

Effect of intranasal triamcinolone acetonide on basal hypothalamic–pituitary–adrenal axis function in children with allergic rhinitis

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ABSTRACT

Intranasal corticosteroids are the most effective medication class for controlling allergic rhinitis (AR) symptoms. However, limited data are available on their effects on basal hypothalamic–pituitary–adrenal (HPA) axis function in children. This study was designed to determine the effect of 6-week triamcinolone acetonide aqueous (TAA-AQ) nasal spray treatment on HPA axis function by measuring 24-hour serum cortisol area under the curve ($AUC_{(0-24h)}$) in children with AR aged 2–11 years. This phase 4, multicenter, double-blind, placebo-controlled, parallel-group study randomized children with AR to receive TAA-AQ (110 μ g, 2–11 years old, or 220 μ g, 6–11 years old) or placebo. At pre- and posttreatment domiciled visits, 24-hour serum cortisol and reflective total nasal symptom scores (rTNSSs) were assessed. Safety assessment included treatment-emergent adverse events (TEAEs) at each visit and trough levels of 24-hour serum cortisol. A total of 140 subjects (mean age, 7.2 years; males, 59%) were randomized; 66 from each group completed treatment. The ratio of TAA-AQ to placebo for change from baseline in serum cortisol $AUC_{(0-24h)}$ was 0.966 (95% confidence interval, 0.892–1.045). Reduction from baseline in mean rTNSS was significantly greater in the TAA-AQ than in the placebo group (difference: least square mean $\pm$ SE = -0.85 ± 0.24 ; $p = 0.0007$). The safety profile was similar (TEAEs, TAA-AQ, 27.5%; placebo, 25.4%), and so was the mean change in serum cortisol trough level (TAA-AQ, -0.4μ g/dL; placebo, -0.1μ g/dL; $p = 0.1818$ for treatment difference) from pre- to posttreatment. TAA-AQ was safe, well tolerated, and not associated with clinically meaningful suppression of serum cortisol $AUC_{(0-24h)}$ in children with AR.

Clinical trial NCT01154153, www.clinicaltrials.gov.

(Allergy Asthma Proc 35:163–170, 2014; doi: 10.2500/aap.2014.35.3728)

Interanasal corticosteroids (INSSs) control symptoms of allergic rhinitis (AR).¹ Nasacort AQ Nasal Spray (Sanofi-Aventis U.S., Bridgewater, NJ) is a microcrystalline suspension of triamcinolone acetonide in an aqueous medium (TAA-AQ), indicated for the treat-

ment of nasal symptoms of seasonal AR and perennial AR (PAR) in adults and children ≥ 2 years old.² Published studies support the efficacy, safety, and tolerability of TAA-AQ once-daily treatment for nasal symptoms of AR in adults and children 2–12 years old.^{3–8}

The hypothalamic–pituitary–adrenal (HPA) axis is vital for basal and stress-related homeostasis. Exogenous glucocorticoids suppress cortisol secretion by the adrenal glands through multilevel effects on the HPA axis.⁹ Therefore, a potential effect of TAA-AQ on the HPA axis can not be disregarded.^{4,10,11} Tests evaluating the basal function of adrenal glands have been extensively reviewed in the literature.^{12,13} Using a single morning plasma cortisol sample for assessment is limited by its broad normal range.¹² Multiple sampling at frequent intervals provides a more accurate assessment of HPA axis function by detecting changes in diurnal rhythm.^{14–16} Therapeutic doses of TAA-AQ nasal spray did not significantly alter adrenocortical function in adults, and effects on plasma cortisol, 24-hour urinary free cortisol, and 17-hydroxycorticosteroid after 250 μ g of cosyntropin infusion were comparable with placebo.¹⁷ In two clinical trials with children aged 6–12 years and 4–10 years, intranasal TAA-AQ did not show significant suppression of morning se-

