
Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension

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Background: Intranasal corticosteroids (INSs) are the most effective treatment for allergic rhinitis (AR). However, available INS safety and efficacy data in children younger than 6 years are limited.

Objective: To report the first well-controlled study assessing the safety and efficacy of an INS in children aged 2 to 5 years with perennial AR.

Methods: In a 4-week, multicenter, double-blind, parallel-group study, patients were randomized to receive triamcinolone acetonide aqueous nasal spray (TAA AQ), 110 μ g once daily, or placebo. A subset of children continued into a 6-month, open-label phase. Efficacy end points included total nasal symptom scores. Safety measures included reports of adverse events, morning serum cortisol levels before and after cosyntropin infusion, and growth as measured using office stadiometry.

Results: A total of 474 patients were randomized to receive TAA AQ (n = 236) or placebo (n = 238); 436 entered the open-label extension phase. Adjusted mean (SE) changes from baseline during the double-blind period in instantaneous and reflective total nasal symptom scores were -2.28 (0.16) and -2.31 (0.15), respectively, in the TAA AQ group ($P = .09$) vs -1.92 (0.16) and -1.87 (0.15) in the placebo group ($P = .03$). Adverse event rates were comparable between treatment groups. There was no significant change from baseline in serum cortisol levels after cosyntropin infusion at study end. The distribution of children by stature-for-age percentile remained stable during the study.

Conclusions: Use of TAA AQ, 110 μ g once daily, for up to 6 months offers a favorable efficacy to safety ratio in children aged 2 to 5 years with perennial AR.

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INTRODUCTION

Allergic rhinitis (AR) is a common childhood disease, affecting up to 42% of children by the age of 6 years.¹ This condition, which can significantly affect a child's quality of

life, may exacerbate comorbidities such as asthma and sinusitis.²

Approximately 50% of causes of rhinitis in children are induced by allergy,³ yet the diagnosis of AR in preschool children can be challenging because the symptoms (sneezing, nasal itching, discharge, and congestion) may be confused with those of infectious rhinitis. To increase the probability of identification, the diagnosis and severity of AR can be derived from surrogate signs, such as noisy breathing, repeated throat clearing, and snoring,⁴ and, as in other disorders, caregiver-rated scales can be used to evaluate patient-reported outcomes.^{5–7}

Intranasal corticosteroids (INSs) are the most effective treatment class for controlling the nasal symptoms of AR, but concerns exist regarding their potential for suppressing hypothalamic-pituitary-adrenal (HPA) axis function and growth in children.^{4,8,9} Of the INSs currently approved in the United States for the treatment of AR, only mometasone furoate, fluticasone propionate, and fluticasone furoate are indicated for children younger than 6 years. However, the presumed efficacy of these agents in this age subgroup is based on data from studies conducted in individuals across a wide age range (eg, 3–11 years for mometasone furoate, 4–11 years for

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fluticasone propionate, and 2–11 years for fluticasone furoate)^{10–15} and in a single small, double-dummy, comparative study of fluticasone propionate vs ketotifen in children aged 2 to 4 years with a questionable diagnosis of perennial AR (PAR).¹⁶ Under the Pediatric Research Equity Act of 2003 in the United States, the safety and effectiveness of medications must be evaluated in all relevant pediatric subpopulations.^{17,18} There is, therefore, a need for well-controlled and well-powered studies that address the efficacy and safety of INSs in 2- to 5-year-olds with AR.

Triamcinolone acetonide aqueous nasal spray (TAA AQ) is currently indicated for the treatment of the nasal symptoms of seasonal AR and PAR in adults and children 6 years and older.¹⁹ Previous studies^{20–28} have demonstrated the efficacy, safety, and tolerability of TAA AQ in adults and children with AR. Herein we report the first randomized, double-blind, placebo-controlled study designed primarily to investigate concomitantly the safety and efficacy of an INS treatment (TAA AQ, 110 µg once daily) in children aged 2 to 5 years with PAR.

METHODS

Patients

Patients aged 2 to 5 years with at least a 1-year history of PAR, positive skin prick test results (wheal at least as large as that caused by histamine or ≥ 3 mm greater than that caused by saline), or positive radioallergosorbent test reactions to a relevant perennial allergen in the patient's environment (cat, dog, molds, dust mites, or other) were included. For inclusion in the HPA axis function evaluation, patients had to have a morning prestimulation serum cortisol level of at least 138 nmol/L and a 30-minute poststimulation serum cortisol level of at least 496 nmol/L at screening.^{29,30}

Patients were excluded from the study if they had asthma requiring long-term use of inhaled or systemic corticosteroids within 6 months of the study; upper respiratory tract infection

or sinus infection requiring antibiotic therapy within 2 weeks of screening or viral upper respiratory tract infection within 7 days of screening; nasal polyps, deviated septum, or nasal/facial anatomical abnormalities; a history of cataract or glaucoma; or hypersensitivity to glucocorticoids.

