

Therapeutic equivalence of triamcinolone acetonide hydrofluoroalkane and chlorofluorocarbon nasal inhalers in patients with seasonal allergic rhinitis

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ABSTRACT

Background: Triamcinolone acetonide (TAA) has been reformulated as an hydrofluoroalkane (HFA) aerosol for intranasal use in patients with seasonal allergic rhinitis (SAR). This study compared the TAA HFA formulation with the previously available chlorofluorocarbon (CFC) nasal inhaler in a dose-ranging study.

Methods: This was a double-blind, parallel-group, multicenter study in 780 adults with SAR. Patients had a history of fall seasonal rhinitis and positive skin tests to ragweed. After meeting minimum symptom requirements during the run-in phase, patients were randomized to one of eight groups: TAA CFC or HFA at 14, 110, or 440 micrograms once daily or matching placebo. Treatment was continued for two weeks and patient completed a daily diary for reflective and instantaneous rating of nasal and ocular allergy symptoms.

Results: All active treatment groups were statistically superior to placebo with respect to the primary outcome variable, total nasal symptoms. Furthermore, the TAA HFA and TAA CFC formulations were statistically comparable over the dose range. Within each formulation, there was a significant mean reduction from baseline in the symptoms of rhinitis that increased with increasing dose. Ocular symptoms were also reduced with both formulations. Both preparations were well tolerated without any safety concerns.

Conclusion: In conclusion, a new formulation of TAA with a HFA propellant was found to be effective in the treatment of SAR and comparable with the previously available TAA CFC formulation. There was a dose response to TAA, with doses as low as 7 micrograms per nostril once daily producing statistically significant improvement in rhinitis symptoms.

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Allergic rhinitis (AR) is one of the most common chronic conditions in western society. Recent surveys estimated that AR affects ~20% of the U.S. population, which corresponds to >40 million Americans.^{1,2} The prevalence and costs associated with AR have continued to increase over recent years, and AR may have a significant impact on quality of life.³ AR is often treated with pharmacotherapy, and it has been shown, in numerous clinical studies, that nasal steroids are the most effective medication in the chronic treatment of AR.⁴ There is no evidence for clinical superiority of any nasal steroid as opposed to another nasal steroid. However, most currently available nasal steroids are formulated as aqueous solutions, which may bother some sensitive patients because of dripping of medication down the throat, a burning sensation, and bad taste or smell.⁵ These complaints may interfere with medication compliance and may be associated with discontinuation of the therapy in some patients (*i.e.*, a recent survey noted this occurred in 20% of children prescribed a nasal steroid).⁶ Triamcinolone acetonide (TAA) is a potent synthetic corticosteroid that has been widely used in the treatment of AR. The chlorofluorocarbon (CFC) nasal inhaler was removed from the U.S. market because of the CFC phaseout. The TAA nasal inhaler was reformulated to use an ozone-safe hydrofluoroalkane (HFA) propellant. This study was designed to study the efficacy and safety of TAA HFA nasal aerosol when compared with placebo and with the previously available CFC nasal aerosol.

METHODS

Study Design

This was a double-blind, double-dummy, parallel-group, multicenter study. The study consisted of a screening phase, a baseline phase, and a

2-week double-blind treatment phase. At the screening visit (visit 1) the patients were screened by means of physical examination and medical and drug histories. Skin-prick tests for ragweed allergens were performed. Diary cards were distributed in order for the patients to record daily rhinitis symptoms. Visit 2 (baseline) was scheduled for all patients when the seasonal (fall ragweed) pollen counts in the vicinity of the investigational site had been elevated over a period of at least 7 days before the visit. The period allowed for enrollment in the double-blind phase of the study was limited to 4 consecutive days at each site. No medication for the relief of rhinitis symptoms was permitted for the 6 days preceding this visit and throughout the treatment period. Daily rhinitis scores were reviewed at this baseline visit, and the patient was randomized only if the aggregated sum of the reflective scores for the four nasal symptoms (nasal discharge, stuffiness, itching, and sneezing) over the previous 3 days plus the morning of the visit was at least 42 points (out of a possible 84).