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Presented as a poster at the annual meeting of the American College of Allergy, Asthma, and Immunology (ACAAI), Boston, Massachusetts, November 3–8, 2011 (the abstract was published in a supplement of the *Annals of Allergy, Asthma, and Immunology* for the annual meeting)

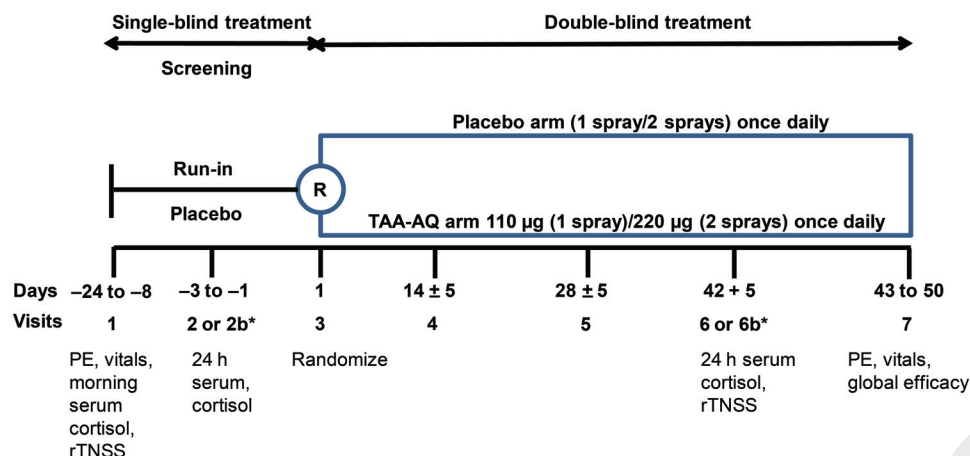
Funded by Sanofi-Aventis

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PE, physical examination; R, randomization; rTNSS, Reflective total nasal symptom score

*Visits 2b and 6b are optional visits in the event that the procedures for Visit 2 and/or Visit 6 need to be repeated due to lost, mishandled, or missed blood samples. Visits 2b and 6b were to occur as soon as possible, but no later than 7 days after Visit 2 and Visit 6, respectively.

Figure 1. Study design.

rum cortisol levels and overnight urine cortisol/creatinine ratio, respectively.^{18,19} Plasma drug concentration of TAA-AQ peaked at ~1.5 hours postdose followed by a rapid decline with little or no systemic accumulation.¹⁸ Recently, a placebo-controlled clinical trial in children aged 2–5 years did not show a significant effect of TAA-AQ on the mean morning plasma cortisol level after 1 µg of cosyntropin infusion.⁴ However, during review of a supplemental new drug application seeking an extension of age indication for children 2–5 years old, the U.S. Food and Drug Administration considered the findings from this 4-week phase 3 study inconclusive and requested further characterization of the effect of TAA-AQ, administered for no less than 6 weeks, on the HPA axis in the pediatric population by using 24-hour cortisol measurements.⁴

This phase 4 study was conducted in children aged 2–11 years with AR to determine the effect of 6-week TAA-AQ at a 110- or 220-µg treatment on the HPA axis function using 24-hour serum cortisol area under the curve (AUC_(0–24h)) measurement.

METHODS

Patients

Male and female subjects aged 2–11 years with documented AR diagnosis, one common nasal symptom of AR rated at least 1 on a 0–3 scale 24 hours before screening, and a morning serum cortisol level of 5–22 µg/dL were enrolled. Detailed inclusion and exclusion criteria have been provided as supplemental material. Subjects and their parents/caregivers had to be willing to be domiciled over 24–36 hours for blood collection,

planned for two 24-hour periods, at baseline and at study completion.

Study Design

This phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at eight centers in the United States in accordance with the Declaration of Helsinki. The protocol complied with applicable U.S. guidelines and was approved by the Schulman Associates Institutional Review Board. Subjects' parents/legal guardians provided written informed consent; subjects aged ≥7 years provided a signed assent form.

