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Does Use of Inhaled Corticosteroid for Management of Asthma in Children Make Them Shorter Adults?

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The purpose of this review is to discuss the effect of daily inhaled corticosteroids (ICSs) on the height of children with asthma. The effect of ICSs on growth and height is dependent on the dose and the therapeutic index of the ICS; however, the effect on final adult height was not clear until recently. New data suggest that if growth suppression occurs with the use of ICSs in children, it is sustained, but not cumulative over the years. The observed reduction in the final adult height is small and does not outweigh the benefits of ICSs, and the growth effect may be minimized by use of newer ICSs and other approaches for management of asthma in children with mild to moderate asthma.

The effect of inhaled corticosteroids (ICSs) on height has been a topic of interest and concern in the pediatric population and has been investigated in different age groups, with different ICS products at different doses and for different durations. Until recently, the effect of ICSs on the final adult height was based on the calculation of projected adult height[1–3] or open label trials.[4] The National Heart, Lung, and Blood Institute's Childhood Asthma Management Program (CAMP) study remains the largest and longest trial in children with mild to moderate asthma. The focus of this review is the recent report of this cohort of children who have been followed to adulthood to address the effect of ICSs on an adult height in a prospective manner.[5]

The original CAMP trial was a randomized, placebo-controlled trial.[1] Over a 2-year enrollment period, 1041 children, 5–13 years old with mild to moderate asthma were randomly assigned to the budesonide dry powder inhaler (DPI) 200 mcg, twice daily; the nedocromil metered dose inhaler 8 mg, twice daily; or placebo and followed for 4–6 years (mean duration of 4.3 years). At the end of the trial, a small transient decrease in the growth velocity in the first 2 years resulted in a mean 1.1 cm decrease in the height of children in the budesonide group compared to the placebo group. The slower growth velocity evident in the first 2 years of treatment with budesonide was similar among treatment arms at the end of the trial.[1] Interestingly, when adult height was projected by using the bone age and other factors, there was no difference between the treatment groups in the projected adult height.[1] At the end of the trial, children were enrolled to an observational study.[5] During this follow-up phase (12.5 years), children were seen by their primary care physician for their asthma management as they made scheduled study visits at CAMP centers for data collection. The height and weight were measured twice daily during the first 4 to 5 years followed by once or twice a year for the next 8 years. Tanner staging was performed till the age of 18 or sexual maturity. The mean age of participants at the end of the observational trial was 24.9 years and the adult height was obtained from 943 participants. The final adult height was defined as the mean of height measurements at the age of 18 and 20 years or older for women and men, respectively. If the height measurement was not performed at these ages, the adult height was defined as the most recent height measurement, which was less than 1 cm greater than the height measured at least one year apart. A multiple linear regression model was used to compare the mean height in the original treatment groups (i.e., budesonide, nedocromil, and placebo) and adjustment was made for age, sex, clinic, race/ethnicity, height, severity of asthma, duration of asthma, and the presence or absence of atopy at the enrollment time. The result showed that the adjusted mean adult height in the budesonide group was 171cm compared to 172.3 cm in the placebo group, a significance difference of 1.2 cm. There was no difference in the mean adult height of the nedocromil group compared to placebo. Looking at the overall duration of the CAMP trail and observational period, the deficit of 1.3 cm in the adjusted mean height in the budesonide group compared to placebo was significant after 2 years of treatment and remained significant at the end of the trial by a 1.2 cm deficit and persisted till the final analysis and end of the observational phase without any progress. The growth velocity differed significantly in the budesonide group

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compared to the placebo group in the first 2 years of the trial and it was primarily among prepubertal children, age 5–10 years. The total dose of ICSs or the cumulative prednisone dose during the trial and observational phase did not affect the adult height. A secondary analysis of the adult height was done in relation to the mean weight with an adjusted dose of daily ICS during the first 2 years of the trial with adjustments for race/ethnicity, sex, Tanner staging, parental height, body mass index, asthma severity, atopy at trial entry, vitamin D level at trial entry, and *in utero* smoking exposure. A lower adult height was significantly associated with a larger daily dose of ICS during the first two years of the trial, Hispanic ethnicity, female sex, higher Tanner staging, atopy, and vitamin D insufficiency/deficiency at baseline. Authors concluded that long-term ICS therapy started at the age of 5–13 years to manage mild to moderate asthma was associated with a mean height deficit of 1.2 cm, which was observed at 1–2 years after treatment, was dose dependent and was sustained into adulthood.

