

A critical review of the effects of inhaled corticosteroids on growth

Ashton K. Bartholow,¹ Derek M. Deshaies,² Julianne M. Skoner,³ and David P. Skoner, M.D.^{1,4}

ABSTRACT

Inhaled corticosteroids (ICSs) are an effective therapy for the treatment of persistent asthma of all severities because they reduce symptoms, improve lung function, and reduce underlying inflammation. Although ICSs are generally safe for long-term use, there is concern among physicians and patients about potential systemic side effects, including growth inhibition in children. This continued concern of systemic side effects may negatively affect the compliance to ICS treatment. Based on the current guidance to industry from the Food and Drug Administration (FDA), some efficacy and safety studies on ICSs performed in the 1990s had limitations in their design to evaluate the effect of ICS therapy on growth as a safety end point. A review of studies performed with currently available ICSs and their level of conformance with the FDA guidance are presented in this article. The 1-year studies show a small, dose-dependent effect of most ICSs on childhood growth, with some differences across various ICS molecules and across individual children. Some ICSs at the doses studied did not affect childhood growth using rigorous study designs. 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 an effect, clearly warranting additional studies.

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Inhaled corticosteroids (ICSs) are recommended as the first-line controller therapy for adults, adolescents, and children with persistent asthma of all severities.^{1,2} These agents are particularly effective at reducing underlying airway inflammation,^{3,4} improving lung function, decreasing airway hyperresponsiveness, and reducing symptoms associated with asthma. In clinical practice and in accordance with guidelines and recent evidence, ICSs are being used earlier in life, for longer durations, and in patients with milder asthma to help control and manage the disease.^{1,2,5,6} In a recent review of 10 randomized clinical trials comparing patients presenting to emergency departments with asthma symptoms, 33.8% of patients placed on placebo required subsequent hospital admission for their symptoms, compared with 20.8% of those receiving systemic corticosteroid therapy and, most interestingly, only 13.7% of those receiving ICSs, indicating the importance of ICS therapy as first-line treatment in effective asthma management.⁷

ICSs were developed to target their delivery to the lungs, exploiting their known benefit in the treatment

of asthma, while reducing the systemic side effects associated with oral corticosteroids. ICSs are well tolerated at recommended doses;⁸ however, systemic side effects such as disruption of hypothalamic–pituitary–adrenal axis function, bone metabolism, osteoporosis, and growth suppression may occur with the use of ICSs.⁴ The effect of ICS on growth is an important systemic safety concern in children because childhood growth is sensitive to exogenous steroids and the effect of ICSs on growth is evident even at low doses used for treating asthma in children.⁴ Clinical evidence on effect of ICSs on growth is available and a thorough understanding of the relative risks and limitations of this clinical evidence for each ICS is essential for their proper use.

Of note, the 2010 Global Initiative for Asthma guidelines have now further delineated the appropriate asthma treatment regimen for preschool children aged ≤ 5 years.⁹ Similar to older pediatric populations, it is recommended that these children and their families receive appropriate education and counseling about asthma, alter their environment to minimize asthma triggers, and then, if that approach alone is not successful, subsequently proceed with a therapeutic regimen that initially includes inhaled β -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. Patient monitoring is still required after reaching this equilibrium point, however, because asthma can have a variable course. In many

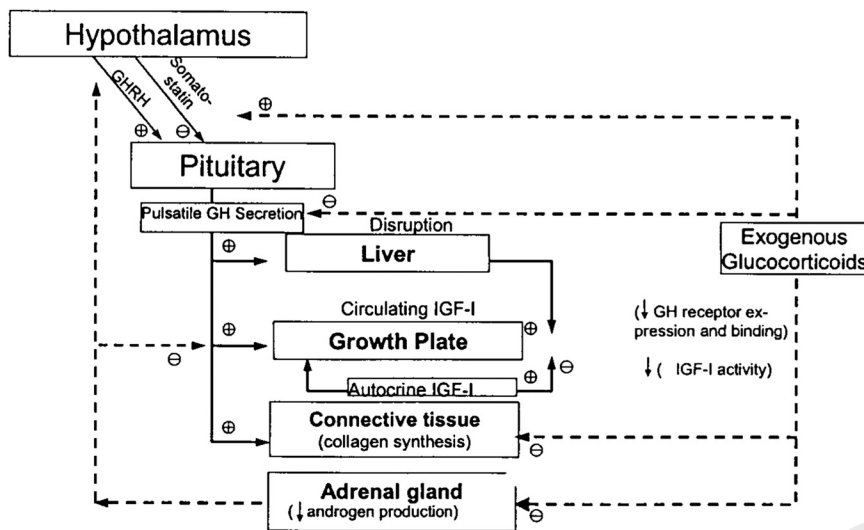
From the ¹Department of Pediatrics, Allegheny General Hospital, Pittsburgh, Pennsylvania, ²Juniata College, Huntingdon, Pennsylvania, ³Saint Francis University, Loretto, Pennsylvania, and ⁴Temple University School of Medicine, Philadelphia, Pennsylvania

D Skoner has served as a consultant for Merck and has participated in Speaker's Bureaus for AstraZeneca, GlaxoSmithKline, Merck, Novartis, and Teva. He has also received grant support from Novartis and Schering-Plough

Address correspondence and reprint requests to David P. Skoner, M.D., Department of Pediatrics Allegheny General Hospital, 420 East North Avenue, Suite 207, Professional Building, Pittsburgh, PA 15212

E-mail address: dskoner@wpahs.org

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cases involving children <5 years old, asthma symptoms may remit, so a formal reassessment should be completed every 3–5 months. If the decision to discontinue the therapy is made, follow-up visits should be scheduled every 3–6 weeks to determine if the patient remains in remission.⁹

EFFECT OF ASTHMA AND ICSs ON GROWTH: CLINICAL CONSEQUENCES

Studies on the growth effects of asthma have shown that most perceived growth failure is caused by pubertal delay and that adult height in asthmatic patients is no different from nonasthmatic patients.^{10–13} Additionally, uncontrolled chronic asthma alone can affect growth by slowing the prepubertal growth spurt, delaying puberty, and slowing the catch-up phase of final adult height.¹⁴ Systemic exposure to ICSs results from inhalation through the oral route as a result of absorption through the gastrointestinal tract and through the lung after deposition and systemic absorption.^{15,16} Potential mechanisms by which systemic exposure to ICSs could impact growth have been suggested (Fig. 1).¹⁷ Irrespective of causality, adverse effects on growth velocity have been noted for most currently available ICSs, although some studies have suggested that the growth-suppressive effects of ICSs are transient, with little impact on final adult height. The systemic side effects associated with ICSs may cause reluctance among some physicians and patients to use ICSs (steroid phobia), especially at higher doses and for longer periods that may be required to help control more severe and persistent asthma symptoms.¹⁸