During the screening period (8–24 days), subjects received a single-blind placebo nasal spray once daily in the morning to practice application. Subsequently, subjects aged ≥2 to <6 years were randomized in a 1:1 ratio to receive 1 spray/nostril of TAA-AQ or placebo, while subjects aged 6–11 years were randomized in a 1:1:1:1 ratio to receive 1 or 2 sprays/nostril of TAA-AQ or placebo, once daily in the morning, for ~6 weeks (Fig. 1). Randomization was stratified by age group (≥2 to <4 years, ≥4 to <6 years, and ≥6 to 11 years) and gender. Each TAA-AQ spray contained 55 µg of the active drug. Claritin syrup (loratadine at 5 mg/mL; Schering-Plough HealthCare Products, Inc, Kenilworth, NJ) was provided as rescue medication for breakthrough symptoms. Treatment adherence was assessed by reviewing subject's diary during the study.

End Points and Assessments

The primary end point variable was change from baseline in serum cortisol AUC_(0–24h) at the end of

treatment (EOT). Blood samples were collected to determine serum cortisol levels over a 24-hour period at the domiciled visits of baseline and EOT. The first sample (0 hours) was collected between 8:00 and 9:00 A.M. preadministration and subsequent samples at 2, 4, 8, 12, 20, and 24 hours postadministration (approximate times: 8:00 A.M., 10:00 A.M., 12:00 P.M., 4:00 P.M., 8:00 P.M., 4:00 A.M., and 8:00 A.M.). Serum cortisol levels were evaluated using a Beckman Coulter Dxl800 instrument (Beckman Coulter Inc, Brea, CA). This cortisol assay is an automated competitive binding immune-enzymic assay, with a reportable range of 2.0–60.0 $\mu\text{g/dL}$. The adopted age-specific normal range for morning serum cortisol in this study was 5–22 $\mu\text{g/dL}$.^{9,20} Serum cortisol $\text{AUC}_{(0-24\text{h})}$ (or $\text{AUC}_{(0-24\text{h})}$ average) was calculated based on the actual blood-draw time points using the trapezoid rule and normalized by dividing the $\text{AUC}_{(0-24\text{h})}$ by sample collection interval from 0- to 24-hour blood-draw time points.²¹ Secondary pharmacodynamic and efficacy variables were serum cortisol levels, 24-hour reflective total nasal symptom score (rTNSS), subject and physician global evaluation of efficacy, and use of rescue medication. rTNSS was calculated as the sum of each subject's scores of the four symptoms of AR (nasal congestion, nasal itching, sneezing, and runny nose) rated on a 0–3 scale (symptom absent, mild, moderate, or severe) by the subject with the help of a parent/guardian at awakening in the morning, before any treatment; this score was reflective of the past 24 hours. Subject and physician global evaluation of efficacy were conducted at the EOT visit on a 5-point scale (0, no relief; 1, slight relief; 2, moderate relief; 3, marked relief; and 4, complete relief). Tanner staging was performed at the screening visit as a reference to the subjects' physical maturity.^{22,23}

Safety

Safety was assessed based on incidence of treatment-emergent adverse events (TEAEs), vital signs, and 24-hour serum cortisol trough levels. Heart rate, blood pressure, respiratory rate, temperature, weight, and height were assessed by the investigators at the screening and end of study visits. The 24-hour serum cortisol trough level was the lowest value of the 24-hour serum cortisol measurements.

Statistical Analysis

Treatment effect was evaluated as the treatment ratio of geometric means of $\text{AUC}_{\text{EOT}}/\text{AUC}_{\text{baseline}}$ between placebo and TAA-AQ. With the common SD of the AUC in log scale estimated as 0.30, a sample of 112 subjects (56/treatment arm) would provide a precision of 1.12-fold for the 95% confidence interval (CI) for the treatment ratio of geometric means. To ensure at least

112 subjects in the primary population for analysis (per protocol [PP] population), which included all randomized subjects without any major protocol deviations, it was planned to randomize and treat a total of 124 subjects (62/treatment arm).

