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The Effects of Inhaled Corticosteroids on Growth in Children

Jim Philip*

Department of Endocrinology, NMC Hospital, Al Mutradeh area, AL AIN, UAE

Abstract: Inhaled corticosteroids (ICS) are recommended as the first-line therapy for children with persistent asthma. These agents are particularly effective in reducing underlying airway inflammation, improving lung function, decreasing airway hyper-reactivity, and reducing intensity of symptoms in asthmatics. Chronic diseases, such as asthma, have growth-suppressing effects independent of the treatment, which inevitably complicates growth studies. One year studies showed a small, dose-dependent effect of most ICS on childhood growth, with some differences across various ICS molecules, and across individual children. Some ICS at the doses studied did not affect childhood growth when rigorous study designs were used. Most studies did not conform completely with the FDA guidance. The data on effects of childhood ICS use on final adult height are conflicting, but one recent well-designed study showed such an effect, clearly warranting additional studies. In spite of these measurable effects of ICS on childhood growth, it is important to understand that the safety profile of all ICS preparations, with focal anti-inflammatory effects on the lung, is significantly better than oral glucocorticoids.

Keywords: Childhood asthma, inhaled Corticosteroids, linear growth.

INTRODUCTION

Inhaled corticosteroids (ICS) have proved effective in the treatment of asthma over the past several decades. Current guidelines for asthma management recommend low-dose ICS as first-line therapy for patients with mild persistent asthma and medium-dose ICS or combination therapy with long-acting beta2-agonists as the preferred therapy for moderately severe asthma [1]. ICS reduce airway inflammation and hyper-responsiveness, decrease symptom severity, and prevent or reduce the occurrence of acute asthma exacerbations. Corticosteroids are effective in the treatment of asthma because of their ability to alter with multiple pathways involved in the inflammatory process [2, 3]. The histological abnormalities that are typical of asthma have been shown to diminish in the airway biopsy specimens, from patients with asthma who have had treatment with ICS. The changes included fewer mast cells, eosinophils and T lymphocytes, in the mucosa and submucosa [4], reduced goblet-cell hyperplasia [5], and decreased vascularity [6].

ICS were developed to target their delivery in to the lungs, to reduce the systemic side effects associated with oral corticosteroids. ICS are usually tolerated well at the recommended doses [7]. However, systemic side effects such as disruption of hypothalamic-pituitary-adrenal (HPA) axis function, bone turnover, osteoporosis, and growth suppression may occur with the use of ICS [8]. Corticosteroids are potent inhibitors of linear growth, exerting various effects at various levels of growth axis [9]. Blunting of pulsatile growth hormone release, inhibition of insulin-like growth factor-1 bioactivity, osteoblast activity and suppression of collagen synthesis and adrenal androgen production are all known mechanisms by which corticosteroids can inhibit growth. Glucocorticoids also inhibit intestinal calcium absorption, increase urinary calcium excretion and promote bone resorption, all of which can negatively impact bone formation and growth. Exogenous corticosteroid in excess of normal physiological requirements can suppress childhood growth.

However, it should be kept in mind that chronic diseases, such as asthma, have growth-suppressing effects by itself and that this can confound studies of ICS on growth. Mechanisms underlying this effect remain obscure, but a growth-suppressing influence of endogenous cytokines and glucocorticoids produced in response to illness and inflammation appear likely. Any resulting delay in the growth process is associated with delays in pubertal development and pronounced growth deceleration in late childhood [10]. In a prospective long-term cohort study of 82 pre-pubertal steroid-naïve asthmatic patients aged 3 years and above, height/age and weight/age Z scores were calculated every three months. A multivariate analysis of the final model showed that severe persistent asthma was associated with a lower height for age Z score ($p = 0.04$) [11].

The systemic side effects associated with ICS may cause reluctance among some physicians and patients to use ICS, especially at higher doses and for longer periods that may be required to control more severe and persistent asthma symptoms [12,13]. Therefore, it is appropriate to carefully examine the possible effects of ICS on childhood growth.