Ethics

This study was performed in accordance with the recommendations of the 18th World Health Congress (Helsinki, 1964) and was approved by independent ethics committees or institutional review boards for each center. Written informed consent was obtained from parents, guardians, or caregivers before the conduct of any study-related procedures.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study immediately followed by an open-label extension period performed between March 4, 2004, and March 6, 2006. The study consisted of a screening period of up to 14 days, a randomization visit, a 4-week double-blind period, and a 6-month open-label period (Fig 1). Treatments for AR symptoms were withheld for 5 days before randomization except for loratadine syrup (Claritin; Schering-Plough Corp, Kenilworth, New Jersey), 5 mg once daily, which could be used as rescue medication throughout the study.

Patients were randomized to receive TAA AQ, 110 µg, or placebo once daily if they had a reflective (during the previous 24 hours) and an instantaneous (immediately before dosing) sum symptom score of at least 18 of 36 for nasal stuffiness, nasal discharge, and sneezing for any 3 of the 5 days before randomization in addition to the morning of randomization. Caregivers were given the option to allow their children to continue into the open-label period, during which all patients received TAA AQ, 110 µg once daily.

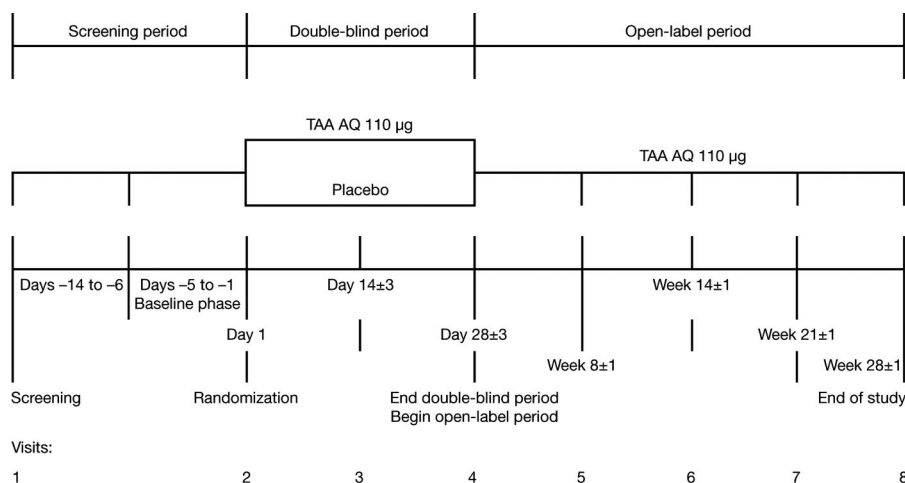


Figure 1. Study design. TAA AQ indicates triamcinolone acetonide aqueous nasal spray.

Efficacy Assessments

The primary end point was the change from baseline in the mean daily instantaneous total nasal symptom score (TNSS) during the double-blind treatment period. The TNSS consisted of the sum of the scores for nasal stuffiness, nasal discharge, sneezing, and nasal itching. Symptoms were recorded by caregivers in daily diaries on arising in the morning immediately before administration of study medication. Symptom severity was rated on a 4-point scale (0 = symptom absent and 3 = severe).

The key secondary end point was the change from baseline in the mean daily reflective TNSS during the double-blind treatment period. Other secondary end points included weekly TNSS, mean daily total symptom score (TSS) (TNSS plus the score for total eye symptoms: itching, tearing, and redness), physician and caregiver global evaluations (rated on a 5-point scale [0 = no relief and 4 = complete relief]), and individual symptom scores.

Safety Assessments

Safety and tolerability were evaluated using treatment-emergent adverse events (TEAEs), as reported by the caregiver or patient; physical examinations; and vital signs. To evaluate adrenal function, eligible patients also underwent a low-dose (1- μ g) cosyntropin stimulation test at screening, at the end of the double-blind period, and at the end of the open-label period. A blood sample (5 mL) was collected at 8 AM $\pm$ 1 hour and again 30 minutes after intravenous injection of 1 μ g of cosyntropin (Amphastar Pharmaceuticals Inc, Rancho Cucamonga, California) to measure serum cortisol levels. Blood samples were centrifuged at 1,500g for 10 minutes and were shipped at ambient temperature on the day of collection to Covance Central Laboratory, Indianapolis, Indiana, for immunoassay (Elecsys 2010 [F. Hoffmann–La Roche Ltd, Basel, Switzerland] and ACCESS 2 immunoassay system [Beckman Coulter Inc, Fullerton, California]). Height was measured using nonstandardized office stadiometry at screening, at the end of the double-blind period, and at the end of the open-label period.