For the primary end point, the primary analysis was based on log-transformed $\text{AUC}_{(0-24\text{h})}$ and multiple imputations for missing serum cortisol values in the evaluable (PP) population, consistent with the Food and Drug Administration draft guidance.²⁴ The 1-spray and 2-spray subgroups were pooled for both TAA-AQ and placebo. Statistical comparison between treatment arms were performed on the change from baseline in serum cortisol $\text{AUC}_{(0-24\text{h})}$ at EOT (expressed as a log-transformed ratio of $\text{AUC}_{\text{EOT}}/\text{AUC}_{\text{baseline}}$). Secondary analysis was performed on the intent-to-treat (ITT) population and on all completers. Additional secondary analyses were performed in original $\text{AUC}_{(0-24\text{h})}$ scale without log transformation and based on observed data only without imputation. An analysis of covariance model was fitted with treatment, gender, and age group as fixed effects and the log-transformed baseline $\text{AUC}_{\text{baseline}}$ as the covariate. To assess potential outliers at EOT, the number of subjects within each treatment group with change from baseline in $\text{AUC}_{(0-24\text{h})}$ outside 1 SD, 2 SD, or 3 SD of the baseline log-transformed AUC was evaluated. Secondary efficacy variable analysis was performed on the ITT and PP populations. Treatment group differences in mean change from baseline in rTNSS were evaluated using the analysis of covariance model with treatment group and randomization stratum as the fixed effect and the baseline value as the covariate. All safety analyses were performed on the safety population (all treated subjects).

RESULTS

Demographics and Compliance

The study screened 179 and enrolled 140 subjects (TAA-AQ, 69; placebo, 71); 132 completed the study (Fig. 2) between June and October 2010. Of these, 59% were male subjects; their mean (SD) age was 7.2 years (2.6 years). Demographics and baseline characteristics were comparable between groups (Table 1). Most subjects were at Tanner stage 1 in both TAA-AQ (87%) and placebo (77.5%) groups (Table 1). At baseline, all randomized subjects had symptoms of PAR and/or seasonal AR for at least 1 year. Treatment compliance ranged from ~90 to 100% in both groups.

Pharmacodynamic Parameters

Based on the PP population analysis, no significant difference was observed between the groups in serum cortisol $\text{AUC}_{(0-24\text{h})}$ at EOT (TAA-AQ/placebo, 0.966; 95% CI, 0.892, 1.045). The geometric mean changes from base-

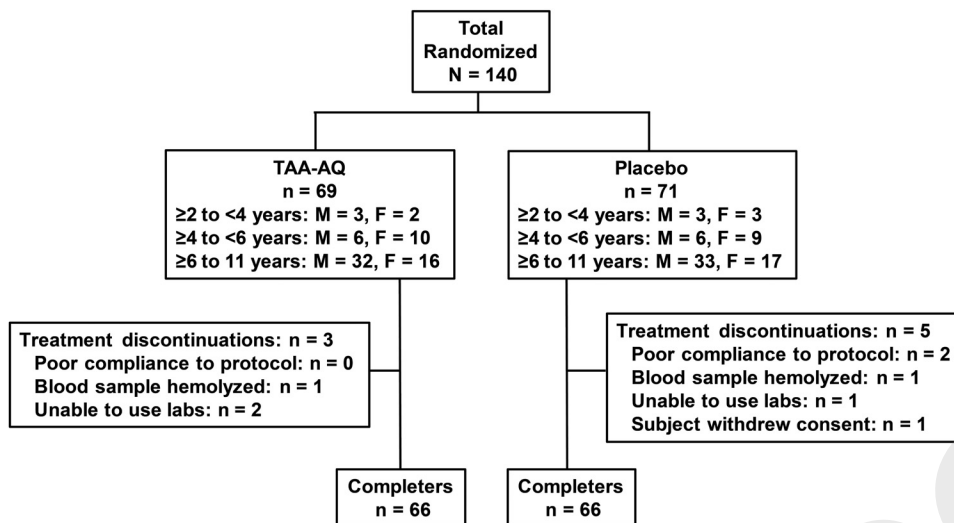


Figure 2. Subject disposition.

