exists among asthmatic subjects who are directed to take their inhaled medications three to four times daily.¹¹⁻¹⁵ Decreasing the frequency of treatment to once or twice daily is one way to improve compliance. The

results of this study suggest that twice daily therapy with inhaled TAA will provide adequate clinical benefit to the patient with mild-to-moderate asthma. Other investigators have suggested that although twice daily dosing is desirable for patient compliance, more frequent dosing (e.g., twice a day or four times a day) may enhance the efficacy of inhaled corticosteroid therapy.²⁶ Additionally, these results indicate that the patient can expect evidence of clinical benefit (in the form of symptom reduction, decreased need for rescue albuterol, and improved peak flow rates) as early as 1 week after treatment begins.

In summary, twice daily therapy with TAA (800 µg/day) improved the asthma status of patients with mild-to-moderate disease. Twice daily dosing with an inhaled antiinflammatory agent may provide a convenient means for patients with mild-to-moderate asthma to control symptoms and to comply with their medication plan.

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