FACTORS INFLUENCING BIOAVAILABILITY OF ICSs

ity, lipid conjugation, protein binding, and clearance from systemic circulation can contribute to systemic side effects (Table 1).¹⁸ Drug formulation and drug delivery devices may also impact the amount of dose delivered to the lungs and systemic availability.^{19–21} Metered-dose inhaler (MDI) devices, with hydrofluoroalkane (HFA) solution formulations have been shown to deliver a higher fraction of smaller particles to the distal airways than chlorofluorocarbon (CFC) formulations and distribute the drug more evenly throughout the lungs, including the peripheral airways.²² One study compared the efficacy and safety of HFA-beclomethasone dipropionate (BDP) versus CFC-BDP inhalers and indicated that the HFA-BDP inhalers may offer the patient an equivalent therapeutic benefit, while at the same time using a lower medication dosage and showing no increase in the number of adverse events compared with the CFC-BDP inhaler.²³ Another study looked at large-particle CFC-BDP versus small-particle HFA-BDP in terms of improvement of lung function. The study showed that it took three times the dose of CFC-BDP to obtain the same forced expiratory volume in 1 second FEV₁ improvement as obtained by HFA-BDP.²⁴

Table 1 Pharmacokinetic and pharmacodynamic properties of ICSs influencing systemic side effects

Formulation	Pulmonary Deposition (%)	Mass Median Aerodynamic Diameter (μm)	Oral Bioavailability (%)	Receptor Affinity	Lipid Conjugation	Protein Binding (%)	Clearance (L/hr)
BDP/17-BMP*	High 55–60 (HFA-BDP)	1.1	15/26	Low 53/high 1345	No	87 (BDP)	Very high 230/high 120
BUD	Moderate 22–32	2.6	11	Moderate 935	Yes	88	High 84
BUD	Moderate 18	2–3	ND	Moderate 935	Yes	ND	Moderate 30
CIC/ des-CIC*	High 52	1.1	<1/<1	Low 12/high 1200	Yes (des-CIC)	99 (des-CIC)	Very high 228
FP	Moderate 12–20	2.5	<1	High 1800	No	90	High 67–90
FP	Moderate 12	5.4	<1	High 1800	No	90	High 67–90
MF	Moderate 14	4.5	<1	High 2200	No	98	Moderate 53.5

Source: Refs. 16, 18, 22, 51, and 97–107.

*Conversion of BDP to 17-BMP and CIC to des-CIC occurs in the lower airways.

#Administered as nebulized suspension.

ICS = inhaled corticosteroids; BDP = beclomethasone dipropionate; BMP = beclomethasone monopropionate; BUD = budesonide; FP = fluticasone propionate; MF = mometasone furoate; CIC = ciclesonide; des-CIC = desisobutyl ciclesonide; DPI = dry-powder inhaler; ND = not determined.

tions were found to be associated with cortisol suppression and were significantly greater after MDI inhalation versus DPI inhalation.²⁸

Studies have also shown that spacers may increase or decrease lung deposition thereby increasing or decreasing systemic bioavailability.^{19–21,29–34} A study from 2002 further discussed the effects of spacers on lung disposition of FP (220 μg , twice daily [b.i.d.], of CFC-MDI for ≥ 2 days) using both InspirEase (Schering Corp; Kenilworth, NJ) and E-Z Spacer (FSC Laboratories; Charlotte, NC). Blood samples were collected at baseline and 0.5, 1, 1.5, 2, 4, and 6 hours after the last dose and assayed for FP. The results showed that InspirEase delivered $\sim 20\%$ more FP than E-Z Spacer.³³ A more recent study using HFA-FP, with conventional and antistatic valve holding chambers, showed that antistatic valve holding chambers increased lung delivery (indirectly measured by FP plasma concentrations) more than conventional chambers.²⁹

Disease severity may also influence systemic bioavailability. A study in 1999 looked at the relationship between airflow obstruction and suppression of cortisol after inhalation of FP. A placebo or a 500- μg single dose of FP was given at 8:00 in the evening (P.M.) over the course of two nights. Cortisol was measured from 10:00 P.M. to 6:00 in the morning (A.M.). All 28 subjects experienced a decrease in cortisol production after FP inhalation. There was a direct correlation between the fall in cortisol production and the FEV₁ of the subjects. Subjects with the lower FEV₁ values had the smallest amount of change in cortisol production, leading the researchers to conclude that FP has more systemic bioavailability in subjects who have less obstructed airways.³⁵

ASSESSMENTS OF GROWTH

Short-term (weeks) effects of ICSs on growth are assessed *via* knemometry by monitoring short-term, linear lower-leg growth rate with a Valk knemometer.³⁶ Long-term effects (≥ 1 year) of ICSs on growth are assessed *via* stadiometry by measuring statural height with a Harpenden stadiometer.³⁷

Knemometry Studies

Knemometry is very sensitive and can detect changes in lower-leg growth rates up to 0.1 mm.³⁶ However, knemometry has limitations. Short-term lower-leg growth rates, can not be extrapolated to intermediate- and long-term growth and are therefore unable to predict statural growth.³⁸ Nevertheless, knemometry results can be a lead indicator of the long-term effects of ICSs on growth.³⁹ Knemometry studies performed with BDP, budesonide (BUD), and FP have established suppression of growth during 2–6 weeks of treatment.^{40–45} Two knemometry studies with ciclesonide (CIC), how-

Table 2 FDA study design guidance on evaluation of the effects of orally inhaled and intranasal corticosteroids on growth in children

Guidance	Rationale
Study design	
Double-blind, placebo-controlled, parallel-group treatment period ≥ 48 wk	Adequately assess the effects of active agent
Single-blind baseline period of ≥ 16 wk	Adequately characterize baseline growth velocity
Follow-up period (preferably with single-blind placebo or nonsteroid treatment) ≥ 8 wk	Identify 'catch-up' growth effects
Repeated stadiometry measurements (at least three during the double-blind treatment period), cortisol measurements, and pulmonary function	Accuracy of measurement
Adequate sample size to construct 95% confidence intervals for the mean per group (≤ 0.5 cm)	Increased precision for interpretation of treatment effect
Subject population	
Inclusion criteria	
Subjects with mild, persistent asthma for ≥ 6 mo (males = 3 to ≤ 10.5 yr; females = 3 to ≤ 9.5 yr)	Unlikely to enter puberty during a 1-yr study and unlikely to require intervention with oral corticosteroids, which could affect growth rates independently of other corticosteroid administration
Exclusion criteria	
Tanner stage >1 during baseline period	Exclusion of pubescent subjects
Baseline growth velocity less than the 3rd or greater than the 97th percentile	To exclude subjects with growth disorders
Weight and body mass index less than the 3rd or greater than the 97th percentile	
Bone age >1 yr different from the subject's chronological age	Conforming with chronological age within normal range

Source: Ref. 48.