line (ratio) were 0.898 and 0.938 for TAA-AQ and placebo groups, respectively. Similar results were observed in the ITT population, in all completers, and based on observed data without imputation. The PP and ITT population analyses on the original $AUC_{(0-24h)}$ scale also showed no significant difference in mean change from baseline of $AUC_{(0-24h)}$ between the groups (PP population difference of TAA-AQ-placebo in $AUC_{(0-24h)}$ average, $-0.2 \mu\text{g/dL}$; 95% CI, $-0.6, -0.3 \mu\text{g/dL}$).

Primary variable evaluation by age and gender in the PP and ITT populations showed consistent trends in the TAA-AQ/placebo ratio of serum cortisol $AUC_{(0-24h)}$ geometric mean among these subgroups, with both—greatest numeric difference and widest CI—occurring in the youngest age group (2 to <4 years; Fig. 3). However, no ratio indicated a significant difference between the groups. In a *post hoc* analysis, the ratio in the age group of 2 to <6 years, *i.e.*, pooling 2 to <4 years and 4 to <6 years groups, also indicated no significant treatment group difference. Secondary analysis of the primary variable by TAA-AQ dose (2 sprays/nostril versus 1 spray/nostril, once daily) in the 6- to 11-year subgroup showed no significant dose effect in both populations. In the PP population, one subject in each treatment group had a change from baseline in $AUC_{(0-24h)}$ outside 3 SD. The percentage of subjects with a change from baseline outside 2 SD was 9.2 and 4.9% for TAA-AQ and placebo groups, respectively, but this difference was not statistically significant ($p = 0.4936$; Fisher's exact test). Similar percentages were observed in the ITT population. *Post hoc* analysis with the overall baseline mean AUC in log scale of the ITT population as the common reference point revealed that one (1.5%) and three (4.6%) subjects on placebo and TAA-AQ, respectively, had a change from baseline population mean in log-transformed $AUC_{(0-24h)}$ outside 2 SD, whereas one (1.5%) receiving TAA-AQ had a value outside 3 SD.

Six weeks posttreatment, the circadian rhythm of serum cortisol was preserved in both groups. The nadir and peak were observed at night (around 8:00 P.M.) and early morning (around 8:00 A.M.), respectively. A transient but significant drop in serum cortisol was noted at 2–4 hours postdose with TAA-AQ but not placebo (Fig. 4). In the PP population, the geometric mean of the change from baseline in serum cortisol at 2 hours was 0.733 (95% CI, 0.644, 0.835) for TAA-AQ and 0.958 (95% CI, 0.871, 1.054) for placebo. At 4 hours, it was 0.551 (95% CI, 0.484, 0.627) for TAA-AQ and 0.901 (95% CI, 0.792, 1.025) for placebo. Similar results were observed in the ITT population. The proportion of subjects with serum cortisol below or above the normal range at the 0- and 24-hour time points after 6 weeks of treatment was similar between groups and the proportion with morning serum cortisol shift from within to below the normal range at the 0- and 24-hour time points was similar between groups.

Efficacy

In the PP population, the respective mean rTNSS (SD) for the TAA-AQ and placebo groups was 5.14 (2.55) and 4.86 (2.76) during the single-blind, and 4.07 (2.49) and 4.65 (2.89) during the double-blind treatment period. The treatment difference in the change from baseline in rTNSS over the double-blind period was statistically significant in favor of TAA-AQ (least squares mean difference [SE], -0.85 (0.24); 95% CI, $-1.34, -0.37$; $p = 0.0007$). A similar statistically significant improvement from baseline in 24-hour rTNSS was observed in the TAA-AQ group versus the placebo group in the ITT population. During the postrandomization period (randomization to EOT visits), rescue medication was used by 29.2% of subjects in the