*Address correspondence to this author at the Department of Endocrinology, NMC Hospital, Al Mutradeh area, AL AIN, UAE;
Tel: +97137030300; E-mail: drjimphilip@hotmail.com

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FACTORS INFLUENCING THE BIOAVAILABILITY OF ICS

Inhaled corticosteroids on inhalation, a significant portion of the dose is deposited in the mouth and pharynx, which if not rinsed out of the mouth, may be swallowed and subsequently absorbed from the gastrointestinal tract [14]. The portion of the drug that escapes inactivation by first pass metabolism in the liver enters the systemic circulation unchanged, causes systemic side-effects [15]. The portion of the ICS dose that is delivered to the lungs exerts the desired pharmacological effect. Also a significant portion of the dose that reaches the airways, can subsequently be absorbed into the general circulation, where it can cause systemic side-effects.

Pharmacokinetic and pharmacodynamic properties of ICS such as bioavailability, lipid conjugation, protein binding, and clearance from systemic circulation can contribute to the systemic side effects [16]. ICS used in asthma are budesonide (BUD), mometasone furoate (MF), fluticasone propionate (FP), beclometasone dipropionate (BDP), ciclesonide (CIC) and Flunisolide (FLU). The particle size of the inhaled steroid molecule is an important determinant of the proportion of ICS that is deposited in the lower airways. The smallest airways have an internal perimeter of ≤2 mm [17]. A particle of <5 mm is more likely to be deposited in bronchi and bronchioles whereas particles of ≥5 mm, are often deposited in the mouth and throat [18]. Larger particles (>5 mm), which are deposited in the oropharyngeal cavity, can cause oral candidiasis and hoarseness [19-21]. The particle size, has important bearing on the efficacy and safety profiles of ICS. Particle size distribution differs significantly between currently available ICS formulations [22-25]. Among the ICS, FP delivered by dry-powder inhaler (DPI)), has the largest mass median aerodynamic diameter (MMAD; ≥6 mm), followed by budesonide DPI (≥2.5 mm). CIC and BDP delivered by hydrofluoroalkane (HFA) metered-dose inhaler (MDI), as solution aerosol formulations, have the smallest particle sizes (MMAD of ≤2 mm). The particle size of the MF formulation used in the HFA-MDI is not known. Because of the detrimental effects of CFCs on the ozone layer, formulations of ICS in solution and suspension with HFA propellant have gradually replaced chlorofluorocarbon (CFC) formulations. HFA solution aerosol formulations (e.g. BDP, FLU and CIC) exist as extra-fine aerosols that penetrate more effectively into the peripheral lung, whereas HFA suspension formulations (e.g. FP and MF) retain the same particle size and lung deposition as the CFC formulations [26]. In a study of BDP-HFA and BDP-CFC, 55-60% of the BDP-HFA dose (ex-actuator) was deposited in the lungs, with 29-30% deposited in the oropharynx [27]. In contrast, deposition of the BDP-CFC dose was 4-7% in the lungs and 90-94% in the oropharynx. In another study, lung deposition of FP-CFC was 12-13%, with 72-78% deposited in the oropharynx [28]. The ciclesonide HFA-MDI delivers small particles (MMAD of 1.1-2.1 mm) and achieves delivery of 50% of the inhaled exactuator CIC dose to the lung (34% in the peripheral airway, 36% in the middle airway and 30% in the central airway) in healthy subjects [29]. Similar results were obtained in asthmatic patients [32]. This minimises the oropharyngeal deposition of CIC to 39%, which is a advantage over other ICS [29, 30].

Limited oral bioavailability is advantageous of ICS as systemic side effects can be relatively low. The oral bioavailability of currently available ICS varies widely, from 1% for CIC, MF and FP, to 26% for beclomethasone monopropionate (BMP) [31-38]. The lipophilicity of an ICS, helps the passage of the drug through the phospholipid bilayer of cell membranes. This correlates positively with the pulmonary retention time and volume of distribution of the drug [39]. The lipophilicity of ICS and the active metabolites varies widely: CIC relative lipophilicity (4.0), FP (3.2), MF (2.0), des-CIC (2.5) and BUD (1) [40].