FDA = Food and Drug Administration.

ever, have shown a lack of growth suppression. In the first study, children 6–12 years of age with mild asthma receiving CIC *via* HFA-MDI at 40, 80, or 160 μg once daily (q.d.) showed no significant difference in lower-leg growth rates versus placebo.³⁶ In the second study, children 6–12 years of age with mild asthma received CIC at 160 μg b.i.d., FP at 250 μg q.d. in the A.M and 125 μg q.d. in the P.M., or placebo for 2 weeks. In this study, CIC did not show any statistically significant effect on lower-leg growth rate whereas growth rates in the FP-treated group were slower versus placebo.⁴⁵ These results with knemometry studies suggest the possibility that ICSs differ in their potential to affect childhood growth.

Stadiometry

Stadiometry over longer periods (≥ 1 year) may represent the most appropriate means of evaluating the long-term effects of ICSs on growth; however, this can be confounded by complications introduced by changes in asthma therapy, systemic use of steroids, pubertal sta-

tus, and normal short-term changes in growth rate, which can be abrupt.^{38,46}

Most of the studies assessing the effect of ICSs on growth conducted in the 1990s were primary efficacy and safety studies with major limitations in their design to evaluate growth as a safety end point.⁴⁷ In 2001, after a review of these studies, the U.S. Food and Drug Administration (FDA) issued a guidance on study design and assessment methodology for orally inhaled and intranasal corticosteroids for evaluation of their effects on growth in children (Table 2).⁴⁸ The new guidance recommended a prepubertal, Tanner stage 1,⁴⁹ 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. A review of studies performed to date with currently available ICSs, their level of conformance with the FDA guidance, and their outcomes are presented here (Tables 2–4).

Table 3 Level of conformance of key ICS growth studies with the FDA study design guidance

ICs	Study Design						Subject Population			Data Analysis		
	Primary Safety Study*	Blinded#	Baseline Period§	Placebo Controlled¶	Treatment period	Follow-Up Period**	Growth Assessments##	Disease Severity§§	Age Limits¶¶	Tanner Stage	Bone Age***	Adequate Sample Size###
BDP												
Doull, 1995 ⁹²	✓	✓		✓		✓		✓				
Verberne, 1997 ⁵⁰		✓		✓	✓							✓
Verberne, 1998 ⁹⁰		✓			✓			✓		✓		✓
Pedersen, 2002 ⁵¹	✓				✓			✓	✓			✓
Becker, 2006 ⁷¹	✓	✓	✓		✓			✓				
Martinez, 2011 ⁵⁴		✓		✓				✓				
BUD												
Agertoft, 1994 ⁵⁶	✓		✓		✓			✓				✓
Skoner, 2000 ⁶⁰	✓				✓			✓				✓
CAMP, 2000 ³⁸		✓		✓	✓	✓		✓				✓
Pauwels, 2003 ⁵⁷		✓		✓				✓				✓
Turpeinen, 2008 ⁵⁹		✓			✓			✓				✓
Gradman, 2009 ³⁹	✓				✓			✓		✓		
CIC												
Skoner, 2008 ⁷²	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓
FP												
Allen, 1998 ⁶⁵	✓	✓		✓	✓			✓	✓			✓
Roux, 2003 ⁶³	✓			✓	✓			✓				✓
Bisgaard, 2004 ⁶²	✓				✓			✓				✓
Teper, 2004 ⁶⁴		✓		✓				✓				✓
Guilbert, 2006 ⁶⁶		✓	✓	✓	✓	✓		✓				✓
Sorkness, 2007 ⁸⁷		✓		✓	✓			✓				✓
MF												
Skoner, 2009 ⁶⁸	✓	✓		✓	✓			✓	✓			✓
Skoner, 2011 ⁶⁹	✓	✓		✓	✓			✓	✓			✓
FLU												
Bensch, 2011 ⁷⁷	✓	✓		✓	✓	✓		✓	✓	✓		✓

Source: Ref. 48.

*Safety as a primary end point.

#Double-blind study design.

§Single-blind baseline of ≥ 16 wk.

¶Placebo-controlled study design.

||Parallel-group treatment period of 48 wk.

**Single-blind follow-up of ≥ 8 wk.

##Repeated growth assessment by stadiometry.

§§Patients with mild, persistent asthma for ≥ 6 mo.¶¶Age range (boys = 3 to ≤ 10.5 yr; girls = 3 to ≤ 9.5 yr).|||Tanner stage < 1 during baseline period.***Bone age < 1 yr different from the patient's chronological age.

###Sample size.

✓ = Meets the FDA guidance criteria; BDP = beclomethasone dipropionate; BUD = budesonide; CAMP = Childhood Asthma Management Program; CIC = ciclesonide; FP = fluticasone propionate; MF = mometasone furoate; FLU = flunisolide; ICSS = inhaled corticosteroids; FDA = Food and drug administration.

Table 4 Results of key ICS growth studies

	Subjects (n)	Age (yr)	Formulation	Dose ($\mu\text{g/day}$)	Dose Level	Asthma Severity/Other	Duration of Treatment (wk)	Effect on Growth vs Placebo (unless otherwise indicated)
BDP								
Doull, 1995 ⁹²	94	7–9	CFC MDI	400	High	Mild	28	1 cm
Verberne, 1997 ⁵⁰	67	6–16	DPI	400	High	Mild, moderate	54	0.28 SDS, no placebo
Verberne, 1998 ⁹⁰	177	6–16	DPI	400–800	High	Moderate	54	0.16 (for 400) 0.27 (for 800) No placebo
Pedersen, 2002 ⁵¹	300	5–11	HFA + CFC MDI	100–400	Low–high	Mild, moderate	52	No placebo, NS
Becker, 2006 ⁷¹	360	6–10	CFC MDI	400	High	Mild	56	0.78 cm
Martinez, 2011 ⁵⁴	843	6–18	HFA MDI	80	Low	Mild	44	1.1 cm (0.3 SDS), NS in BDP rescue
BUD								
Agertoft, 1994 ⁵⁶	278	3–11	CFC MDI + DPI	400–800	Medium	Mild, moderate	3–6 yr	No placebo, NS (0.1 cm)
Skoner, 2000 ⁶⁰	670	6 mo to 8 yr	Neb	500–1000	Low, medium	Mild, moderate, severe	52	0.8 cm (for trial A) NS (for trials B, C)
CAMP, 2000 ⁵⁸	1041	5–12	DPI	400	Low	Mild, moderate	4–6 yr	1.1 cm
Pauwels, 2003 ⁵⁷	7241	5–66	DPI	200–400	Low	Mild	3 yr	1.34 cm
Turpeinen, 2008 ⁵⁹	176	5–10	DPI	200–800	Low, medium	Mild	52	1 cm
Gradman, 2009 ³⁹	52	5–11	DPI	200	Low	Mild	52	1 cm vs montelukast, no placebo
CIC								
Skoner, 2008 ⁷²	661	5–8.5	HFA MDI	40, 160	Low, medium	Mild	52	NS, 0.02 cm (for 40 μg) NS, 0.15 cm (for 160 μg)
FP								
Allen, 1998 ⁶⁵	325	4–11	DPI	100, 200	Low	Mild	52	NS
Roux, 2003 ⁶³	174	6–14	DPI	200	Low	Mild	2 yr	NS, no placebo
Bisgaard, 2004 ⁶²	626	1–3	CFC MDI	200	Low	Wheezing*	52	NS, no placebo
Teper, 2004 ⁶⁴	30	7–24 mo	CFC MDI	100, 250	Low, medium	Wheezing*	24	NS
Guilbert, 2006 ⁶⁶	285	2–3	CFC MDI	176	Low	Wheezing*	2 yr	1.1 cm (at end of 24 mo) 0.7 cm (at end of 36 mo)
Sorkness, 2007 ⁶⁷	285	6–14	DPI	100, 200	Low	Mild, moderate	48	No placebo, NS (0.4 cm) vs montelukast