Table 1 Demographics and baseline characteristics

	TAA-AQ (n = 69)	Placebo (n = 71)
Age, yr, mean (SD)	7.1 (2.5)	7.3 (2.7)
Median (range)	7.0 (2–11)	7.0 (2–11)
Age group, yr, n (%)		
≥2 to <4	5 (7.2%)	6 (8.5%)
≥4 to <6	16 (23.2%)	15 (21.1%)
≥6–11	48 (69.6%)	50 (70.4%)
Gender, n (%)		
Male	41 (59.4%)	42 (59.2%)
Female	28 (40.6%)	29 (40.8%)
Race, n (%)		
Caucasian/white	42 (60.9%)	43 (60.6%)
Black	22 (31.9%)	22 (31.0%)
Asian/Oriental	0	2 (2.8%)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	5 (7.2%)	4 (5.6%)
Ethnicity, n (%)		
Hispanic	19 (27.5%)	18 (25.4%)
Non-Hispanic	50 (72.5%)	53 (74.6%)
Tanner classification, n (%)		
Stage 1	60 (87.0%)	55 (77.5%)
Stage 2	9 (13.0%)	12 (16.9%)
Stage 3	0	4 (5.6%)
Stage 4	0	0
Stage 5	0	0
Primary diagnosis, n (%)		
Only PAR	12 (17.4%)	11 (15.5%)
Only SAR	3 (4.3%)	5 (7.0%)
Both PAR and SAR	54 (78.3%)	55 (77.5%)
Time from first AR symptom to screening visit, yr, mean (SD) yr, mean (SD)	4.79 (2.48)	4.82 (2.70)

AR = allergic rhinitis; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis, TAA-AQ = triamcinolone acetonide aqueous nasal spray.

TAA-AQ group and 39.3% in the placebo group ($p = 0.2480$). The mean percentage of days of rescue medication usage was 3.07% (SD, 11.82) in the TAA-AQ group and 4.02% (SD, 12.77) in the placebo group. Based on the PP population analysis, both the subject and physician global evaluations of efficacy revealed that the mean evaluation score corresponded to moderate relief in the TAA-AQ group and to slight-to-moderate relief in the placebo group. Similar results were obtained in the ITT population.

Safety Evaluations

Safety profile was similar between the groups. TEAEs were reported in 19 (27.5%) and 18 (25.4%) subjects in the TAA-AQ and placebo groups, respectively (Table 2). There was one serious AE (humerus fracture) in the placebo group and none in the TAA-AQ group. All TEAEs were mild to moderate, and few subjects (TAA-AQ, 4 [5.8%]; placebo 4 [5.6%]; Table 2) experienced TEAEs that were considered investigational product related. No AEs led to treatment discontinuation, and no deaths were reported. Changes in heart rate, blood pressure, weight, height, temperature, and respiratory rate were comparable between the groups. Increases in weight of ≥5% from baseline were observed in nine (13.4%) and three (4.4%) subjects in the TAA-AQ and placebo groups, respectively. At EOT, mean serum cortisol trough levels for the TAA-AQ and placebo groups were 1.8 and 1.7 $\mu\text{g}/\text{dL}$, respectively. The difference in change from baseline to EOT in the 24-hour serum cortisol trough level between TAA-AQ ($-0.4 \mu\text{g}/\text{dL}$) and placebo groups ($-0.1 \mu\text{g}/\text{dL}$) was not statistically significant ($p = 0.1818$).