Statistical Analyses

Four hundred patients were required to achieve 90% power to reject the null hypothesis of no difference between treatments in the primary end point when the expected mean difference for the changes from baseline in instantaneous TNSS was no less than 0.65 U, assuming a common standard deviation of 2.0 U. The choice of instantaneous vs reflective TNSS as the primary variable was arbitrarily set, and the sample size would have been the same in either case. Between-treatment differences for the changes in TNSS and TSS from baseline were analyzed using an analysis of covariance model, with treatment and pooled site as class variables and the baseline value as the covariate. Physician and caregiver global evaluations of efficacy were analyzed using a Cochran-Mantel-Haenszel procedure controlling for pooled site while using modified RIDIT scores.

The mean changes from screening in morning serum cortisol levels before and after cosyntropin stimulation were analyzed using analysis of variance, with patients and visit as class effects. An analysis of covariance model was used to evaluate the difference between treatments from screening for the changes in morning serum cortisol levels after cosyntropin stimulation. Treatment and pooled sites were included as class variables, and screening values were analyzed as the covariate.

The difference between treatments for the adjusted mean changes in height from screening was evaluated using an analysis of covariance model. Treatment and pooled sites were included as class variables, and screening values were analyzed as the covariate. Centers for Disease Control and Prevention growth chart standards were used to establish the height percentile for each patient by sex.³¹

RESULTS

Patients

Double-blind period. Patient disposition is shown in Figure 2. A total of 474 patients who received at least 1 dose of the investigational product constituted the safety population. All the patients had either a documented positive skin prick test or radioallergosorbent test reaction to at least 1 perennial allergen (Table 1). Mean (SD) exposure to treatment was 28.3 (4.5) and 28.3 (5.1) days for the TAA AQ and placebo groups, respectively.

The intention-to-treat population consisted of 464 patients (TAA AQ, $n = 231$; placebo, $n = 233$). Sixty-one patients (TAA AQ, $n = 33$; placebo, $n = 28$) were evaluable for cortisol concentration. There were no significant differences between the treatment groups for any demographic variable (Table 2).

Open-label period. Four hundred thirty-six patients were enrolled, and 357 completed the open-label extension phase of the study (Fig 2). Forty-nine patients were evaluable for cortisol concentration. Demographic characteristics were similar for the open-label and double-blind periods (Table 2). Mean (SD) exposure to TAA AQ was 152.1 (41.5) days.

Efficacy Analyses

Double-blind period. For the primary end point, adjusted mean (SE) change from baseline in instantaneous TNSS was -2.28 (0.16) for the TAA AQ group and -1.92 (0.16) for the placebo group (TAA AQ vs placebo, $P = .09$) (Fig 3). The individual symptom score for nasal itching showed a significantly greater reduction with TAA AQ vs placebo ($P = .02$).

There was a significantly greater reduction in reflective TNSS from baseline (adjusted mean [SE] change) in the TAA AQ group (-2.31 [0.15]) vs the placebo group (-1.87 [0.15]; $P = .03$) during the double-blind period (Fig 3). The individual symptom scores for sneezing and nasal itching showed a significantly greater reduction with TAA AQ vs placebo ($P = .01$ and $P = .009$, respectively).

There were also greater reductions from baseline in the TAA AQ group compared with the placebo group for the