Table 4 Continued							
	Subjects (n)	Age (yr)	Formulation	Dose ($\mu\text{g}/\text{day}$)	Dose Level	Asthma Severity/Other	Duration of Treatment (wk)
MF	Skoner, 2009 ⁶⁸	4–9	HFA MDI/ DPI	100	Low	Mild	52
	Skoner, 2011 ⁶⁹	4–9	DPI	100, 200	Low(100)	Mild	52
FLU	Bensch, 2011 ⁷⁷	4–10	HFA MDI	340	Medium	Mild	52
*Asthma predictive index. ICS = inhaled corticosteroids; BDP = beclomethasone dipropionate; BUD = budesonide; CAMP = Childhood Asthma Management Program; CIC = ciclesonide; FP = fluticasone propionate; MF = mometasone furoate; FLU = flunisolide; MDI = metered-dose inhaler; DPI = dry-powder inhaler; CFC = chlorofluorocarbon; HFA = hydrofluoroalkane.							
		Effect on Growth vs Placebo (unless otherwise indicated)					
		NS (for MDI or DPI)					
		NS (for 100 μg) 0.7 cm (for 200 μg)					
		NS (0.18 cm)					

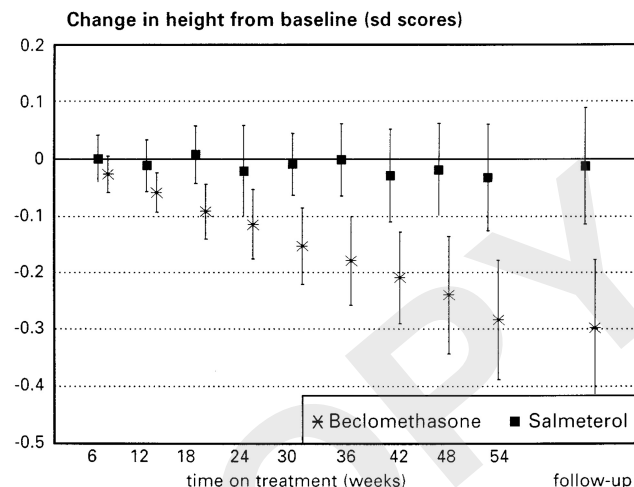


Figure 2. Change in height (standard deviation scores) after treatment with beclomethasone dipropionate (BDP) or salmeterol. SD, standard deviation. (Adapted with permission from Verberne et al., *Am J Respir Crit Care Med* 1997;156:688–695.⁵⁰)

STUDIES ON INDIVIDUAL ICSs (MOST CONDUCTED PRIOR TO THE FDA GUIDANCE AND NOT PRIMARY GROWTH/SAFETY STUDIES) AND THEIR EFFECT ON GROWTH

Beclomethasone Dipropionate

A study comparing BDP with salmeterol showed that children treated with BDP at 200 μg b.i.d. showed significantly slower growth rates than those treated with salmeterol at 50 μg b.i.d. (Fig. 2).⁵⁰ The mean increase in height was significantly lower in BDP-treated subjects compared with salmeterol-treated subjects (Tables 3 and 4).

In a comparative study of prepubescent children that were treated with HFA-BDP at 100–200 $\mu\text{g}/\text{day}$ or CFC-BDP at 200–400 $\mu\text{g}/\text{day}$, the HFA-BDP group showed a similar, dose-dependent effect on growth from baseline compared with the CFC-BDP group (Tables 3 and 4).⁵¹ However, the small number of subjects receiving higher doses and the lack of a placebo control group limited the interpretation of these findings. Wolthers *et al.* conducted an open-label, randomized, crossover study using knemometry to assess short-term lower-leg growth in children ($n = 63$; 5–11 years) with asthma during treatment with BDP-HFA at 100 μg b.i.d. with an AeroChamber Plus (Lupin Pharmaceuticals; Mumbai, Maharashtra, India) spacer and BDP-CFC at 200 μg b.i.d. with the Volumatic (Allen & Hanburys Ltd; Bethnal Green, London, UK) spacer. No statistically significant differences were found between the active treatments. However, results of the pairwise comparisons of active treatments with run-in showed an estimate of difference of -0.09 ($p < 0.01$)

and -0.13 ($p < 0.001$), respectively, corresponding with a relative suppression of 25.0 and 36.1%, respectively.⁵² 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 (Table 1).⁵³

In a recent randomized double-blind placebo-controlled trial involving 5- to 18-year-old patients with mild persistent asthma, Martinez *et al.* documented linear growth in two groups receiving regular therapy with 40 μg , b.i.d., of BDP-HFA; one group receiving rescue BDP plus albuterol only (no regular therapy); and one group receiving rescue albuterol only (no regular therapy). Compared with the rescue albuterol group, linear growth was 1.1 cm less in both groups using regular b.i.d. BDP, whereas no significant difference was seen in the BDP plus albuterol rescue group (Tables 3 and 4).⁵⁴

Another study, further examining the potential effects of ICSs 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 $\mu\text{g}/\text{day}$.⁵⁵

Budesonide

The effect of BUD on growth rates was assessed in one of the longest prospective growth studies (Tables 3 and 4).⁵⁶ Results from this study showed no significant differences in growth rate between the control group (treated with theophylline, β_2 -agonists, and sodium cromoglycate) and BUD groups at study entry, the end of the run-in period, or at the end of the treatment period. However, an exploratory subanalysis of the results suggested that subjects who received high doses of BUD (>400 $\mu\text{g}/\text{day}$) had significantly reduced height compared with the run-in period and to subjects receiving a lower dose of BUD (≤ 400 $\mu\text{g}/\text{day}$).