Protein-binding of ICS can occur and varies from 71-99% among currently available ICS [34,37-39,41-44]. The degree of protein-binding controls their unbound systemic concentrations and limits their systemic side-effects, since only the free drug is pharmacologically active. So high protein-binding of an ICS effectively reduces the potential for systemic side-effects. Both CIC and des-CIC are highly protein-bound (99%) in the systemic circulation, thereby reducing systemic exposure to des-CIC and resulting in minimal cortisol suppression [40].

EFFECTS OF ICS ON GROWTH

Short-term (weeks) effects of ICS on growth are assessed by monitoring, linear lower-leg growth rate with a Valk knemometer. Knemometry is very sensitive and can detect changes in lower-leg growth rates up to 0.1 mm [45]. However, knemometry has its limitations. Short-term lower leg growth rates, can not be extrapolated to intermediate or long-term growth, and are therefore relatively inaccurate to predict final height. Long-term effects (≥1 year) of ICS on growth are assessed using stadiometry by measuring statural height with a Harpenden stadiometer. Stadiometry over longer periods (≥1 year) may represent the most appropriate means of evaluating the long-term effects of ICSs on growth. But this can be confounded by factors such as, changes in asthma therapy, systemic use of steroids, pubertal changes, and normal short-term changes in growth rate.

Most of the earlier studies assessing the effect of ICSs on growth conducted were primary efficacy and safety studies with major limitations in their design to evaluate growth as a safety end point. In 2001, the U.S. Food and Drug Administration (FDA) issued guidelines on the study design and methodology for orally inhaled and intranasal corticosteroids for evaluation of their effects on growth in children [46]. The new guidelines recommended a pre-pubertal, Tanner stage 1, [37] mild, persistent asthma subject population and a placebo-controlled study design with a 16-week baseline growth velocity data collection period, a double-blind 48-week treatment period, a 8-week follow up period, and repeated stadiometry measurements.

Beclometasone Dipropionate (BDP)

The Dutch Paediatric Asthma Study Group, comparing BDP with salmeterol showed that children treated with BDP at 200 μg twice daily showed significantly slower growth rates than those treated with salmeterol at 50 μg twice daily

[47]. In an open label randomized study of prepubescent children that were treated with HFA-BDP at 100-200 µg/day or CFC-BDP at 200-400 µg/day, the HFA-BDP group showed a similar, dose-dependent effect on growth from baseline compared with the CFC-BDP group. Results from these studies indicate that BDP may be associated with growth suppression. This little difference in level of effect on growth between the CFC- BDP and HFA-BDP despite large differences in lung delivery of CFC-BDP (4-7%) versus HFA-BDP (55-60%) may be caused by the high oral bioavailability of BDP [48]. In a recent randomized double-blind placebo-controlled trial, TREXA study, involving 5- to 18-year-old patients with mild persistent asthma, linear growth was measured in two groups receiving regular therapy with 40 µg, twice daily of BDP-HFA; one group receiving rescue BDP plus albuterol only; and the other group receiving rescue albuterol only. Compared with the rescue albuterol group, linear growth was 1.1 cm less in both groups using regular twice daily BDP, whereas no significant difference was seen in the BDP plus albuterol rescue group [49]. Another study, further examining the potential effects of ICS on growth in infants and toddlers, indicated no reduction in mean linear growth rates when a MDI-BDP inhaler was administered at a dosage of 200 µg/day [50].