DISCUSSION

INS are an effective treatment for AR symptoms; however, concerns remain regarding their effects on growth and HPA axis function in children.^{9,25} Numerous clinical trials have found that intranasal TAA-AQ is well tolerated and effective in controlling AR symptoms in children.^{3,4,26,27} The present study characterized the effect of a 6-week, once-daily TAA-AQ treatment on basal HPA axis function by measuring the 24-hour serum cortisol level in children aged 2–11 years (mostly prepubertal) with AR. TAA-AQ treatment at the age-approved dosing regimens was not associated with clinically meaningful suppressions in serum cortisol $\text{AUC}_{(0-24\text{h})}$. Over the 24-hour period, preserved normal circadian rhythms of serum cortisol were comparable between TAA-AQ treatment and placebo. This is consistent with a report on the once-daily use of fluticasone furoate at 110 μg , where the treatment-versus-placebo ratio for serum cortisol-weighted mean (0–24 hours) was 0.97 in children aged 2–11 years with PAR after a 6-week treatment.²⁸ TAA-AQ was well tolerated, with the largest numerical treatment effect and variability in $\text{AUC}_{(0-24\text{h})}$ observed in the youngest age group (2–4 years). However, this should be interpreted with caution because of the small sample size (nine subjects) of this group. A transient but significant drop in serum cortisol level was noted at 2 and 4 hours after TAA-AQ administration, which coincides with TAA-AQ's C_{max} ; however, this relationship can not be ascertained because simultaneous pharmacokinetic data were not measured.¹⁵ No be-

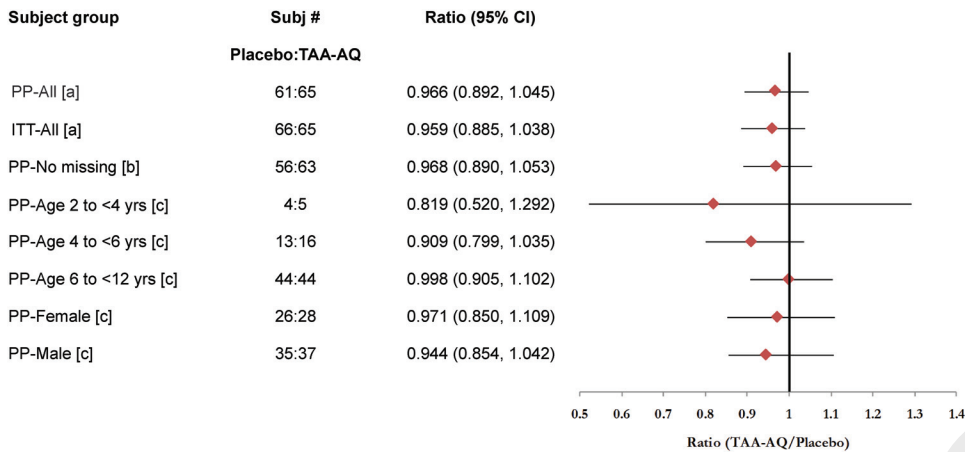


Figure 3. The ratio between treatment arms in serum cortisol 24-hour serum cortisol area under the curve ($AUC_{(0-24h)}$) geometric mean change from baseline.

[a] Missing cortisol values were imputed by multiple imputation.
 [b] Subjects with missing cortisol values were excluded.
 [c] Missing cortisol values were imputed by the average of multiple imputed data.
 Subj #: the number of subjects in placebo:the number of subjects in TAA-AQ.
 The error bars represent 95% Confidence Interval

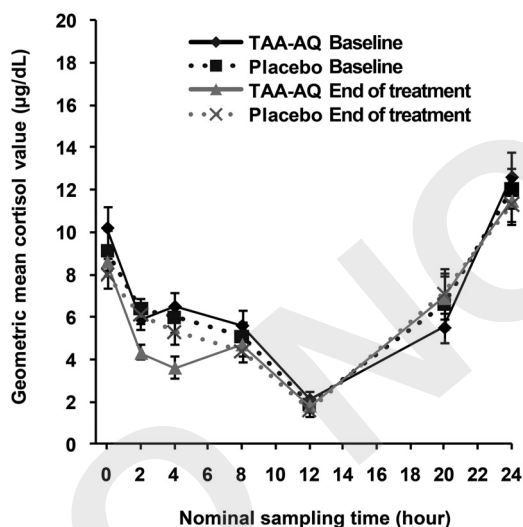


Figure 4. Serum cortisol geometric mean across nominal sampling time at baseline and end of treatment (EOT) by treatment arm-per protocol (PP) population. The error bars represent 95% confidence interval (CI).