The effects of BUD on growth were also assessed during the landmark Steroid Treatment As Regular Therapy in Early Asthma and Childhood Asthma Management Program (CAMP) studies.^{57,58} In the Steroid Treatment As Regular Therapy in Early Asthma study BUD at 200 μg administered q.d. *via* a DPI was shown to reduce the growth of children <11 years of age with mild 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.⁵⁷ 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 sub-

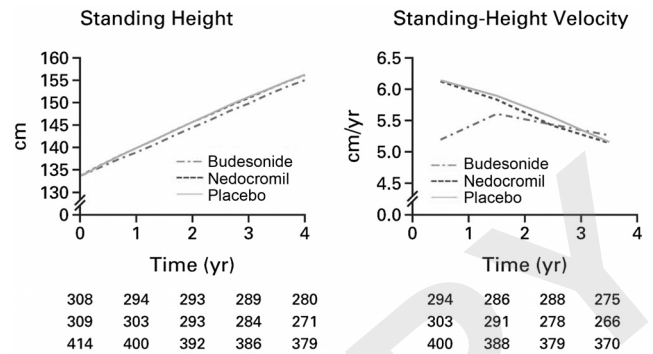


Figure 3. Standing height and growth velocities in children receiving budesonide (BUD), nedocromil, or placebo (Childhood Asthma Management Program [CAMP] study). (Adapted with permission from The Childhood Asthma Management Program Research Group, *N Engl J Med* 343:1054–1063, 2000.^{48,58}).

jects who received BUD at 200 μg q.d. (subjects <11 years of age at randomization) and those who received BUD at 400 μg q.d. (subjects ≥ 11 years of age at randomization).⁵⁷

Results from the CAMP study showed that BUD at 200- μg treatment administered b.i.d. *via* a Turbuhaler (AstraZeneca; Wilmington, DE) 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 b.i.d. or placebo (Fig. 3).⁵⁸ 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 prepubertal children with newly diagnosed asthma.⁵⁹ In this study, the “continuous” BUD group received BUD at 400 μg b.i.d. for the 1st month, and then BUD at 200 μg b.i.d. for 5 months, followed by BUD at 100 μg b.i.d. for 12 months. The “as-needed” BUD/placebo group received BUD at 400 μg b.i.d. for the 1st month and BUD at 200 μg b.i.d. for 5 months, followed by 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; the as-needed group was associated with 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.

A recent study compared the effect of BUD at 200 μg administered q.d. in the A.M. *via* a DPI on growth with montelukast at 5 mg q.d. in prepubertal children with mild asthma.³⁹ In this study, lower-leg growth rate and

height velocity were assessed by knemometry and stadiometry respectively over 52 weeks of treatment. A more pronounced growth suppression was observed with BUD compared with montelukast by knemometry as well as stadiometry after 52 weeks of treatment (Tables 3 and 4).

The effect of treatment with BUD inhalation suspension (BIS) on growth in pediatric subjects was investigated in three independent open-label extension trials.⁶⁰ In the first trial, steroid naïve subjects with mild persistent asthma received BIS up to 1 mg/day or conventional asthma therapy (including short-acting oral or inhaled β_2 -agonists, methylxanthines, cromolyn sodium, or constant or periodic treatment with ICSs). In the second trial, subjects with moderate-to-severe asthma who had bronchodilator and ICS therapy before study entry received BIS up to 2 mg/day or conventional asthma therapy; and in the third trial, subjects with mild-to-moderate asthma who had received either bronchodilator or ICS therapy before study entry received BIS up to 1 mg/day or conventional asthma therapy. A small, but statistically significant, effect on growth was observed in the steroid naïve BIS-treated subjects with mild persistent asthma versus the conventional asthma therapy group, whereas no significant differences in growth were observed between the BIS-treated groups versus conventional asthma therapy groups in the other two trials, indicating the likely effect of disease severity or prior exposure to ICSs on growth in these studies. The majority of evidence from the studies discussed previously suggests that BUD may be associated with transient growth slowing, especially at higher doses.

A recent study done 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 nightly), or daily nebulized BUD (0.5 mg b.i.d.), over the course of a year in preschool children between 12 and 53 months of age and found that the changes were not significant.⁶¹

Fluticasone Propionate

In a study of infants with recurrent wheezing, a lack of growth suppression was observed with FP-MDI at 100 μg b.i.d. administered *via* a Babyhaler (Glaxo-SmithKline; London, UK) spacer compared with sodium cromoglycate at 5 mg administered four times daily *via* MDI and a Nebuhaler (AstraZeneca) spacer device (Tables 3 and 4).⁶² This result is similar to those from a study of children with persistent asthma, during which subjects received FP at 100 μg b.i.d. *via* DPI or nedocromil sodium at 8 mg/day *via* MDI, and both groups were shown to have similar growth rates.⁶³ Treatment with FP-MDI at 50 μg b.i.d. or 125 μg b.i.d. for 6 months has also shown a lack of dose-dependent

growth suppression in a study of young infants with recurrent wheezing,⁶⁴ and no growth suppression was observed in another study of prepubertal children with persistent asthma treated with FP-DPI at 50 μg b.i.d. or FP-DPI at 100 μg b.i.d..⁶⁵

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 b.i.d. with an AeroChamber 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 (Fig. 4; Tables 3 and 4). However, during the subsequent observational year, the growth velocity of the ICS group was greater than that of the placebo group (7.0 ± 1 cm versus 6.4 ± 1 cm).⁶⁶ Although earlier studies with FP indicated no effects on growth, this later result may indicate that a transient growth-suppressive effect is associated with FP. In a more recent study, intermittent treatment with high-dose FP (750 μg b.i.d.) 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.⁶⁷ The results of these studies with FP may warrant further clarification in specifically designed growth studies to help ascertain potential adverse effects on growth and their magnitude.

Mometasone Furoate

Two studies have examined the growth effects of MF in children with asthma (Tables 3 and 4).^{68,69} In the first study, treatment with MF-DPI at 100 μg /day q.d. in the A.M. did not have any significant effect on growth velocity compared with placebo.⁶⁹ However, higher doses of MF-DPI (200 μg q.d. in the A.M.) did significantly reduce growth velocity compared with placebo. In the second study, children with persistent asthma receiving MF-MDI at 100 μg q.d. in the P.M. did not exhibit any effect on growth velocity versus placebo.⁶⁸ 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 cortisol effects.⁶⁹ 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 but additional studies may be required to confirm these observations.

Triamcinolone Acetonide

Growth effects of moderately severe asthmatic patients aged 6–11 years on triamcinolone acetonide (TAA) were compared with asthmatic patients on a