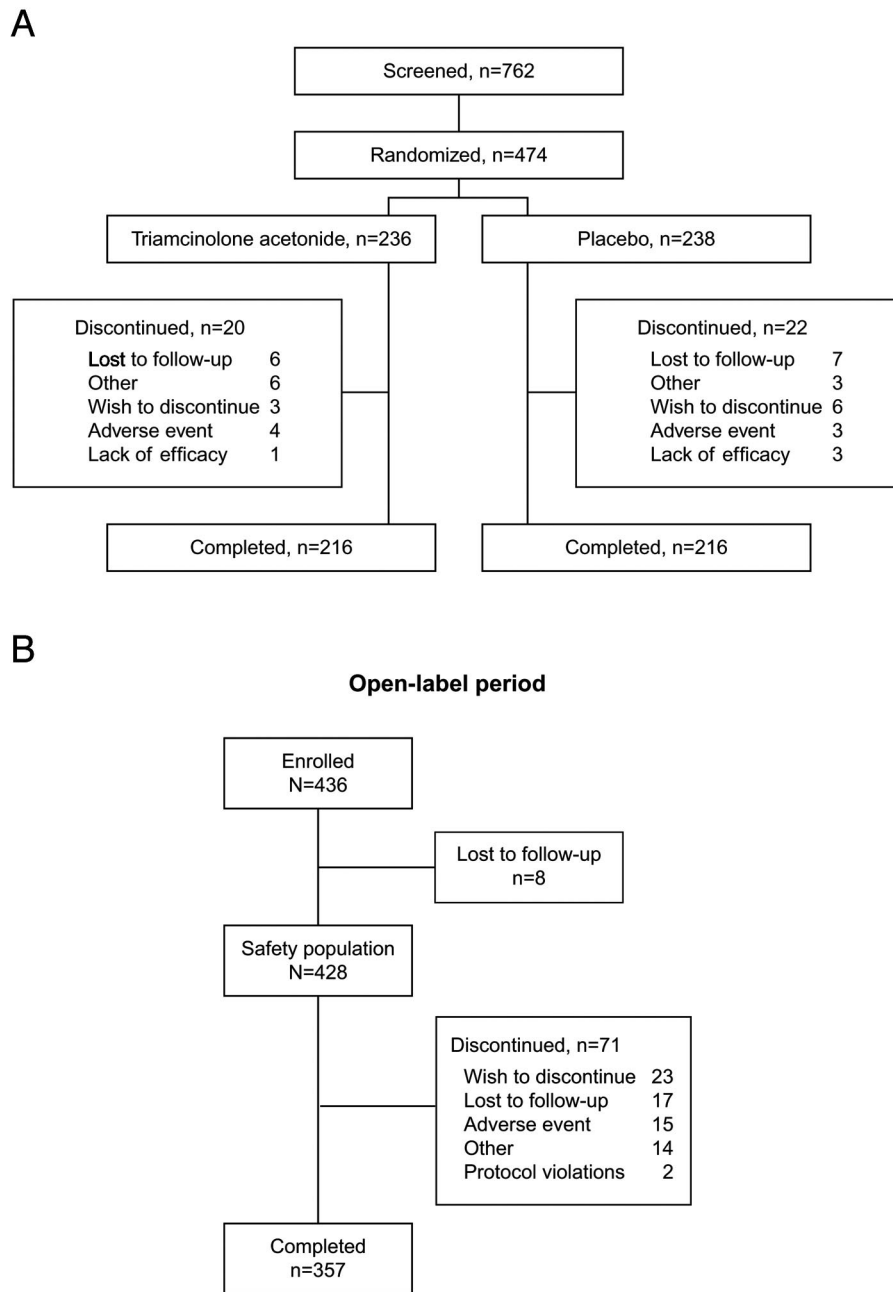


Figure 2. Patient disposition during the double-blind (A) and open-label (B) periods.

weekly TNSS; however, these differences did not reach significance except in week 4 for the reflective TNSS ($P = .04$). Reductions from baseline in TSS were also numerically greater in the TAA AQ group vs the placebo group; however, there was no statistically significant treatment effect.

The Cochran-Mantel-Haenszel test with the modified RIDIT score was used to evaluate the consistency of effect for the physician and caregiver global evaluations between TAA AQ and placebo across sites. There was a significant

difference for the physician global evaluation, with 60.7% of the TAA AQ group and 47.9% of the placebo group having evaluations of moderate, marked, or complete relief ($P = .004$). There was a trend toward a difference for the caregiver global evaluations, with 62.0% of the TAA AQ group and 52.0% of the placebo group having evaluations of moderate, marked, or complete relief ($P = .07$). When 2-year-olds were excluded from the analysis, the caregiver global evaluation was significant ($P = .02$). Few patients in the TAA AQ ($n =$

Table 1. Perennial Allergen Sensitization (Safety Population)

Disease qualification	Patients who tested positive, No. (%)	
	Placebo group (n = 238)	TAA AQ group (n = 236)
Skin prick test		
Cat	91 (38.2)	111 (47.0)
Dog	140 (58.8)	119 (50.4)
Molds	81 (34.0)	93 (39.4)
Dust mites	46 (19.3)	57 (24.2)
Other	56 (23.5)	63 (26.7)
Radioallergosorbent test	10 (4.2)	8 (3.4)
≥1 Perennial allergen	238 (100.0)	236 (100.0)

Abbreviation: TAA AQ, triamcinolone acetonide aqueous nasal spray.

1) and placebo (n = 3) groups withdrew from the study due to insufficient therapeutic effect after 2 weeks.

Post hoc analyses were conducted to identify potential factors contributing to the efficacy findings. The post hoc analysis of the primary variable (adjusted mean [SE] change from baseline in instantaneous TNSS) that excluded patients aged 2 years revealed a significantly greater reduction in the TAA AQ group (−2.25 [0.18]; n = 188) vs the placebo group (−1.62 [0.19]; n = 181; *P* = .01). Significantly greater reductions persisted in reflective TNSS from baseline (adjusted mean [SE] change) in the TAA AQ group (−2.20 [0.18]) vs the placebo group (−1.61 [0.18]; *P* = .01) in patients aged 3 to 5 years. In addition, significantly greater reductions from baseline in instantaneous and reflective TSSs were seen in the TAA AQ group vs the placebo group in patients aged 3 to 5 years (*P* = .02 and *P* = .02, respectively).

Open-label period. At the end of the open-label period, the mean (SD) scores for the physician and caregiver global evaluations of efficacy had numerically improved compared with the end of the double-blind period (2.38 [1.02] and 2.53 [1.01], respectively). No patients withdrew from the study during the open-label period due to insufficient therapeutic effect.