The CAMP trial is the only prospective longitudinal study that was started at childhood and followed the patients to the adulthood to address the issue about attained adult height and use of ICSs in children. Although the attained height was not a primary objective of this trial, the height was monitored regularly, frequently, and precisely with a stadiometer. How should this result be interpreted or applied to the clinical practice? Two components need to be discussed further: patients' characteristics and ICSs. The growth velocity deficit during the first 2 years was mainly reported in prepubertal children on budesonide compared to placebo, which was shown to be a weight-based, dose-dependent effect.[5] Other ICS studies have also shown a greater reduction in prepubertal children compared to pubertal.[6,7] In a study in preschool children, the use of ICSs for two years in children 2–3 years of age with recurrent wheezing and a positive modified Asthma Predictive Index, the younger children and of lesser weight had significantly less linear growth compared to the entire children in the study, which may be explained by an exposure to a higher dose of ICSs.[8] In the CAMP trial, atopy and a longer duration of asthma were identified as independent risk factors for shorter adult height as they have been reported by other studies.[5,9,10]

The second component to discuss is the use of ICSs in CAMP and other trials; clearly, ICSs remain the most effective therapy for persistent asthma.[11] ICSs are the most effective controller medication for improving impairment and reducing risk; furthermore, ICSs are the only medication that decreases mortality due to asthma. It is also well known that systemic absorption (hence, adverse event) of ICSs are dose dependent and can occur with any ICS if a sufficient dose is administered.[12] Studies have shown that growth retardation can occur with low to medium doses of ICSs and it depends on the type of ICSs and the delivery device.[8,13–17] In all of the long-term clinical trials ($\geq$1 year), the study medication dose remained constant at a minimum dose. In CAMP trial, patients were on budesonide DPI, 400 mcg daily for more than 4 years.[1] This fixed dose was chosen to assure the efficacy for both children with mild or moderate asthma (the guideline recommends a dose of 180–400 and >400–800 mcg/day for mild and moderate asthma in children 5–11 years of age). Although the exacerbations were managed by oral corticosteroid bursts and some of the children had to add another ICS to their regimen, a step-down approach guided by an algorithm to decrease the dose of and stop study medication if patients went into remission, but 89% of patients remained at full dose budesonide throughout the trial. The guideline recommendation is to evaluate asthma control after 2–6 weeks from the first consult/visit.[11] Regular follow-up is recommended and it may be from 1–6 months depending on the severity of asthma or patient's reliability. Once asthma is controlled for 3 months, a step down in therapy is recommended to identify the minimum dose of medication.[11] It is also important to identify those children who have asthma symptoms related to season, allergies, or viral respiratory infection. These children may need to be started on a controller medication or a step up during certain seasons. It is now known that the daily use of ICSs early on does not prevent the development of asthma in infants at a high risk of developing asthma[8,18] nor does it prevent the loss of lung function.[1] These findings support frequent follow-up visits to identify the smallest effective dose of ICSs and even seasonal discontinuation of the medication. As more data become available for the use of needed ICSs in children with mild persistent asthma, other approaches may become available to decrease the total exposure dose to ICSs.[19,20] The two clinical trials in children, comparing the use of daily ICSs to as need use of ICS and β_2 agonist in children with mild persistent asthma, reported significant reduction in asthma exacerbation with daily ICS when compared to β_2 agonist.[21,22] Both trials showed a decrease in the growth rate with daily ICSs, but not the other arms. Current data provide opportunity for future trials to identify children who may benefit from a different approach rather than use of daily ICSs.

In conclusion, the data support growth retardation, not suppression, in adult heights of children who were treated with ICSs; however, the effect is sustained and not cumulative. The effect may also be reduced or even eliminated with appropriate selection of ICSs with the highest therapeutic index and considering different approaches in patients with mild to moderate asthma. Close follow up of children on ICSs is highly recommended to find the lowest effective dose and to identify the seasonal pattern or other circumstances associated with increased impairment or risk component of asthma severity. More clinical trials are warranted to identify the patients at a higher risk of growth retardation.

Author Disclosure Statement

Dr. Raissy is coauthor of the CAMP article discussed in this editorial.

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