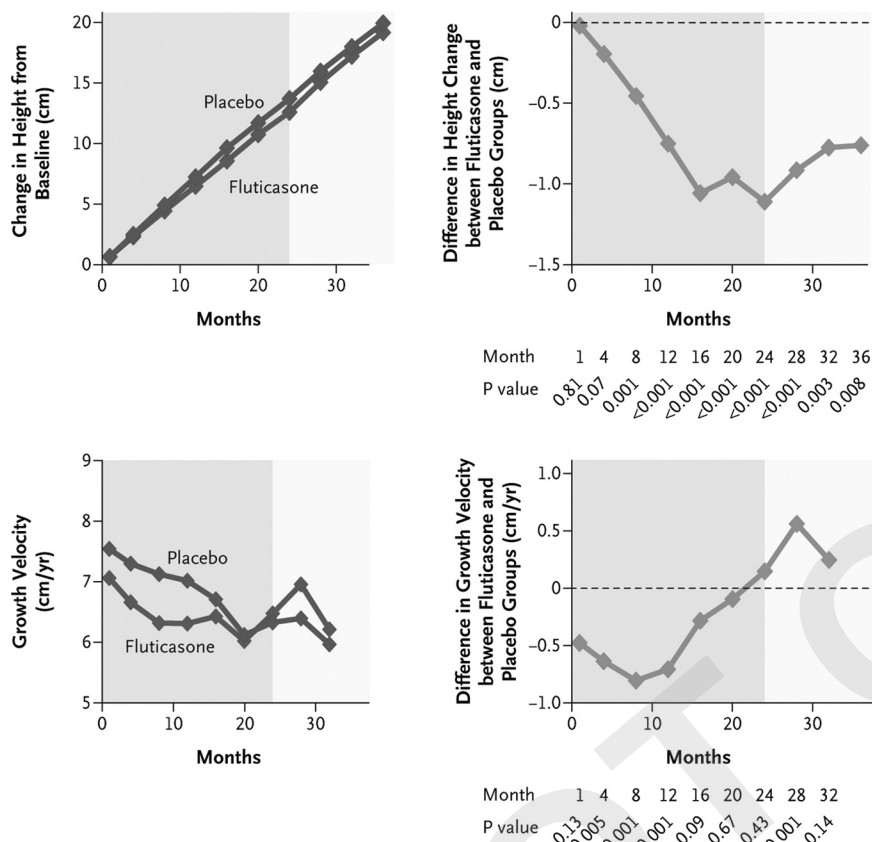


Figure 4. Change in height and growth velocity following 2 years of treatment with fluticasone propionate (Prevention of Early Asthma in Kids PEAK study). Adapted with permission from Guilbert et al N Engl J Med 2006;354: 1985–1997.⁶⁶

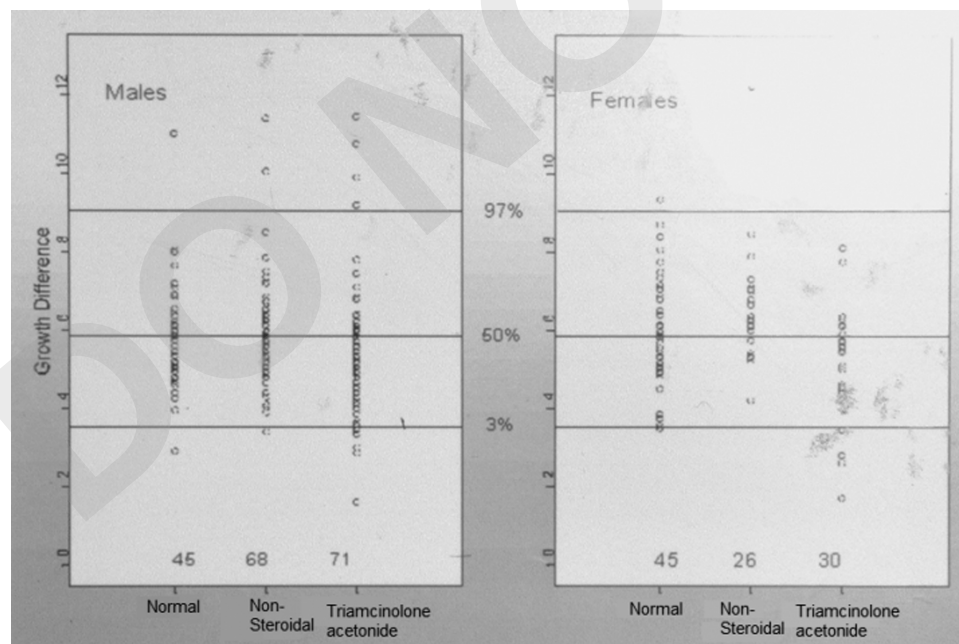


Figure 5. Growth differences of asthmatics on triamcinolone acetoneide (TAA) or nonsteroidal treatment, and untreated nonasthmatic patients in “real-world” study.⁷⁰ The upper and lower horizontal lines indicate the normal range of growth differences for male (left) and female (right) patients.

nonsteroidal therapy in a “real-world” dose titration setting to achieve clinical effect and nonasthmatic children over the course of a year. The TAA group grew 0.79 cm less than the nonsteroidal group and 0.59 less than the nonasthmatic group (Fig. 5).⁷⁰ This study is important because it illustrated that the growth effects seen in highly controlled, fixed-dose ICS studies were

replicated in a real-world setting that allowed ICS dose reductions and more closely resembled what is done in clinical practice. Moreover, the study also illustrated that slowing of growth is only a risk for an individual child on ICSs, because not all are affected. In fact, some of the most rapid growers in the study were using TAA.

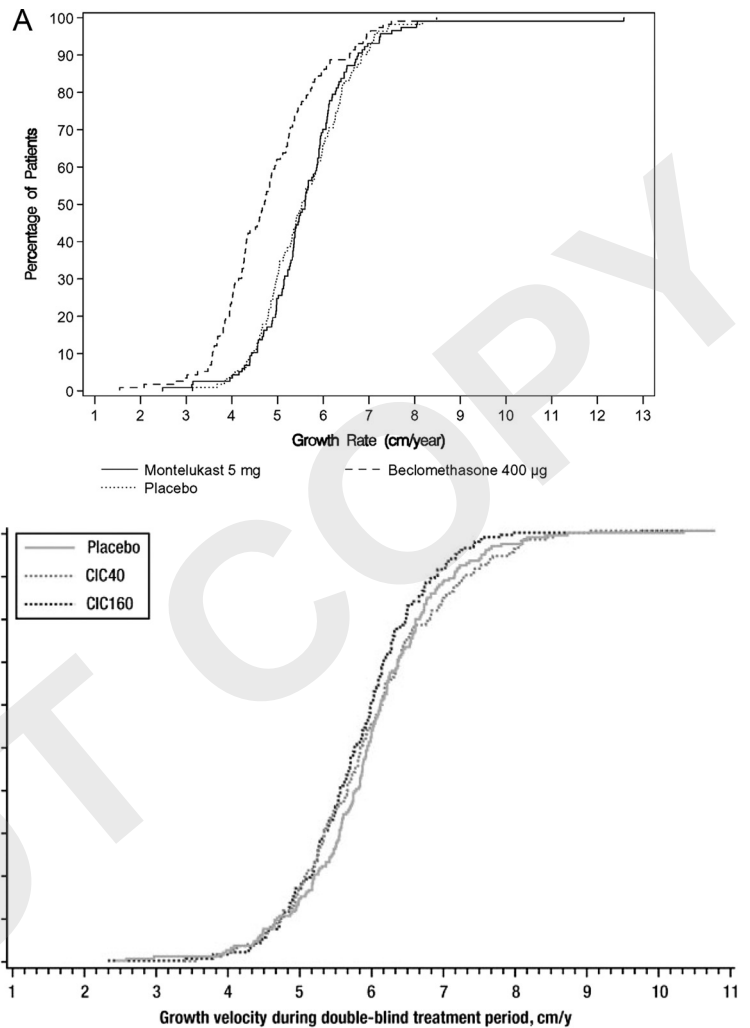


Figure 6. (A) Growth rates after 56 weeks of treatment with montelukast, placebo, or beclomethasone dipropionate (BDP). (Adapted with permission from Becker et al., *Ann Allergy Asthma Immunol* 96:800–807, 2006.⁷¹) (B) Growth rates after 52 weeks of treatment with ciclesonide (CIC). (Adapted with permission from Skoner et al., *Pediatrics* 121:e1–e14, 2008.⁷²)

PRIMARY SAFETY/GROWTH STUDIES CONDUCTED WITH ICSs THAT CONFORMED TO THE FDA GUIDANCE (UNLESS OTHERWISE NOTED)

Beclomethasone Dipropionate

The design of a recent growth study with BDP in children randomized to montelukast at 5 mg q.d., placebo, or BDP-CFC-MDI at 200 µg b.i.d. was in conformance to a high degree with many aspects of the FDA guidance⁷¹ (Tables 3 and 4). The mean growth velocity observed in this study was significantly slower in the BDP group compared with either placebo or montelukast (Fig. 6 A).

