Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone

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Background: The effect on linear growth of daily long-term inhaled corticosteroid therapy in preschool-aged children with recurrent wheezing is controversial.
Objective: We sought to determine the effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing.
Methods: Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores were randomized to a 2-year treatment period of chlorofluorocarbon-delivered fluticasone propionate (176 μg/d) or masked placebo delivered through a valved chamber with a mask and then followed for 2 years off study medication. Height growth determined by means of stadiometry was compared between treatment groups.
Results: In the study cohort as a whole, the fluticasone group did not have significantly less linear growth than the placebo group (change in height from baseline difference, −0.2 cm; 95% CI, −1.1 to 0.6) 2 years after discontinuation of study treatment. In *post hoc* analyses children 2 years old who weighed less than 15 kg at enrollment and were treated with fluticasone had less linear growth compared with those treated with placebo (change in height from baseline difference, −1.6 cm; 95% CI, −2.8 to −0.4; $P = .009$).
Conclusion: Linear growth was not significantly different in high-risk preschool-aged children with recurrent wheezing treated with 176 μg/d chlorofluorocarbon-delivered fluticasone compared with placebo 2 years after fluticasone is discontinued. However, *post hoc* subgroup analyses revealed that children who are younger in age and of lesser weight relative to the entire study cohort had significantly less linear growth, possibly because of a higher relative fluticasone exposure. (J Allergy Clin Immunol 2011;128: 956-63.)

Key words: *Asthma Predictive Index, atopy, clinical trials, early childhood asthma, fluticasone, inhaled corticosteroids, intermittent wheezing, linear growth, research network*

Interpretation of study results evaluating linear growth in childhood asthma is difficult because of competing effects on growth related to the uncontrolled disease itself versus those

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Supported by grants HL071742, HL004519-04, 5U10HL064287, 5U10HL064288, 5U10HL064295, 5U10HL064307, 5U10HL064305, and 5U10HL064313 from the National Heart, Lung, and Blood Institute. This study was carried out in part in the General Clinical Research Centers at Washington University School of Medicine (M01 RR00036) and under Colorado CTSA grant 1 UL1 RR025780 from the National Institutes of Health (NIH) and National Center for Research Resources (NCRR).

Disclosure of potential conflict of interest: T. W. Guilbert has consulted for GlaxoSmithKline, AstraZeneca, MAP Pharmaceutical, Merck/Schering-Plough, and Genentech/Novartis; has designed and presented a CME-accredited series on respiratory syncytial virus disease for Peerpoint Medical Education Institute; and has received research support from Altus Pharmaceuticals, Inspire Pharmaceuticals, and the National Institutes of Health (NIH). R. S. Zeiger has consulted for AstraZeneca, Aerocrine, Genentech, Novartis, Merck and Co, Schering-Plough, and MedImmune and has received research support through Kaiser Permanente or the Childhood Asthma Research and Education Network Clinical Trial from Aerocrine, Genentech, GlaxoSmithKline, Merck and Co, AstraZeneca, and TEVA Pharmaceuticals. R. F. Lemanske, Jr has given lectures for Merck, AstraZeneca, Doembecher Children's Hospital, Washington University, Medicus Group, Park Nicolet Institute, the LA Allergy Society, the Michigan Allergy/Asthma Society, the Medical College of Wisconsin, the Fund for Medical Research and Education (Detroit), Children's Hospital of Minnesota, the Toronto Allergy Society, Beaumont Hospital (Detroit), the University of Illinois, the Canadian Society of Allergy and Clinical Immunology, New York Presbyterian, the American College of Allergy, Asthma & Immunology, and the American Academy of Allergy, Asthma & Immunology; has consulted for AstraZeneca, Map Pharmaceuticals, Gray Consulting, Smith Research, Quintiles/Innovax, RC Horowitz & Co, International Meetings and Science, and Scienomics; has written for Up-to-Date; and has edited a textbook for Elsevier. S. J. Szefler has consulted for GlaxoSmithKline, Genentech, Merck, Boehringer-Ingelheim, Novartis, and Schering-Plough and has received research support from the National Institute of Allergy and Infectious Diseases (NIAID), GlaxoSmithKline, the National Institute of Environmental Health Sciences/Environmental Protection Agency, and the NIH/National Heart, Lung, and Blood Institute (NHLBI). L. B. Bacharier has received honoraria from AstraZeneca; received honoraria and served on an advisory board for Genentech, GlaxoSmithKline, Merck, Schering-Plough, and Aerocrine; and received research support from the NIH/NHLBI. R. Covar has received research support from the NIH/NHLBI. C. A. Sorkness has served on advisory boards for GlaxoSmithKline, Schering-Plough, AstraZeneca, and Novartis and received research support from Schering-Plough and Compleware/Sandoz. F. D. Martinez has served on an advisory board for and received lecture fees from Merck; has consulted for GlaxoSmithKline and MedImmune; has received lecture fees from Pfizer; and has received research support from the NIH. The rest of the authors have declared that they have no conflict of interest.

Further details on the study group are provided in Appendix E1 in this article's Online Repository at www.jacionline.org.

Received for publication July 1, 2010; revised June 6, 2011; accepted for publication June 23, 2011.

Available online August 4, 2011.

