Original Article

Growth Velocity Reduced with Once-Daily Fluticasone Furoate Nasal Spray in Prepubescent Children with Perennial Allergic Rhinitis

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What is already known about this topic? Growth suppression with intranasal corticosteroid treatment ranges from −0.2 to −0.9 cm during 1 year of treatment. Previous intranasal corticosteroid studies have inadequate power or controls for normal variability in growth patterns, which resulted in a lack of clarity on the true effect.

What does this article add to our knowledge? This study of approximately 450 prepubescent children was able to detect a small reduction in growth velocity (−0.27 cm/y [95% CI, −0.48 to −0.06 cm/y]) after 52 weeks of treatment with fluticasone furoate nasal spray 110 mcg once daily compared with placebo.

How does this study impact current management guidelines? Clinicians will need to balance the reduction in growth observed with fluticasone furoate nasal spray to its potential for clinical benefit.

BACKGROUND: The effect of fluticasone furoate nasal spray (FFNS) on growth in prepubescent children has not been evaluated.
OBJECTIVE: To characterize the difference in mean prepubescent growth velocities, as determined by stadiometry, between patients treated continuously for 1 year with FFNS 110 mcg once daily and placebo nasal spray.
METHODS: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 76-week safety study. Nasal symptom assessments were used as a measure of adherence. Eligible patients were ages 5 to <8.5 years at screening and had at least a 1-year clinical history and diagnosis of perennial allergic rhinitis, including a positive skin test or specific IgE to an appropriate perennial allergen within the past year.
RESULTS: One hundred eighty-six patients in the FFNS group and 187 patients in the placebo group completed the entire 52-week treatment period. During treatment, the least squares mean growth velocity was 5.19 cm/y for the FFNS group and 5.46 cm/y for the placebo group; mean difference, −0.270 cm/y (95% CI, −0.48 to −0.06 cm/y). Other safety assessments, including 24-hour urinary cortisol excretion, were comparable between the treatment groups. Daily reflective total nasal symptom scores declined similarly in both the FFNS and placebo groups.
CONCLUSION: Once-daily treatment with FFNS over 52 weeks in prepubescent children resulted in a small reduction in growth velocity compared with placebo. Clinicians will need to balance the reduction in growth observed with FFNS to its potential for clinical benefit. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

Key words: *Stadiometry; Children; Intranasal corticosteroid; 24-Hour urinary cortisol; Randomized clinical trial; Placebo controlled*

Allergic rhinitis is one of the most common chronic conditions of childhood and affects up to 40% of children.[1,2] Intranasal corticosteroids (INS) are the most effective therapy for treating allergic rhinitis; however, physicians may be reluctant to prescribe INS long term for children due to concerns about potential growth suppression.[3] Evidence for growth suppression was confirmed in a clinical trial in which children treated with intranasal beclomethasone dipropionate 168 mcg twice daily for 1 year demonstrated a 0.9 cm difference in standing height from those treated with placebo.[3]

Stadiometry is the criterion standard for measuring growth in children.[4] The growth velocity of prepubescent children

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Abbreviations used
FFNS- Fluticasone furoate nasal spray
ICS- Inhaled corticosteroid
INS- Intranasal corticosteroid
ITT- Intent-to-treat population
rTNSS- Reflective total nasal symptom score
TNSS- Total nasal symptom score

undergoing linear, hormone-dependent growth is more constant and less confounded than results obtained in other pediatric age groups. Furthermore, the variability in growth velocity requires a long run-in period to establish an accurate baseline growth velocity, and a large sample size is required to precisely measure differences in growth. These considerations were made in the design of the current study to distinguish it from other studies of corticosteroids and growth.

Fluticasone furoate nasal spray (FFNS) has demonstrated efficacy for both seasonal and perennial allergic rhinitis in children as young as 2 years of age.[5-7] However, the effect of FFNS on growth in prepubescent children has not been evaluated. This study evaluated the effect of FFNS 110 mcg on growth velocity in prepubescent children by using stadiometry.