Ciclesonide

A study of CIC in prepubertal children who were randomized to treatment with placebo, CIC-HFA-MDI at 40 µg q.d. or CIC-HFA-MDI at 160 µg q.d. (Tables 3 and 4)⁷² was designed to meet the recommendations of the current FDA guidance on evaluating the effects of ICSs on growth in children. After 52 weeks of treat-

ment, there was no detectable effect on growth velocity in either CIC treatment group versus placebo (Fig. 6 B). It is possible that the absence of an effect of CIC on growth may have been caused by poor compliance.⁷³ However, canister weights and diary recordings of medication intake suggested good compliance to the study medication.^{72,74,75} Future studies evaluating the dose-response and proof of medication use and delivery in a safety study may clarify the effect of CIC on growth.

In another multicenter, double-blind, placebo-controlled, 12-week study designed primarily for efficacy (and not safety), children ($n = 1073$; 6–11 years) with persistent asthma were randomized to CIC at 40, 80, or 160 µg (q.d. in the P.M.) *via* MDI or MDI plus spacer and no effect on growth was detected by stadiometry for any of the doses or delivery methods.⁷⁶

Flunisolide

In a double-blind study, 218 prepubescent (Tanner stage 1) children, ranging from ages 4 to 10 years old,

with mild persistent asthma were randomized into groups receiving either 2 puffs (85 $\mu\text{g}/\text{puff}$) of flunisolide (FLU) HFA b.i.d. or placebo. Compliance was determined by self-recording of the number of puffs used as well as weight of the drug canisters when returned to the site. At the end of the 52-week treatment, the mean growth velocity for FLU HFA was 6.01 ± 1.84 cm/yr with a placebo growth velocity of 6.19 ± 1.30 cm/yr ($p = \text{NS}$). During the 1-year study, the bone age, assessed through hand and wrist radiographs, was 0.93 ± 0.46 years and 1.01 ± 0.41 years for FLU and placebo groups, respectively. This study suggested that FLU HFA did not suppress growth or bone maturation over 1 year at the highest approved dose for children with persistent asthma.⁷⁷ (Tables 3 and 4)

HEAD-TO-HEAD COMPARISON OF ICSs AND THEIR EFFECT ON GROWTH

In addition to trials conducted on individual ICSs, several head-to-head studies have been conducted to compare the effects of different ICSs on growth. However, the relative potency, delivery device used, amount of ICS deposition in the lung, and different doses of ICSs being studied should be considered when reviewing and interpreting data from these studies.

BDP versus FP

In a study comparing treatment with BDP-DPI at 200 μg b.i.d. to FP-DPI at 200 μg b.i.d. for 12 months in prepubertal children 4–11 years of age with asthma, BDP-treated subjects showed a significantly slower mean growth rate than FP-treated subjects.⁷⁸ Similar results were observed in another trial comparing treatment with BDP-MDI at 200 μg b.i.d. to FP-MDI at 100 μg b.i.d., both administered *via* a Volumatic spacer for 82 weeks in children 5–10 years of age with moderate-to-severe asthma.⁷⁹ However, in a third study comparing treatment with BDP-MDI at 750 μg b.i.d. to FP-MDI at 375 μg b.i.d. for 12 weeks administered *via* a large volume spacer in children 5–15 years of age with persistent severe asthma, no difference in growth velocity was noted among the treatment groups.⁸⁰

BUD versus FP

A study comparing treatment with FP at 100 μg b.i.d. administered *via* a Diskus (GlaxoSmithKline) to BUD at 200 μg b.i.d. administered *via* a Turbuhaler in children 6–9 years of age with mild-to-moderate asthma for 52 weeks⁸¹ indicated that treatment with BUD resulted in significantly lower mean growth velocity versus FP. Results from other studies have also suggested that BUD has a greater growth-slowing effect when compared with FP.^{43,82} One study in children 4–12 years of age with moderate-to-severe asthma, who received either FP-DPI at 200 μg b.i.d. or BUD-DPI at 400

μg b.i.d. for 20 weeks showed that subjects in the BUD group grew 6.2 mm less than those treated with FP.⁸² In contrast, other studies have indicated that FP and BUD have similar effects on growth.^{83,84} In a study of children 4–11.5 years of age with moderate persistent asthma who were randomized to FP-MDI at 125 μg b.i.d. or BUD-MDI at 200 μg b.i.d. for 52 weeks, no significant difference in linear growth was noted between the treatment groups.⁸³ Similarly, results from a study of children 7–13 years of age with moderate asthma indicated that those treated with BUD at 400 $\mu\text{g}/\text{day}$ or FP at 250 $\mu\text{g}/\text{day}$ had similar growth rates compared with children in the control group.⁸⁴

BUD versus CIC

In a 12-week study, children 6–11 years of age with mild persistent asthma were randomized to BUD at 400 μg q.d. (*via* Turbuhaler) or CIC 1at 60 μg (*via* HFA-MDI plus spacer) q.d. in the P.M.⁸⁵ Stadiometry was performed in a subset of subjects. At study end, the increase in height was significantly greater in the CIC group versus the BUD group.

Montelukast versus FP

In the Montelukast Study of Asthma in Children, children 6–14 years of age with mild persistent asthma were treated with montelukast at 5 mg q.d. or FP (*via* MDI) at 100 μg b.i.d. for 12 months.⁸⁶ The overall growth rate was lower in the FP group versus the montelukast group over the 12 months of treatment.