Table 2 Treatment-emergent adverse events

Category	TAA-AQ (n = 69)	Placebo (n = 71)
Subjects with any TEAEs	19 (27.5%)	18 (25.4%)
Subjects with any possibly related TEAEs	4 (5.8%)	4 (5.6%)
Subjects with any treatment-emergent serious AEs	0	1 (1.4%)
Most common TEAEs (in $\geq 2\%$ subjects in any arm)		
Pyrexia	4 (5.8%)	2 (2.8%)
Cough	3 (4.3%)	1 (1.4%)
Epistaxis	3 (4.3%)	7 (9.9%)
Headache	2 (2.9%)	4 (5.6%)
Upper respiratory tract infection	2 (2.9%)	0
Vomiting	2 (2.9%)	0

AE = adverse event; TAA-AQ = triamcinolone acetonide aqueous nasal spray; TEAE = treatment-emergent adverse event.

tween-group differences were observed in the proportion of subjects with serum cortisol level below the prespecified normal range at the early morning time points (0 and 24 hours). However, one 8-year-old boy receiving 2 sprays/nostril (220 μg) of TAA-AQ had a cortisol $AUC_{(0-24h)}$ outside the 3 SD range of baseline population mean in log scale. This suggests that some children may have heightened sensitivity to the effects of INS. In this study we also observed more subjects with weight increase $\geq 5\%$ from baseline on TAA-AQ (9/67; 13.4%) versus placebo (3/68; 4.4%). A *post hoc p* value from Fisher's exact test was 0.0769, indicating the difference could be caused by randomness because the

study did not control for eating habits and baseline weight trend and was not designed to evaluate body weight specifically. To minimize the systemic effects of INS, titrating, each patient's dose to the lowest dosage that can effectively treat symptoms is recommended.

Owing to the circadian rhythmicity and pulsatility of cortisol concentration, a single morning cortisol level has low sensitivity for detecting adrenal insufficiency in children because the time of peak morning cortisol concentration may vary across patients.^{12,16} The cosyn-

tropin test is most useful for detecting clinically significant corticosteroid effects; however, it is relatively insensitive for detecting systemic presence of corticosteroids with short-term use.²⁹

In several aspects, this study design offers many advantages through timed, frequent 24-hour plasma cortisol sampling and incorporation of a placebo arm. Timed, frequent plasma cortisol sampling after corticosteroid inhalation detects changes in diurnal variation due to the delayed rise in cortisol levels after the nocturnal nadir.^{14,15} Because accepted normal and abnormal ranges do not exist for AUC and time plots, comparisons are often made with placebo²⁸ or active control.²¹ Furthermore, compared with the 24-hour urinary excretion of 17-hydroxycorticosteroids or free cortisol, 24-hour integrated plasma cortisol concentration is a more sensitive measure of HPA axis function for differentiating patients with Cushing's syndrome or hypertension from normal individuals.³⁰ Despite the logistical inconvenience, domiciling subjects during the 24-hour urine or plasma collection periods is feasible and can help ensure reliability and completion of study-related procedures.^{21,24} Admittedly, this approach is not suitable for screening HPA axis activity in outpatients in clinical practice.

One study limitation was that no active comparator was used. However, considering the young age of the population and the nonserious nature of the diagnosis, it is difficult to justify exposure to systemic corticosteroids in this study. An active treatment with an alternative INS (e.g., beclomethasone dipropionate³¹) was not adopted because it would have required a double-dummy approach requiring 2 nasal sprays/subject during the study (active and placebo), potentially diluting the topical concentration of the active INS and interfering with the outcome.

In conclusion, TAA-AQ was well tolerated, and not associated with a significant suppression of serum cortisol AUC_(0-24h) when compared with placebo in children with AR.

ACKNOWLEDGMENTS

The authors thank all of the TRICA_L_04286 study subjects, parents, and clinical investigators. Article writing support was provided by Dr. Sangita P. Patil at Cactus Communications.

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