Safety Analysis

TEAEs. In the double-blind period, there were comparable rates of TEAEs for the TAA AQ (n = 120 [50.8%]) and placebo (n = 115 [48.3%]) groups (Table 3). No serious TEAEs were reported in either treatment group, and discontinuation rates were comparable between the groups; 7 patients (TAA AQ, n = 4 [1.7%]; placebo, 3 [1.3%]) discontinued due to TEAEs. The number of patients with TEAEs considered possibly related to study medication in the double-blind period was low and similar between treatment groups (TAA AQ, n = 13 [5.5%]; placebo, n = 20 [8.4%]).

The type, number, duration, severity, and resolution of TEAEs were comparable for the TAA AQ–treated patients during the double-blind and open-label periods (Table 3). Eight serious AEs were reported in 7 patients (1.6%) during the open-label period, none of which were considered by

Table 2. Demographic and Baseline Characteristics

Characteristic	Double-blind period (intention-to-treat population)		Open-label period (safety population), TAA AQ (n = 428)
	Placebo (n = 233)	TAA AQ (n = 231)	
Age			
Mean (SD), y	3.5 (1.04)	3.6 (1.05)	3.6 (1.05)
Range, y	2–5	2–5	2–5
2 y, No. (%)	52 (22.3)	43 (18.6)	85 (19.9)
3 y, No. (%)	67 (28.8)	53 (22.9)	110 (25.7)
4 y, No. (%)	70 (30.0)	77 (33.3)	136 (31.8)
5 y, No. (%)	44 (18.9)	58 (25.1)	97 (22.7)
Sex, No. (%)			
M	143 (61.4)	123 (53.2)	246 (57.5)
F	90 (38.6)	108 (46.8)	182 (42.5)
Race, No. (%)			
White	157 (67.4)	148 (64.1)	281 (65.7)
Black	29 (12.4)	39 (16.9)	60 (14.0)
Other	34 (14.6)	27 (11.7)	58 (13.6)
Multiracial	8 (3.4)	10 (4.3)	18 (4.2)
Asian	5 (2.1)	7 (3.0)	11 (2.6)
Height, cm			
Mean (SD)	102.13 (9.27)	103.10 (9.69) ^a	102.60 (9.44) ^a
Range	81.0–122.0	77.0–124.0 ^a	77.0–124.0 ^a
Weight, kg			
Mean (SD)	17.31 (3.87)	17.63 (4.12)	17.49 (4.01)
Range	8.3–33.2	10.0–34.5	8.3–34.5
Body mass index ^b			
Mean (SD)	16.50 (2.14)	16.49 (2.05) ^a	16.51 (2.08) ^a
Range	6.9–25.7	12.7–24.6 ^a	6.9–25.7 ^a
Baseline TNSS, mean (SD)			
Instantaneous	7.56 (2.24)	7.51 (1.98)	NA
Reflective	7.86 (2.09)	7.98 (1.96)	NA

Abbreviations: NA, not applicable; TAA AQ, triamcinolone acetonide aqueous nasal spray; TNSS, total nasal symptom score.

^a One patient did not have height recorded.

^b Calculated as weight in kilograms divided by height in meters squared.

investigators to be related to the study medication: asthma, appendicitis, tonsillar and adenoidal hypertrophy, foreign body trauma, lymphadenitis, diabetic ketoacidosis, and aseptic meningitis. All the patients recovered without sequelae except for the patient with diabetic ketoacidosis, who recovered with sequelae (new-onset diabetes mellitus). Fifteen patients (3.5%) discontinued due to AEs, of which 1 (nasal discomfort) was considered possibly related to study medication.

Vital signs. There were no clinically meaningful changes in any of the vital signs analyzed for TAA AQ compared with placebo at the end of the double-blind period or during the open-label period.

HPA Axis Evaluation

At screening and at the end of the double-blind period, the TAA AQ and placebo groups demonstrated a significant

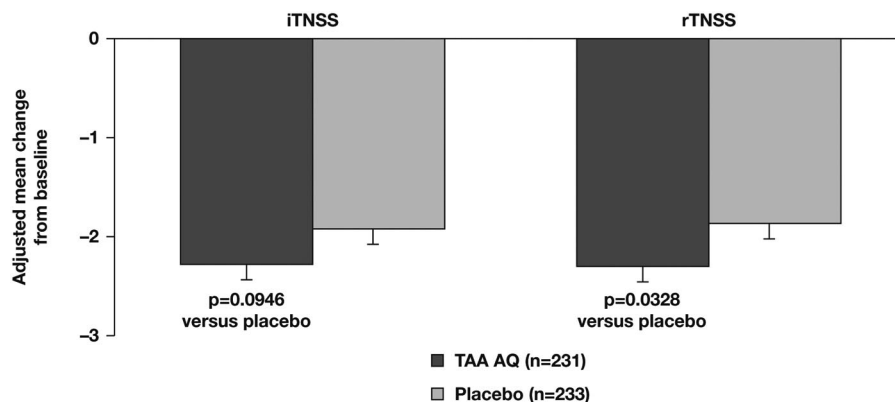


Figure 3. Adjusted mean change in total nasal symptom scores from baseline during the double-blind treatment period in the intention-to-treat population. Error bars represent SE. iTNSS indicates instantaneous total nasal symptom score; rTNSS, reflective TNSS; and TAA AQ, triamcinolone acetonide aqueous nasal spray.