COMBINATION THERAPIES WITH ICSs AND THEIR EFFECT ON GROWTH

ICSs in Combination with Long-Acting β_2 -Agonists

In the Pediatric Asthma Controller Trial, children 6–14 years of age with mild-to-moderate persistent asthma were randomized to FP-DPI at 100 μg b.i.d., FP-DPI at 100 μg /salmeterol-DPI 50 μg in the A.M. and salmeterol at 50 μg in the P.M., or montelukast at 5 mg in the P.M. for 48 weeks.⁸⁷ No statistically significant effect on growth was observed in the FP, FP/salmeterol, or montelukast group over 48 weeks of treatment. In another multicenter, randomized, parallel-group, double-blind, 26-week study primarily designed for efficacy, Vaessen-Verberne *et al.* also compared the growth effects of salmeterol/FP at 50/100 μg b.i.d. and FP at 200 μg b.i.d. Diskus in 158 children with symptomatic asthma (6–16 years) and no difference was detected by stadiometry.⁸⁸

In another trial of prepubertal children 6–13 years of age with severe asthma, the effect of adding 12 μg of formoterol to BUD-DPI at 100 μg b.i.d. treatment versus BUD-DPI at 200 μg b.i.d. for 6 weeks on lower-leg growth rate was assessed by knemometry. Lower-leg growth rate was found to be lower in the BUD at 200

μg b.i.d. group whereas the addition of 12 μg of formoterol to the BUD at 100 μg b.i.d. group did not affect lower-leg growth rate.⁸⁹

EFFECT OF ICS DOSE AND THE TIME OF ADMINISTRATION OF ICSs ON GROWTH

ICSs are prescribed for treatment of asthma of all severities. However, ICS dose and time of administration (q.d. or b.i.d.) is governed by the severity of the disease, approved dose of the ICS prescribed, and additional nonsteroid therapies as required. ICS administered at higher doses are known to affect growth and use of the lowest effective dose with limited potential for systemic side effects is critical in asthma therapy. In a study by Verberne *et al.*, children 6–16 years of age with moderate asthma receiving BDP-DPI at 200 μg b.i.d. treatment were randomized to additional BDP-DPI at 200 μg b.i.d., salmeterol at 50 μg b.i.d., or placebo treatment for 54 weeks. In subjects already receiving BDP-DPI at 200 μg b.i.d. treatment, an additional BDP-DPI at 200 μg b.i.d. treatment resulted in significant slowing of growth compared with the additional salmeterol or placebo groups showing a dose-dependent effect of BDP⁹⁰ (Tables 3 and 4).

The time of administration of ICSs and its effect on growth has also been evaluated. In a study of children 5.6–12.5 years of age with intermittent asthma, lower-leg growth rate after treatment with 400 μg of BUD-MDI b.i.d. (administered with a Nebuhaler spacer) for 4 weeks was significantly lower whereas treatment with 800 μg of BUD-MDI q.d. in the A.M. did not suppress growth, indicating P.M. dosing may have a greater risk of growth suppression.⁴² This observation is in agreement with the known suppressive effect of ICSs on the hypothalamic–pituitary–adrenal axis by affecting the circadian rhythm of cortisol and nocturnal growth hormone secretion.⁹¹

ONSET AND DURATION OF EFFECT OF ICSs ON GROWTH

The onset and duration of effect of ICS treatment on growth has been evaluated and data from several trials indicate that the largest effect on growth suppression is observed in the initial phase of ICS treatment. In a study of steroid naïve children 7–9 years of age with mild asthma treated with BDP at 200 μg b.i.d. *via* Diskhaler, inhibition of growth in the BDP group versus the placebo was established.⁹² In this study, growth suppression was most apparent during the first 6 weeks of treatment with the majority of growth suppression occurring in the first 18 weeks of BDP treatment compared with placebo. However, when compared with their growth during the steroid naïve period, children's growth in the BDP-treated group returned to their normal growth rate during the re-

maining part of the study.⁹³ Similarly, in the Prevention of Early Asthma in Kids study by Guilbert *et al.*, the effect of FP treatment on growth velocity was prominent in the first 12 months of FP treatment, whereas growth velocity was similar between the FP and placebo treatment groups during the subsequent 12 months of FP treatment.⁶⁶ Growth velocity was higher in the FP group than the placebo group in the following observation year with no FP treatment. In the Helsinki Early Intervention Childhood Asthma Study,⁵⁹ growth velocity was substantially lower during the first 6 months of high-dose BUD at 400 μg b.i.d. followed by BUD at 200 μg b.i.d. treatment period versus the 7–18 months of placebo and low-dose BUD at 100 μg b.i.d. as-needed treatment period. In the 18-month follow-up period, growth velocity was normal within 12 months of initiation of low-dose BUD at 100 μg b.i.d. treatment.

ADULT HEIGHT

Studies conducted to date have indicated that growth suppression with ICSs is transient, and children treated with ICSs for asthma attain a final adult height within the normal range.⁹⁴ A recent follow-up trial of the CAMP study, however, showed that the decrease in height during the 4.3 years of BUD at 200 μg b.i.d. treatment versus placebo was significant and remained significant for an additional 4.8 years after the CAMP trial.⁹⁵ This height decrease was observed in girls but not in boys. Therefore, more studies with appropriate design are needed to determine the effect of ICS on adult height.

An update to the CAMP study was published in 2012 and looked at the final adult height of the subjects in the original, “Long-Term Effects of Budesonide or Nedocromil in Children with Asthma,” published in 2000.⁵⁸ While adjusting for demographic characteristics, asthma features, and height at trial entry, the mean adult height was 1.2 cm lower in the BUD group than in the placebo group. Additionally, the final adult height was 0.2 cm lower in the nedocromil group than in the placebo group. This indicates that the initial decrease in height associated with ICS use in children results in a reduction in the final adult height, although this reduction was not progressive or cumulative.⁹⁶

SUMMARY

The effects of ICSs on growth can be of concern to physicians and parents of children with asthma. Therefore, it is important to establish no detectable effects on growth in children using an ICS in a rigorously designed study to provide confidence, allay concerns, and improve adherence to ICS therapy, thereby potentially improving outcomes. The newly available ICS formulations have relatively low systemic exposure

and fewer side effects. Current asthma therapies with these formulations are aimed at providing relief of asthma symptoms at low doses, improving quality of life, and increasing adherence.

To date, only three studies have been conducted that conform to the elements of the FDA guidance on study design for orally inhaled and intranasal corticosteroids evaluating their effect on growth in children (Table 2).⁴⁸ The first showed a significant suppressive effect of BDP on growth when compared with placebo and montelukast.⁷¹ In the second study, CIC had no detectable effect on growth compared with placebo; however, treatment compliance could not be assured in this study.⁷² In the third study, the highest approved dose of FLU HFA, for children with persistent asthma, did not suppress growth or bone maturation over the course of 1 year.⁷⁷

Current evidence from the studies reviewed in this article indicates that ICS treatments for asthma may differ in their effects on growth. Available long-term data are reassuring, but additional, rigorously designed studies may be warranted to further show the lack of suppression of growth by some of the currently available ICS treatments for asthma. The study design to define the ideal ICS dose, duration, and time of administration should reflect the content of the FDA guidance and include multiple doses to establish a dose-response effect and a "no-effect" dose, a method to reliably monitor adherence, dosing for 3 years with long-term follow-up, and once-a-day dosing preferably in the A.M.,⁴² to minimize the potential effects on the nocturnal growth process. The 1-year studies show a small, dose-dependent effect of most ICSs on childhood growth, with some differences across various ICS molecules and across individual children. Some ICSs at the doses studied did not affect childhood growth using rigorous study designs. 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.

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