METHODS

Objectives

The primary objective was to estimate the difference in mean prepubescent growth velocities, via stadiometry, between patients treated continuously for 1 year with once-daily FFNS 110 mcg (Veramyst [fluticasone furoate] nasal spray; GlaxoSmithKline, Research Triangle Park, NC) and those on placebo nasal spray. Secondary objectives of the study included nasal examinations, routine laboratory assessments, 24-hour urinary free cortisol excretion, and adverse events.

Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 76-week study. The study was conducted at 77 sites within the United States, Canada, France, Argentina, Chile, and Peru between November 2007 and March 2011 (GlaxoSmithKline Study FFR101782; NCT00570492 and ClinicalTrials.gov Identifier: NCT00570492). The study protocol and statement of informed consent were reviewed and approved by an institutional review board or ethics committee before study initiation, and written informed consent was obtained from the patient's legal parent or guardian before study participation.

Patients were screened for eligibility and entered a 16-week baseline period to assess baseline growth velocity during which all patients received single-blind, placebo nasal spray. The patients were randomized 1:1 to receive either double-blind FFNS 110 mcg (2 sprays per nostril [27.5 mcg per spray]) or placebo once daily for 52 weeks. After treatment, the patients entered an 8-week, single-blind, follow-up period, during which all the patients received placebo nasal spray. All the patients were provided with loratadine syrup as rescue medication to treat uncontrolled symptoms of perennial allergic rhinitis throughout the study.

Patient population

Eligible patients were ages 5 to <7.5 years old for girls and 5 to <8.5 years old for boys at screening, and had a 1-year clinical history and diagnosis of perennial allergic rhinitis, including a positive skin test or specific IgE to an appropriate perennial allergen within the past year. A positive skin test was defined as a wheal $\geq$3 mm larger than the diluent control for skin prick testing.

Patients were required to have a reflective total nasal symptom score (rTNSS) (the average of the morning and evening assessments of individual nasal symptom scores for nasal congestion, rhinorrhea, nasal itching, and sneezing) of $\geq$5 on any 4 of the last 7 days before their second clinic visit (clinic visits 1-4 were scheduled to occur at 28 $\pm$ 4 days during the 16-week single-blind, baseline period).[6] During each baseline visit, the patients had to be prepubescent (Tanner staging, 1) and have current height, body weight, and body mass index measurements within the 3rd and 97th percentiles according to US Centers for Disease Control and Prevention.[8,9] Skeletal age was required to be within $\pm$1 year of the patient's chronological age as determined by a central reader of a left hand and/or wrist radiograph during the baseline period. Baseline growth velocity also had to be within the 3rd to 97th percentiles according to the North American longitudinal standard growth velocity charts and any local longitudinal standard growth velocity charts for age and sex.

Patients were excluded from the study if they had a history or evidence of a significant concomitant medical condition or abnormal growth, or were taking a medication that affects growth. Use of inhaled corticosteroids (ICS), INS, or high-potency topical corticosteroids within 6 weeks and systemic corticosteroids within 12 weeks before screening or during the baseline period was exclusionary.

Primary safety measure: growth velocity

The primary safety end point was the mean difference in growth velocities between patients treated with FFNS 110 mcg once daily and those treated with placebo nasal spray. Triplicate height assessments were conducted at each clinic visit 4 weeks apart during the entire 76-week study period by site personnel trained in stadiometry technique and calibration procedures by using a Harpenden Stadiometer (Model 602VR, Holtain Ltd, London, UK).

Other safety measures

Adverse events and serious adverse events were collected. Hypothalamic-pituitary-adrenal axis function was assessed by measurement of 24-hour urinary-free cortisol (ARUP Laboratories, Salt Lake City, Utah).

Efficacy measurements

Efficacy was measured daily by nasal symptom assessments (rTNSS) to assess adherence to study treatment. Rescue medication use also was recorded.

Adherence

Additional measures of adherence to treatment included daily e-diary recordings of the number of doses taken and nasal spray device weights before and after use.

Statistical analysis

The study was designed to measure the estimated mean treatment difference between FFNS and placebo in growth velocity of prepubescent subjects. The sample size was calculated to ensure that the 95% CI of the estimated mean treatment difference was no wider than 0.5 cm/y.[4] The intent-to-treat (ITT)