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0091-6749/$36.00

doi:10.1016/j.jaci.2011.06.027

Abbreviations used
CAMP: Childhood Asthma Management Program
CARE: Childhood Asthma Research and Education
ΔHt: Change in height from baseline difference
ICS: Inhaled corticosteroid
PEAK: Prevention of Early Asthma in Kids

related to its treatment. Children with persistent asthma of at least moderate severity eventually attain adult height, usually in the predicted range.[1] However, these children might demonstrate a delay in linear growth[2] associated with inhaled corticosteroid (ICS) therapy. In the Prevention of Early Asthma in Kids (PEAK) study, we previously reported that toddler-aged children with recurrent wheeze at high risk for the development of asthma treated for 2 years with fluticasone (176 μg/day) demonstrated a 1.1-cm reduction in height gained at the end of this treatment period caused by a delay in linear growth compared with those treated with placebo.[3] However, after cessation of regularly scheduled fluticasone therapy in the next year, between-group differences were no longer significant because of an increase in linear growth in the ICS-treated group. On the basis of these findings, we hypothesized that the cohort of ICS-treated children overall would have linear growth similar to that of the placebo group 2 years after treatment discontinuation. However, we also evaluated whether particular subgroups of children could be at higher risk for growth-suppressing effects from ICS exposure.

METHODS

A detailed description of the screening, recruitment, design, algorithms for the addition and reduction/cessation of supplementary medications (eg, open-label ICS or montelukast), and criteria for assignment of treatment failure status and statistical analysis for the PEAK trial has been reported in detail elsewhere[4] but will be described briefly here.

Study design and treatments

PEAK is a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison trial of inhaled fluticasone with placebo in children 24 to 35 months (2 years) and 36 to 47 months (3 years) of age at high risk for the development of asthma.[4] These children were treated for 2 years by using an AeroChamber with a mask (donated by Monaghan Medical, Plattsburgh, NY) with fluticasone propionate or Flovent, 44 μg/puff, 2 puffs twice daily, through a metered-dose inhaler or matching placebo (both donated by GlaxoSmithKline, Research Triangle Park, NC), and then randomized treatment was stopped. Adherence was promoted by using a standardized educational approach and measured with an electronic meter (Doser), as detailed previously.[4] The children were then followed for an additional year during which the primary outcome indicators were measured. Of the 285 children in the original study cohort, 204 were enrolled in a 12-month extension and completed the entire 4-year study. The primary safety analysis in the PEAK study was linear growth, and thus continued observation of this cohort was a high priority for the Childhood Asthma Research and Education (CARE) Network. The enrolled children had no clinically significant medical disorders apart from wheezing or allergy and were at high risk for asthma-like symptoms to continue during the school years based on a positive modified Asthma Predictive Index score.[3,5]

Institutional review boards at all participating centers approved the protocol and consent forms; the trial was monitored by the CARE Network's Data and Safety Monitoring Board. The role of commercial sponsors was limited to donating drug and matched placebo, which they did after reviewing the drafted protocol. The text of the manuscript was made available to all the commercial sponsors 2 weeks before submission for finalization for comments.

Outcome measures

Height was measured every 4 months during the 36 months of the study and at the 48-month extension study visit with an upright stadiometer (Harpenden, Holtain, United Kingdom) by using established CARE Network procedures.[4,6] A medical history and symptom evaluation, family and environmental history, and eosinophil count were obtained during the enrollment visit. An exacerbation was defined as the need for a prednisolone course to control asthma-like symptoms as directed by protocol. Skin prick testing with a core battery of 10 allergens in all clinical centers was performed at enrollment.[3,4,7]

Statistical analyses

The primary analysis focused on the difference in linear growth between the ICS-treated group and the placebo-treated group in the 204 children who completed the 4-year study including the extension. Growth was characterized as change from baseline with 2 different metrics: absolute height measured in centimeters and height z scores calculated with age- and sex-standardized growth charts (Centers for Disease Control and Prevention [CDC], 2000).[8] Linear mixed-effects regression with absolute height (in centimeters) or height z score as the outcome was used to model the longitudinal effects of treatment at each study visit while adjusting for baseline covariates and for open-label ICS and oral corticosteroid use during both the treatment and follow-up periods. Linear contrasts were used to estimate the difference between treatment groups with respect to change from baseline at each study visit. We first examined models that incorporated age and weight as continuous variables. These analyses indicated a larger effect of ICSs among the younger children of lesser weight (results are fully reported below). Sensitivity analyses indicated that the results of the stratified analyses were very similar over a range of weight cut points between 15 and 17 kg and age cut points near 3 years. We further examined the effect of ICSs by incorporating an interaction between age dichotomized at 3 years and weight dichotomized at 15 kg. The selected cut points were chosen based on 2 considerations: first, that they were consistent with the effects seen in the continuous variable model, and second, that they were clinically useful. A complete description of the statistical methods is included in the Methods section in this article's Online Repository at www.jacionline.org.

Linear mixed-effects regression was performed with PROC MIXED in the SAS statistical software system, version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Study population

In the original cohort of 285 children, the 2 treatment groups were similar with respect to all baseline characteristics,[3] except for a higher percentage of peripheral blood eosinophils in the ICS group. There were no significant differences in the number of completed clinic visits, dropouts, treatment failures, or serious adverse events between groups.[3] Less than 12% were lost to follow-up (dropouts) in both groups 1 year after treatment discontinuation,[3] with a total of 28% two years after treatment discontinuation, leaving 204 children for analysis (see Fig E1 in this article's Online Repository at www.jacionline.org).

The baseline characteristics of these 204 children who completed the extension study were similar to those of the original study cohort of 285 ($P > .5$ for all, see Table E1 in this article's Online Repository at www.jacionline.org). It should be noted that the results did not change when the analyses also included partial follow-up data from children who did not complete the study or if the models did not include baseline covariates.

Overall growth analysis of the 204 children who completed the 4-year study

Further data on the overall growth analysis of the 204 children who completed the 4-year study can be found in Fig E2 (available