Budesonide (BUD)

In the Steroid Treatment As Regular Therapy in Early Asthma study which was a randomised, double-blind trial in 7241 patients from 32 countries to assess the effects of budesonide in patients who had mild persistent asthma for less than 2 years and who had not had previous regular treatment with glucocorticoids, BUD at 200 µg administered daily *via* a DPI was shown to reduce the growth of children younger than 11 years of age with persistent asthma over 3 years of treatment compared with placebo, with the greatest reduction in growth occurring in the 1st year of treatment and less pronounced but significant reductions in growth during each subsequent year [51]. The reduction in growth was greatest in the first year of treatment (0.58 cm) than years 2 and 3 (0.43 cm and 0.33 cm, respectively). Additionally, growth rate was significantly lower in the BUD group compared with the placebo group in children 5-15 years of age at randomization. No dose-related effect was noted between subjects who received BUD at 200 µg daily (subjects less than 11 years of age at randomization) and those who received BUD at 400 µg daily (subjects more than 11 years of age at randomization) [57]. The CAMP study was designed to evaluate whether continuous, long-term treatment (over a period of four to six years) with either an inhaled corticosteroid (budesonide) or an inhaled non-corticosteroid drug (nedocromil) safely produces an improvement in lung growth when compared with treatment for symptoms only (with albuterol and, if necessary, prednisone, administered as needed). Results from the CAMP study showed that BUD at 200µg treatment administered twice daily *via* a Turbohaler was associated with a lower height after 4-6 years of treatment and slower growth velocity during the 1st year of treatment compared with nedocromil at 8 mg twice daily or placebo [52]. However, subjects reaching pubertal age at the completion of this study limited clear interpretation of the results. The Helsinki Early Intervention Childhood Asthma study investigated the effect of inhaled BUD-DPI in pre-pubertal children with newly diagnosed asthma [53]. In this study, the "continuous" BUD group received BUD at a dose of 400 µg twice daily for the 1st month, and then BUD 200 µg twice daily for 5 months, followed by BUD 100 µg twice daily for 12 months. The "as-needed" BUD/placebo group received BUD at a dose of 400 µg twice daily for the 1st month and BUD 200 µg twice daily for 5 months, followed BUD as needed for exacerbations for 12 months. A third group received 10 mg of disodium cromoglycate (DSCG) three times a day for 18 months. From baseline to 6 months, the mean standing height velocity in both BUD treatment groups was slower than that in the DSCG group. Height velocity increased in both BUD groups from months 7-18, while the as-needed group showed more rapid catch-up growth and a higher growth velocity compared with the continuous BUD group. Height velocity was higher in the DSCG group after 18 months of treatment than both the BUD treatment groups.

In a randomized open-label parallel group study of 52 pre-pubertal children to assess the relationship between short-term lower leg and 1-yr height increase in children with asthma treated with inhaled budesonide 200 µg once daily in the morning or montelukast 5 mg once daily, length of the lower leg and height were measured by knemometry and stadiometry respectively, at study entry and after 2, 4, 12, 20, 28, 36, 44 and 52 weeks. Lower leg and height growth rates were significantly lower in the budesonide than in the montelukast group. Mean 2-weeks lower leg growth rate was 0.17 mm/week in the budesonide and 0.39 mm/week in the montelukast treated children ($p = 0.02$). Mean 1-year height growth rate was 5.51 cm/year in the budesonide and 6.51 cm/year in the montelukast group [54]. A recent study by Zeiger *et al*. looked at changes in height, weight, and head circumference during the use of either placebo, intermittent nebulized BUD (1.0 mg at night), or daily nebulized BUD (0.5 mg twice daily), over the course of a year in preschool children between 12 and 53 months of age and found that the changes were not significant [55].