Randomized patients received 2 weeks of treatment with study medication. The patients were randomly assigned to one of eight treatment groups, two of which were placebo. The six active treatments were 14, 110, and 440 μg everyday (*i.e.*, 7, 55, and 220 μg , respectively, per nostril, once a day) of either the TAA CFC or the HFA. The design incorporated known effective doses (110 and 440 $\mu\text{g}/\text{day}$) and a suboptimal dose to (1) provide evidence of comparability/equivalence between the formulations and (2) show adequate sensitivity of the clinical model to discriminate between the active treatment doses. Patients returned in 1 week (visit 3, day 8) for a midtreatment assessment and in 2 weeks for a final assessment (visit 4, day 15).

Patients

This study was approved by the Essex Institutional Review Board, Lebanon, NJ and all patients signed an informed consent agreement before entry into the study. Eligible patients were at least 18 years of age with a history of fall seasonal AR (SAR) for at least 2 years. Each patient needed to have a positive skin-prick test to ragweed. Exclusion criteria included medical conditions that could interfere with the study, acute or chronic sinusitis, nasal polyposis or other gross anatomic nasal deformities, systemic corticosteroid use within 42 days of screening, or nasal corticosteroid use within 30 days of screening, initiation of immunotherapy within 6 months, pregnancy, or breast-feeding.

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Measures

Throughout the baseline and treatment periods, patients continued to assess nasal and ocular symptoms in a daily diary. Reflective scoring was performed twice a day; immediately before dosing in the morning (A.M. measurement) and 12 hours later (evening [P.M.] measurement) to reflect daytime symptoms. The symptoms of nasal discharge, nasal stuffiness, nasal itching, and sneezing were assessed on a 0 (no symptoms) to 3 (severe, interferes with activities of daily living or sleep) scale. Total eye symptoms (itchiness, tearing, and redness) were also scored on the 0–3 scale. Instantaneous ratings were performed in the morning at 10 investigational sites. At the end of the study, the physician and the patient independently assessed their global impression of treatment on a 5-point scale.

Safety assessments included adverse events, standard hematology, and clinical chemistry tests obtained during the screening period and at last visit. Additionally, physical examinations including nasal examinations were performed at screening and at the last visit.

Statistics

The primary variables were the mean change from baseline averaged over the double-blind period of the following symptom scores: nasal stuffiness, nasal discharge, sneezing, and nasal index (the sum of the scores for nasal discharge, nasal stuffiness, and sneezing) for the reflective 24-hour score. Secondary outcome measures included the mean change from baseline of the reflective primary variable averaged over each week separately, as well as days 1 through 4, and P.M. (first 12 hours) and A.M. scores (second 12 hours) scores. Other secondary end points include change from baseline in nasal itching and ocular symptoms.

For all analyses to assess treatment differences, a two-way analysis of variance model was used with treatment and investigator as main effects and no interaction term at the 0.05 level of significance. The two placebo groups were combined and the analysis of variance was based on seven groups. For comparison within each TAA formulation, a two-sided Bonferroni adjusted *t*-test was applied to the six pairwise comparisons: placebo versus each active treatment groups. The two formulations of TAA were compared for therapeutic equivalence, which was defined as the difference between the treatment groups within 30% of each other. The null hypotheses were that the treatment groups are not equivalent versus the alternative hypothesis that the groups are therapeutically equivalent. Two one-sided test procedures were used to evaluate equivalence. The 90% symmetric confidence interval (CI) around the ratio of comparative efficacy was determined. If this 90% CI at a given dose of TAA is between 0.7 and 1.3, then the two preparations were considered equivalent.

Sample size calculation was based on a two one-sided 90% CI method of establishing equivalence of two means. The sample size of ~98 patients per treatment group was chosen based on an expected change from baseline of the nasal index of 1.7 and standard deviation of 0.75. The power of this test was 80% at the 0.025 level of significance.