Table 3. Treatment-Emergent Adverse Events (TEAEs)^a

TEAE	Double-blind period		Open-label period,
	Placebo (n = 238)	TAA AQ, 110 µg once daily (n = 236)	TAA AQ, 110 µg once daily (n = 428)
Patients with TEAEs, No. (%)	115 (48.3)	120 (50.8)	307 (71.7)
Cough	22 (9.2)	18 (7.6)	84 (19.6)
Pyrexia	19 (8.0)	16 (6.8)	94 (22.0)
Headache	10 (4.2)	13 (5.5)	34 (7.9)
Pharyngolaryngeal pain	10 (4.2)	13 (5.5)	25 (5.8)
Epistaxis	12 (5.0)	12 (5.1)	18 (4.2)
Nasopharyngitis	9 (3.8)	12 (5.1)	50 (11.7)
Upper abdominal pain	2 (0.8)	11 (4.7)	14 (3.3)
Vomiting	8 (3.4)	8 (3.4)	30 (7.0)
Diarrhea	3 (1.3)	7 (3.0)	9 (2.1)
Asthma	5 (2.1)	6 (2.5)	24 (5.6)
Rash	4 (1.7)	6 (2.5)	15 (3.5)
Excoriation	0	6 (2.5)	5 (1.2)
Rhinorrhea	4 (1.7)	5 (2.1)	28 (6.5)
Upper respiratory tract infection	2 (0.8)	4 (1.7)	36 (8.4)
Sinusitis	5 (2.1)	3 (1.3)	27 (6.3)
Viral infection	2 (0.8)	3 (1.3)	23 (5.4)
Ear infection	3 (1.3)	2 (0.8)	27 (6.3)
Otitis media	1 (0.4)	2 (0.8)	28 (6.5)

Abbreviation: TAA AQ, triamcinolone acetonide aqueous nasal spray.

^a Includes TEAEs that occurred in at least 2% of patients during the double-blind period or at least 5% during the open-label period. Data are given as number (percentage) of TEAEs except where indicated otherwise.

increase in mean cortisol level in response to cosyntropin stimulation ($P < .001$). This was also observed in the TAA AQ group at the end of the open-label period ($P < .001$).

At the end of the double-blind period, the mean increase in morning serum cortisol level in response to cosyntropin was not significantly different from that seen at screening for

either TAA AQ or placebo (Fig 4). There was no significant between-treatment difference from screening for the adjusted mean (SE) change of the increase in cortisol levels after cosyntropin infusion at the end of the double-blind period (placebo – TAA AQ = 29.54 [53.58] nmol/L; $P = .58$). After the 6-month open-label period, there was no significant difference from screening in the mean increase in morning serum cortisol level after cosyntropin infusion (Fig 4).

An abnormal response to cosyntropin (peak serum cortisol level <496 nmol/L) at screening and at the end of the double-blind period was observed in 1 (3.0%) and 4 (12.1%) patients in the TAA AQ group, respectively, and in 0 and 2 (7.1%) of patients in the placebo group, respectively. Cortisol levels below that cutoff value were seen in 0 and 6 (12.2%) patients in the TAA AQ group at screening and at the end of open-label treatment, respectively. The detailed cortisol assessments after cosyntropin infusion for these individuals are given in Table 4.

Stature-for-Age Evaluation

No significant treatment effect was observed in adjusted mean height increase during the double-blind period between the TAA AQ and placebo groups (adjusted mean difference of placebo – TAA AQ [95% confidence interval] = -0.25 cm [-0.84 to 0.34 cm]). On the basis of the Centers for Disease Control and Prevention standards,³¹ the distribution of patients by stature-for-age percentile remained stable from screening to the end of the 6-month open-label period (Fig 5).

DISCUSSION

Overall, the results of this study indicate a favorable efficacy and safety profile of TAA AQ, 110 µg once daily, in children aged 2 to 5 years with PAR. Numerical trends in favor of TAA AQ vs placebo were seen in the overall instantaneous 24-hour TNSS, and confirmed efficacy was demonstrated by a significant difference in the overall reflective 24-hour TNSS (Food and Drug Administration–recommended primary end point)³² in favor of TAA AQ vs placebo.