BUD and Adult Height

Most studies conducted to date have indicated that growth suppression with ICS is transient, and children treated with ICS for asthma attain a final adult height within the expected normal range [56]. A follow-up trial of the CAMP study, however, showed that the decrease in height during the 4.3 years of BUD at a dose of 200µg twice daily versus placebo was significant and remained significant for an additional 4.8 years after the CAMP trial [57]. This height decrease was observed in girls (1.7 cm) but not in boys (0.3 cm only; insignificant). An update to the CAMP study was published in 2012 [58], which showed that the mean adult height was 1.2 cm lower in the BUD group than in the placebo group (P=0.001) and was 0.2 cm lower in the nedocromil group than in the placebo group (P=0.61). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (-0.1 cm for each microgram per kilogram of body weight) (P=0.007). The reduction in adult height in the BUD group as compared with the placebo group was similar to that seen after 2 years of

treatment (-1.3 cm). During the first 2 years, decreased growth velocity in the BUD group occurred primarily in pre-pubertal participants. The authors concluded that, the initial decrease in attained height associated with the use of inhaled glucocorticoids in pre-pubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative [58].

Fluticasone Propionate (FP)

In a study in children with persistent asthma in which subjects received FP at 100 µg twice daily *via* DPI or nedocromil sodium at 8 mg/day *via* MDI, both groups were shown to have similar growth rates. Adjusted mean growth rates were 6.1 cm/year with FP and 5.8 cm/year with nedocromil [59]. Treatment with FP-MDI at 50 µg twice daily or 125 µg twice daily for 6 months has also shown a lack of dose-dependent growth suppression in a study of young infants with recurrent wheezing [60]. In a double-blind, randomized, parallel-group, multicenter study, 325 prepubescent children with persistent asthma and normal growth rates were treated with placebo or inhaled fluticasone propionate powder 50 µg or 100 µg administered twice daily by a breath-actuated device for 1 year. Growth was evaluated monthly, whereas other safety variables and pulmonary function were evaluated periodically. The prepubescent patients showed no statistically significant differences in mean height, mean growth velocity, or mean skeletal age between any of the treatment groups at any time [61]. In contrast to these earlier studies, results from the Prevention of Early Asthma in Kids study in which children who were at high risk for asthma, received FP at 88 µg twice daily with an Aero-Chamber spacer and a face mask or placebo for the first 2 years and then discontinued ICS treatment in the 3rd year (observation year) showed that after 2 years, subjects in the FP group were significantly shorter than subjects in the placebo group. In a more recent study, intermittent treatment with high dose FP (750 µg twice daily) starting at the onset of an upper respiratory tract infection (recurrent wheezing) was associated with slowing of growth compared with placebo in children 1-6 years of age [62].

Mometasone Furoate (MF)

Two studies have examined the growth effects of MF in children with asthma [63, 64]. In the first study, treatment with MF-DPI at 100 µg/day in the morning did not have any significant effect on growth velocity compared to placebo [69]. However, higher doses of MF-DPI (200 µg daily in the morning) did significantly reduce growth velocity compared with placebo. In the second study, children with persistent asthma receiving MF-MDI at 100 µg daily in the evening did not exhibit any effect on growth velocity versus placebo [64]. The use of a daily dose of 100 µg of MF-DPI in children aged 4-9 years with mild persistent asthma is supported by the lack of significant difference in growth velocity and absence of drug-related adreno-cortical effects [64]. However, the relatively small sample size was a limitation in both of these studies. These results suggest that at higher doses MF may have an effect on growth.

Ciclesonide (CIC)

A study of CIC in pre-pubertal children who were randomized to three groups, treatment with placebo, CIC-HFA-MDI at 40 µg daily or CIC-HFA-MDI at 160 µg daily [65]. There was no detectable effect on growth velocity in either CIC treatment group versus placebo after 52 weeks of treatment. In a 12-week multicenter, double-blind, placebo-controlled, study designed primarily for efficacy, children (n = 1073; 6-11 years) with persistent asthma were randomized to CIC at 40, 80, or160 µg (daily in the afternoon) *via* MDI or MDI plus spacer had no effect on growth was detected by stadiometry for any of the doses or delivery methods [66]. The above two studies met the recommendations of the current FDA advisory on evaluating the effects of ICS on growth.