RESULTS

A total of 780 patients were enrolled and 732 (94%) completed the study. The number of premature withdrawals was low and is summarized in Table 1. All patients (773) with any diary data were included in the intent-to-treat population. The demographic data for patients (Table 2) showed that the mean age was 36 years, most patients were white (84%) with more men (55%) than women (45%). There were no significant differences in demographic characteristics between groups. Baseline characteristics for the primary end point, reflective symptom scores, are presented in Table 3. The baseline rhinitis symptoms were similar across treatments for all variables, although numerically it was somewhat lower for the TAA HFA at 110 μg treatment group. Individual symptom scores were generally around 2, which indicate a moderate intensity of symptoms.

Compared with placebo, all doses of TAA were associated with statistically significant decreases in reflective symptom scores (Table 4). Not only was the combined reflective score (nasal index) statistically significant for each dose of both formulations, but most of the individual symptom scores were also significantly improved. Furthermore, the two formulations were found to be therapeutically equivalent, *i.e.*, within 30% effect of each other. The mean and 90% CIs for the ratio of HFA to CFC treated groups for the reflective symptom scores were 1.03 (90% CI, 0.82, 1.23), 0.91 (90% CI, 0.75, 1.07), and 0.93 (90% CI, 0.78, 1.09) for the 14-, 110-, and 440- μg doses, respectively. The therapeutic equivalence criteria were also met for the first and second 12 hours after dosing for all doses studied.

Dose response is shown in Fig. 1. For both formulations there was a clear dose response, with increasing dose corresponding to further improvement in allergy symptoms. The response in the groups treated with TAA at 440 μg was significantly superior ($p < 0.05$) to those treated with 14 μg and numerically superior to those treated with TAA at 110 μg .

Significant ($p < 0.05$ versus placebo) improvements in nasal symptoms was seen as early as day 1 for TAA HFA at 110 and 440 μg and day 2 for the 14- μg dose. The instantaneous nasal index gave similar results to the reflective scores, although the 14- μg dose of TAA CFC or TAA HFA did not show statistically significant improvement over placebo. There were only 550 patients that completed the instantaneous scale, which decreased statistical power.

At the final visit the patient and physician conducted a global evaluation of efficacy. All doses for both preparations were significantly better than placebo for both the patient and the physician evaluations. In the patient global evaluation, 60.7, 68.3, and 75% of TAA HFA-treated patients (14, 110, and 440 μg , respectively) felt improved when compared with 45.9% of placebo-treated patients. In the CFC-treated patients, the percent of subjects who felt improved were 60.7, 78.1, and 72.2% for the three doses, respectively. In the physician global evaluation, 59.0, 79.0, and 72.3% of TAA HFA-treated patients (14, 110, and 440 μg , respectively) were felt to have improved when compared with 45.9% of placebo-treated patients. In

Table 1 Patient disposition

	Placebo <i>n</i> = 111	CFC			HFA		
		14 μg <i>n</i> = 113	110 μg <i>n</i> = 115	440 μg <i>n</i> = 108	14 μg <i>n</i> = 113	110 μg <i>n</i> = 107	440 μg <i>n</i> = 113
Lost to follow-up	1	0	1	0	1	2	0
Drug ineffective	7	6	1	1	1	1	2
Adverse event	1	0	1	0	2	0	0
Protocol deviation	0	1	2	2	0	1	3
Consent withdrawn	0	0	0	0	1	0	1
Other	2	3	2	0	1	1	0

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane.

Table 2 Patient demographics

	Placebo n = 111	CFC			HFA		
		14 µg n = 113	110 µg n = 115	440 µg n = 108	14 µg n = 113	110 µg n = 107	440 µg n = 113
Gender (M/F %)	54/46	56/44	54/46	56/44	59/41	54/46	53/47
Age (yr)	36	35	36	36	38	36	36
Race (white; %)	84	86	89	81	77	89	83
Height (cm)	170	172	171	172	172	172	171
Weight (kg)	76	79	82	80	79	77	79

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane.