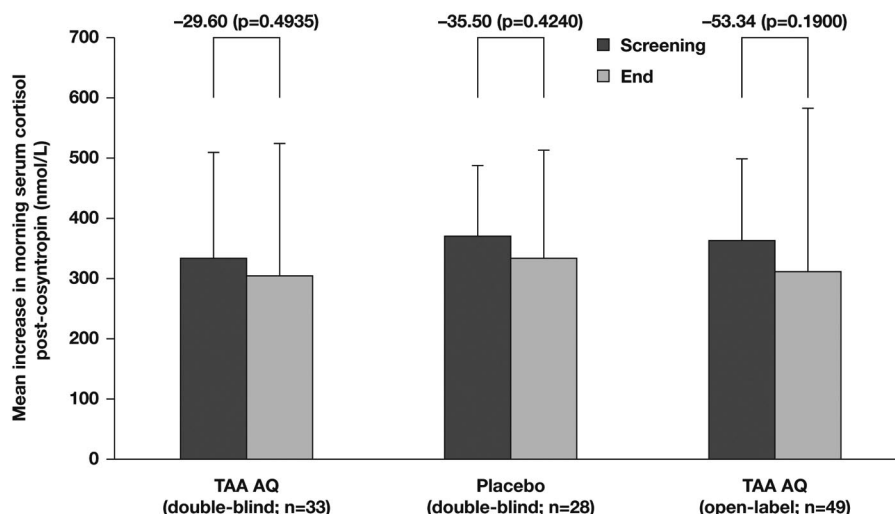


Figure 4. Mean increase in morning serum cortisol level after cosyntropin infusion in the cosyntropin-evaluable population. Error bars represent SD. TAA AQ indicates triamcinolone acetonide aqueous nasal spray.

Table 4. Patient Stratification by Serum Cortisol Level After Cosyntropin Infusion

Period	Treatment	Criteria	Patients, No. (%)	
			Screening (BL)	End of treatment
Double blind (DB)	TAA AQ	<496 nmol/L	1 (3.0) ^a	4 (12.1) ^b
		≥496 nmol/L	32 (97.0)	29 (87.9)
	Placebo (PBO)	<496 nmol/L	0	2 (7.1) ^c
		≥496 nmol/L	28 (100.0)	26 (92.9)
Open label (OL)	TAA AQ	<496 nmol/L	0	6 (12.2) ^d
		≥496 nmol/L	49 (100.0)	43 (87.8)

Abbreviation: TAA AQ, triamcinolone acetonide aqueous nasal spray.
^a Patient No. 0038045: BL = 490 nmol/L, DB TAA AQ = 519 nmol/L, OL not performed.

^b Patient No. 0017003: BL = 635 nmol/L, DB TAA AQ = 469 nmol/L, OL not performed; patient No. 0038039: BL = 696 nmol/L, DB TAA AQ = 283 nmol/L, OL not performed; patient No. 0059038: BL = 773 nmol/L, DB TAA AQ = 359 nmol/L, OL = 637 nmol/L; patient No. 0073005: BL = 828 nmol/L, DB TAA AQ = 490 nmol/L, OL = 936 nmol/L.

^c Patient No. 0073008: BL = 552 nmol/L, DB PBO = 136 nmol/L, OL = 469 nmol/L; patient No. 0073009: BL = 910 nmol/L, DB PBO = 136 nmol/L, OL = 786 nmol/L.

^d Patient No. 0017013: BL = 552 nmol/L, DB TAA AQ = 800 nmol/L, OL = 372 nmol/L; patient No. 0038041: BL = 667 nmol/L, DB TAA AQ = 637 nmol/L, OL = 490 nmol/L; patient No. 0009004: BL = 635 nmol/L, DB PBO = 579 nmol/L, OL = 441 nmol/L; patient No. 0038036: BL = 519 nmol/L, DB PBO = 873 nmol/L, OL = 460 nmol/L; patient No. 0073008: BL = 552 nmol/L, DB PBO = 136 nmol/L, OL = 469 nmol/L; patient No. 0073012: BL = 828 nmol/L, DB PBO = 725 nmol/L, OL = 401 nmol/L.

Low TEAE rates were observed throughout the study in all groups, and they were generally consistent with the adverse drug reactions usually reported with INSs and in preschool

children. Although the study was not designed to evaluate growth velocity, the real-world office stadiometry data collected suggested that stature-for-age distribution did not seem to shift during treatment with TAA AQ. A longer-term evaluation of growth velocity using standardized instruments and a double-blind, placebo-controlled design is needed to better evaluate the effect of TAA AQ on growth. As with all inhaled corticosteroids and INSs, routine monitoring of growth in pediatric patients receiving TAA AQ is warranted.