Flunisolide (FLU)

In a double-blind, placebo-controlled study, meeting the recommendations of the current FDA guidance on evaluating the effects of ICS on growth, 218 prepubescent (Tanner Stage 1) children with mild persistent asthma ranging in age from 4 to 10 years were randomized to 2 puffs FLU-HFA twice daily (85 µg/puff) or placebo for 52 weeks. Height was assessed by stadiometry at each visit. At the end of double-blind treatment, mean growth velocity was 6.01 ± 1.84 cm/52 weeks for FLU-HFA and 6.19 ± 1.30 cm/52 weeks for placebo (p value not significant). Mean advancement in bone age during the 1-year study was similar for the 2 groups. This study indicated that in children with persistent asthma, FLU-HFA had no deleterious effect on growth or bone maturation1 year at the highest approved dose [67].

BUD *vs* FP

One study in children 4-12 years of age with moderate-to-severe asthma, who received either FP-DPI at 200 µg twice daily or BUD-DPI at 400 µg twice daily for 20 weeks showed that subjects in the BUD group grew 6.2 mm less than those treated with FP [68]. In contrast, other studies have indicated that FP and BUD have similar effects on growth [69, 70]. No significant change in height velocity was seen between the treatment groups, in a study of 100 children 4-11.5 years of age, 51 boys and 49 girls, with moderate persistent asthma who were randomized to FP-MDI at 125 µg twice daily or BUD-MDI at 200 µg twice daily for 52 weeks [69]. In a study of children with moderate asthma aged, 7-13 years suggested that BUD at a dose of 400 µg/day or FP 250 µg/day no difference in growth rate was seen compared to children in the control group [70].

BUD *vs* CIC

In children with mild persistent asthma 6-11 years of age were randomized to BUD at 400 µg daily (*via* Turbohaler) or CIC at 60 µg (*via* HFA-MDI plus spacer) daily in the evening [71]. Stadiometry was performed in a subset of subjects. At end of the study, at 12 weeks there was significantly less growth suppression in the CIC group

versus the BUD group and there was less evidence of adrenal suppression in the CIC group. However, a Cochrane review comparing the efficacy and side effect profile of CIC with other ICS did not show an advantage of CIC over other molecules [72].

Montelukast *vs* FLP

Children 6-14 years of age, with mild persistent asthma were treated with montelukast at 5 mg daily or FP (*via* MDI) at 100 µg twice daily for one year, in the Montelukast Study of Asthma in Children (MOSAIC study) [73]. The overall growth suppression was more in the FP group versus the montelukast group over the 12 months of treatment.

ICS in Combination with Long-Acting β2-Agonists

In the Pediatric Asthma Controller Trial, 285 children (ages 6-14 years) with mild-moderate persistent asthma were randomized to: fluticasone 100 µg twice daily, fluticasone 100 µg/salmeterol 50 µg in the morning and salmeterol 50 µg in the evening, and montelukast 5 mg in the evening. The observed growth over 48 weeks in all the three groups was comparable, with no statistically significant difference between the groups fluticasone: 5.3 cm; salmetrol and fluticasone combination: 5.3 cm; montelukast: 5.7 cm [74].

In a multicenter, randomized, parallel-group, double-blind study comparing salmeterol/FLP 50/100 µg twice a day compared with FLP 200 µg twice a day in children with symptomatic asthma, no significant differences were found, after 26 weeks of treatment between either groups on growth in children aged 6-16 yrs [75].

In a randomised double-blind, placebo-controlled crossover study to study impact of beta 2 agonist in reducing dose of ICS, and to study effects on short term growth and collagen turnover, formoterol was added to half the glucocorticoid dose in children with asthma treated with inhaled BUD over two six-week periods. Mean lower leg growth rate was 0.14 mm/week ($p = 0.02$) lower in children on BUD 200 µg twice daily than on that during the period of treatment with formoterol and BUD. Identical statistically significant effects on markers of collagen turnover were found, whereas inflammation markers and asthma control did not vary significantly between the two periods [76].