Table 3 Baseline efficacy data

	Placebo n = 110	CFC			HFA		
		14 µg n = 113	110 µg n = 114	440 µg n = 106	14 µg n = 113	110 µg n = 106	440 µg n = 111
Nasal stuffiness	2.3	2.5	2.4	2.4	2.4	2.3	2.3
Nasal discharge	2.3	2.4	2.3	2.3	2.4	2.2	2.3
Sneezing	2.1	2.1	2.0	2.1	2.2	1.9	2.1
Nasal index*	6.7	7.0	6.7	6.7	7.1	6.4	6.8
Itchy nose	2.1	2.1	2.1	2.1	2.2	2.0	2.1
Eye symptoms	2.0	2.0	1.9	2.0	2.0	1.8	2.0

Each symptom rated from 0 (absent) to 3 (severe, interferes with daily activities).

*Sum of scores for nasal stuffiness, nasal discharge, and sneezing.

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane.

Table 4 Change from baseline in efficacy end points

	Placebo n = 110	CFC			HFA		
		14 µg n = 113	110 µg n = 114	440 µg n = 106	14 µg n = 113	110 µg n = 106	440 µg n = 111
Nasal stuffiness	−0.36	−0.62 [#]	−0.83 [#]	−0.88 [#]	−0.64 [#]	−0.71 [#]	−0.75 [#]
Nasal discharge	−0.44	−0.72 [#]	−0.84 [#]	−0.94 [#]	−0.69 [#]	−0.75 [#]	−0.89 [#]
Sneezing	−0.58	−0.72	−0.88 [#]	−1.03 [#]	−0.79	−0.83 [*]	−1.01 [#]
Nasal index	−1.39	−2.05 [*]	−2.55 [#]	−2.84 [#]	−2.11 [#]	−2.29 [#]	−2.64 [#]
Itchy nose	−0.53	−0.74 [*]	−0.92 [#]	−1.01 [#]	−0.76 [*]	−0.85 [#]	−0.94 [#]
Eye symptoms	−0.38	−0.59 [*]	−0.66 [#]	−0.72 [#]	−0.56	−0.56	−0.69 [#]

**p* < 0.05 vs placebo; # *p* < 0.01 vs placebo.

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane.

the CFC-treated patients, the percent of subjects who were felt improved by physician evaluation were 59.8, 79.0, and 75.9% for the three doses, respectively.

Safety

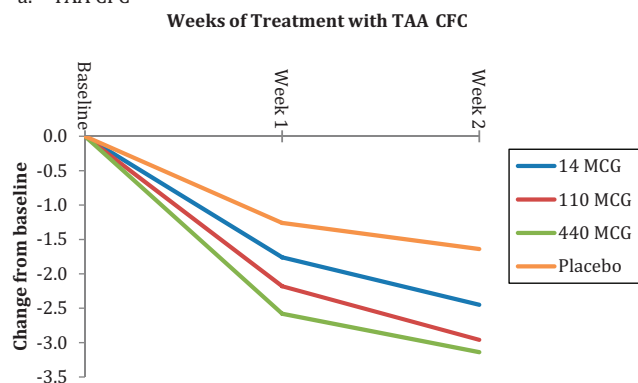
The total number of adverse events was similar in all groups, ranging from 31.5 (for TAA CFC at 440 µg) to 39.8% (TAA HFA at 14 µg). There were no serious adverse clinical events or clinically significant changes in physical exam, vital signs, or laboratory measures. Four patients discontinued the study because of adverse events: one patient treated with placebo (pharyngitis), one with TAA CFC at 110 µg (nausea), and two with TAA HFA at 14 µg (rhinitis). The rates of adverse events were similar between active treatments and placebo. The most frequent adverse event was headache (7.0–15.7%) without any dose response and similar rates across all groups and placebo. Topical adverse events are shown in Table 5, and summarized across treatment groups, because there was no significant dose–response relationship.

DISCUSSION

The results of this double-blind, placebo-controlled study indicate that TAA HFA nasal inhaler administered once daily is equivalent in efficacy to the previously marketed TAA CFC nasal inhaler and superior to placebo in the treatment of SAR. Each of the three doses of TAA, administered either as the HFA or CFC nasal aerosol, was superior to placebo in reflective nasal symptoms, either measured daily or divided into two 12-hour intervals. Furthermore, the improvement in symptoms started as early as day 1 of use. Each preparation was also effective in reducing ocular allergy symptoms.