Dynamic HPA axis function was evaluated in this study using the low-dose (1-μg) cosyntropin test. This test is recommended as a preliminary screening procedure for adrenal reserve and is a better predictor of clinically relevant adrenal dysfunction than is basal 24-hour serologic and urinary free cortisol.^{33,34} It has been extensively evaluated and has been suggested to be more sensitive than the high-dose (250-μg) cosyntropin stimulation test, allowing the detection of mild forms of secondary hypoadrenalism that escape detection by the conventional high-dose cosyntropin stimulation test.³³

It is assuring that no significant difference in mean cortisol levels after cosyntropin stimulation was observed between the TAA AQ and placebo groups after 4 weeks of double-blind treatment. There were 6 reported cases (2 with placebo, 4 with TAA AQ) with serum cortisol levels less than 496 nmol/L after cosyntropin stimulation at the end of double-blind treatment; however, no consistent trend was seen owing to absent follow-up values or subsequently improved levels at the end of the 6-month open-label treatment period. In conclusion, this study suggests that adrenal suppression with TAA AQ, 110 μg once daily, seems unlikely in children aged 2 to 5 years with PAR; however, as with other INSs, an effect of TAA AQ on HPA axis function cannot be ruled out.

Overall, the efficacy, safety, and tolerability results from this study are consistent with those from previous studies with TAA AQ in patients 4 years and older with AR, which

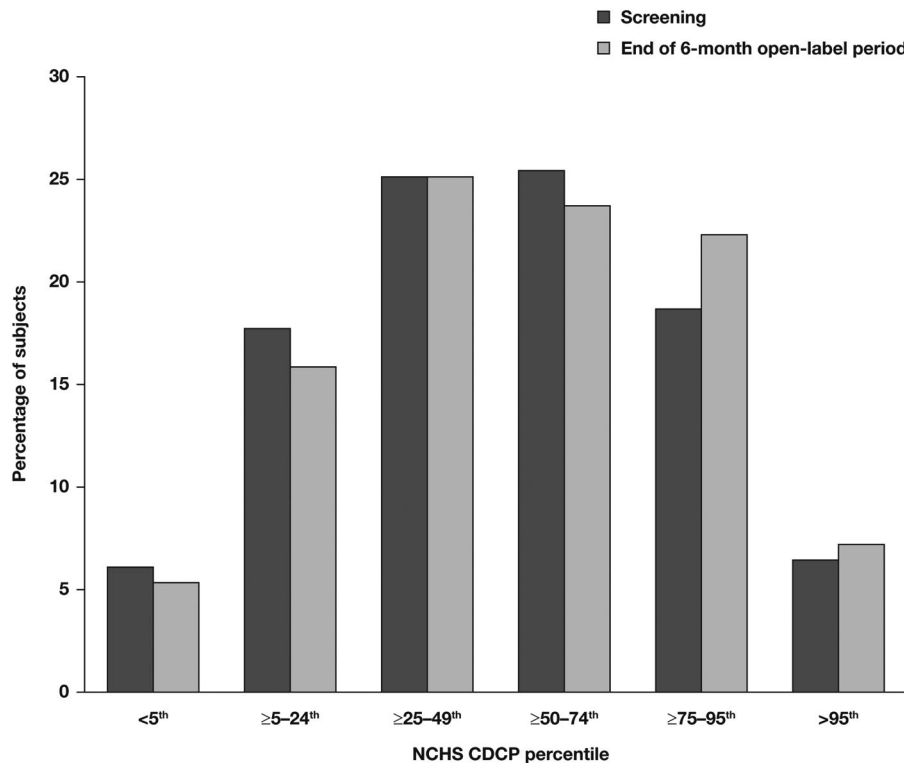


Figure 5. Distribution of 353 patients by stature-for-age percentile at baseline and at the end of the 6-month open-label period based on the National Center for Health Statistics, Centers for Disease Control and Prevention (NCHS CDCP) standards.

have shown that TAA AQ is effective at relieving AR symptoms and has a favorable safety and tolerability profile in this age group.^{21,23,25–28}

For a variety of reasons, the participation of children aged 2 to 5 years in clinical studies of INSs has been limited to a relatively small sample encompassing a wide age range.^{10–14,16} The present study is the first placebo-controlled, sufficiently powered study designed specifically to investigate the safety and efficacy of an INS in individuals aged 2 to 5 years. The post hoc analysis in patients aged 3 to 5 years presented herein highlights the difficulty experienced by caregivers in rating AR symptoms and underlines the difficulty of a physician's diagnosis of PAR in patients younger than 3 years. The global ratings of efficacy suggest that physicians are more likely to appreciate improvements in AR symptoms than are caregivers in the 2- to 5-year age group. Currently, there are no data regarding the responsiveness of the subjective symptom scoring used in children with AR aged 2 to 5 years. The development of age-specific instruments for measuring symptoms in preschool-aged children, incorporating specific instructions to the parent or caregiver, may help address this issue.

To our knowledge, no other published, large, randomized, placebo-controlled, sufficiently powered studies have concomitantly examined the efficacy and safety of INSs in preschool-aged children with PAR. This study, therefore, is the

first to directly address these 2 questions in this population. The findings demonstrate a favorable efficacy and safety ratio of TAA AQ treatment administered once daily for up to 6 months in children aged 2 to 5 years diagnosed as having PAR, with or without seasonal AR.

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