ADRENAL AXIS SUPPRESSION DUE TO ICS

The time of administration of ICS and its impact on growth has also been studied. In a study among children 5.6 -12.5 years of age with intermittent asthma, lower leg growth rate after treatment with 400 µg of BUD-MDI twice daily (administered with a Nebuhaler spacer) for 4 weeks was significantly lower whereas treatment with 800 µg of BUD-MDI once daily in the morning did not suppress growth, suggesting evening dosing may have a greater risk of growth suppression [77]. Children who have severe asthma requiring consistent high dose ICS therapy [78] or who are receiving corticosteroids for coexisting diseases(e.g., dermal for eczema or rheumatological diseases) are at an increased risk for HPA axis suppression. If there is a clinical suspicion of adrenal axis suppression, and if morning plasma cortisol levels are less than 10 µg/decilitre, a low-dose adrenocorticotrophin (ACTH) test is indicated [79]. Reduced cortisol responsiveness to low-dose ACTH suggests the need of additional hydrocortisone for significant illness or injury.

The 2010 Global Initiative for Asthma guidelines have now delineated the appropriate asthma treatment regimen for preschool children aged less than 5 years [80]. It is essential that these children and their families receive appropriate education about asthma, alter their environment to minimize asthma triggers, and then, if that approach alone is not successful, to proceed with a therapeutic regimen that initially includes inhaled beta agonists, augmented with increasing doses of ICS to optimize the patient's asthma management. After the patient has attained control for 3 months, the ICS dose is to be gradually decreased until the minimum necessary dose to maintain control is reached.

BONE METABOLISIM, VITAMIN D SUPPLEMENTATION AND FRACTURES

Studies have been done to investigate the effect of inhaled steroids on bone metabolism, and whether vitamin D supplementation ameliorates these effects. Seventy-five children with new asthma were enrolled into BUD, FLP or cromoglycate treatment groups. The initial BUD dose was 800 µg/day and 400 µg/day after two months. The initial FLP doses were 500 and subsequently 200 µg/day. Bone turnover markers were measured before treatment and after 2 and 4 months of therapy. In the steroid treated children whose height standard deviation score decreased during the first 12 months of therapy, bone formation markers serum osteocalcin (OC) decreased by 20% and carboxyterminal propeptide of type I procollagen (PICP) decreased by 21%, during the initial 4 months both significantly. In the children who did not have growth suppression, the changes were not significant: -4% in OC and +13% in PICP respectively. In children who had evidence of adrenal axis suppression (on the basis of a low-dose ACTH stimulation test), OC decreased more (23%, $p < 0.01$) than in those with normal adrenocortical function (10%, $p = 0.06$) [81]. Population based studies of children aged 4-17 years in the UK estimated incidence rates of fracture among children 4-17 years old taking ICS, have suggested, that the increased risk of fracture is probably a result of the underlying illness, rather than being directly attributable to ICS therapy [82]. In a study supplementation of 25-hydroxyvitamin D did not affect short-term growth or markers of bone turnover in children with asthma treated with inhaled dry-powder BUD 400 µg daily [83].

CONCLUSION

The risk of adverse effects on growth of inhaled corticosteroids can be minimized by using the minimum effective dosage, decreasing systemic availability of the drug through careful selection of the inhalation device and proper technique, the concomitant use of alternative anti-inflammatory agents and, appropriate choice of the ICS medication with least effect on growth. Current evidence from the studies reviewed in this article indicates that ICS treatments for asthma may differ in their effects on growth. However, additional, rigorously-designed studies may be warranted to further clarify the effects of ICS on the degree

of suppression of growth. The 1-year studies show a small, dose-dependent effect of most ICS on childhood growth, with some differences across various ICS molecules. Some ICS types, at the doses studied, did not show an effect on childhood growth when rigorous study designs were used. Most studies did not conform completely with the FDA guidance. The evidence of childhood ICS use on final adult height are conflicting, but one recent study by Kelly *et al*. showed such an effect. In spite of these measurable effects of ICS on the growth, it is important to recall that the safety profile of all ICS preparations, which focus anti-inflammatory effects on the lung, is markedly better than the oral glucocorticoids.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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