Of particular interest was the finding of a dose response to TAA in the treatment of SAR. This allowed for a valid comparison of the two formulations from a suboptimal daily dose of 14 µg to the highest approved dose of 440 µg. Most studies of nasal steroids have found a flat dose response curve, and hence many nasal steroids have only one approved dose.^{7–9} This study shows that even doses as low as 14 µg/day (7 µg per nostril once daily) is effective in treating symp-

a. TAA CFC



b. TAA HFA

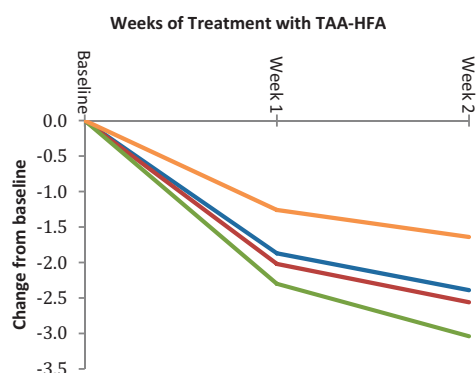


Figure 1. Dose response for reduction in nasal index for (A) triamcinolone acetate (TAA) chlorofluorocarbon (CFC) and (B) TAA hydrofluoroalkane (HFA).

Table 5 Summary of local adverse events

Adverse Event	Placebo	TAA CFC	TAA HFA
Epistaxis	1.8%	1.8%	1.5%
Nasal irritation	3.6%	4.1%	7.5%
Congestion	0	0.9%	2.1%
Throat Discomfort	1.8%	1.8%	0.6%
Dry mucous membranes	0	0	0.3%

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane; triamcinolone acetate.

toms, although the effects may not last a full 24 hours as shown by the A.M. instantaneous score. The reason for this difference between dose-response studies is unclear. The potency of TAA is indicated by the efficacy of a suboptimal dose of 14 $\mu\text{g}/\text{day}$. It is possible that the aerosol preparation provides better distribution to the nasal mucosa than aqueous inhalers and hence the efficacy at lower doses.

The improvement in AR symptoms seen in this study compare well with that achieved in other studies, although it is always difficult to compare across trials because of differences in design, patient populations, and allergen exposure. A recent meta-analysis across all published studies of AR found that the median change from baseline in total nasal symptom scores was -22.2% for antihistamines and -40.7% for nasal steroids.¹⁰ In the current study, the change from baseline was 40.1% for the 110- μg dose and 43.8% for the 440- μg dose. To use the same measure as in these trials, the nasal itching score was added to the nasal index. To date, no nasal steroid has been shown to be more effective than any other nasal steroid. Prior studies indicated therapeutic equivalence of TAA and fluticasone propionate in the treatment of AR.¹¹

Most currently available nasal steroids are formulated as aqueous solutions, which may bother some sensitive patients because of a sensation of the medication dripping down the throat (41%), a burning sensation (17%), and bad taste or smell (32%).¹² These symptoms may result in the discontinuation of therapy. A recent white paper points out the need for aerosol nasal sprays.¹³ This consensus statement notes that some sensitive patients may prefer a nasal aerosol because of the ease of use, lack of dripping, and no anterior or posterior runoff. A study that compared TAA aerosol with fluticasone aqueous formulation in the treatment of SAR showed similar efficacy, but patients generally preferred the TAA aerosol formulation because of less medication running down the throat or out the nose, less sore throat, and less taste.¹⁴ A recent retrospective study showed higher compliance rates and lower overall health care costs in patients using aerosolized nasal steroids than aqueous ones.¹⁵ It must be pointed out that there are no direct comparisons of TAA administered *via* aerosol or *via* aqueous formulations.

In conclusion, this study shows that TAA HFA is more effective than placebo and equivalent to TAA CFC. The study showed a dose-response relationship with efficacy starting with a suboptimal dose of 14 $\mu\text{g}/\text{day}$. Nasal aerosols, such as TAA HFA, provide an alternative to the aqueous nasal sprays.

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