Asthma Frequently Asked Questions

What are the effects of inhaled corticosteroids on growth in children?

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Asthma FAQ's

Question 2: What are the effects of inhaled corticosteroids on growth in children?

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Educational aims

To describe the mechanism of inhibitory effects of inhaled corticosteroids on growth

To review evidence from randomized trials and "real life" observational studies regarding medium and long-term effects of inhaled corticosteroids on growth in children with asthma

To summarize the effects of uncontrolled asthma on growth

SUMMARY

This review summarizes the current evidence regarding the effects of inhaled corticosteroids (ICS) on growth in children with asthma. The evidence from randomized trials showed a mean reduction of -0.48 cm/year (95% CI -0.65 to -0.30) in linear growth velocity and of -0.61 cm (95% CI -0.83 to -0.38) in height during a one-year treatment with ICS. Some first-generation drugs had a slightly larger suppressive effect on growth than newer drugs, with a mean reduction in linear growth velocity of -0.91, -0.59, -0.08 and -0.39 cm/year for beclomethasone, budesonide, ciclesonide and fluticasone, respectively. There was evidence of a dose-response relationship, with medium doses (HFA-beclomethasone or equivalent, 100 to 200 μg/day) producing a greater reduction than low doses (50 to 100 μg/day,) in height, but not in linear growth velocity. ICS-induced growth suppression was less pronounced during subsequent years of treatment.

Most "real life" observational studies did not show significant suppressive effects of ICS on long-term growth or adult height, and some studies found an initial growth reduction related to ICS which did not persist in subsequent years. It remains unclear to what extent long-term ICS use in childhood has an effect on final adult height. IIt appears that the deleterious effects of ICS on adult height, if any, are small (max 1.2 cm).

In conclusion, use of ICS in prepubertal children with asthma is associated with a small but dose-dependent depression in growth in the first year of treatment, but no clinically relevant effect on adult height.

Key words: inhaled corticosteroids, growth, growth velocity

1. Introduction

Inhaled corticosteroids (ICS) are the cornerstone of asthma management in children. However, because of the well-known deleterious effects of systemic corticosteroid formulations, numerous studies have assessed the risk of ICS systemic side effects since their introduction in the 1970s. The main concern about systemic side effects relates to linear growth and growth velocity among infants and pre-pubertal children. Novel ICS have been developed with the aim of reducing systemic availability, and improving topical activity. However, each ICS carries a risk of systemic side effects.

2. Mechanism of ICS inhibitory effect on growth

Factors such as bioavailability, receptor-binding affinity, lipid conjugation, protein binding, and clearance from systemic circulation contribute to systemic adverse effects [1]. The systemic effects are related to the glucocorticoid activity of the molecule, the total amount absorbed and the rate of corticosteroid clearance from the body. Systemic bioavailability is the sum of the amount of drug that becomes available systemically after lung absorption and after gastrointestinal absorption [2]. In other words, ICS can only reduce growth after they become available systemically. Systemic side effects of ICS are determined by absorption from the lung and the gut [3].

The amount of ICS reaching the systemic circulation is the sum of the bioavailable pulmonary and oral fractions. The fraction deposited in the mouth will be swallowed and the systemic availability will be determined by absorption from the gastrointestinal tract and degree of first pass metabolism. The fraction deposited in the airways will be almost completely absorbed into the systemic circulation, as there is no evidence of metabolic inactivation of any ICS currently available in airway tissue. The systemic concentration will be reduced by continuous recirculation and inactivation of the drug by the liver [2].

3. Stadiometry and knemometry

Short-term effects of ICS on growth are assessed via knemometry by measuring linear growth of the lower leg within weeks. Several randomized, placebo-controlled, double blind, crossover, knemometry studies have shown dose-dependent growth suppressive effects (roughly, 0.1 mm/week) of ICS [4-7]. However, short-term lower-leg growth rate correlates poorly with statural growth and tends to overestimate potential effects of ICS on medium-term statural growth [2]. Despite these limitations, knemometry is probably superior in assessing the systemic activity of ICS compared to other non-invasive tests such as 24-hour urine free cortisol excretion [8].

4. Medium-and long-term effects of inhaled corticosteroids on growth

4.1. *Evidence from randomized trials*

A large number of randomized trials have assessed the effects of ICS on growth in children with asthma. The trials varied in duration, sample size, drug formulation/delivery device, daily dose, control group, patient's age, and growth measurement.

Medium and long-term effects of ICS on growth are assessed via stadiometry by measuring statural height over months to years. A recent Cochrane review identified 25 randomized trials with duration of at least three months that assessed the effects of ICS on growth in children with mild to moderate persistent asthma [9].

In contrast to the effect on lower leg growth velocity measured by knemometry, which was observed within a few weeks after treatment, a detectable suppressive effect of ICS on the patient's statural height may occur months later. Several 3-month growth studies did not report an effect of ICS on height [10-14]. Statistically significant suppressive effect of ICS on both linear growth velocity and change from baseline in height was observed during a six to eight month treatment period [15-18]. Twenty-one trials provided data on the effects of ICS on growth over a treatment period ranging from 44 weeks to 4-6 years. Compared to placebo or nonsteroidal drugs, ICS significantly reduced linear growth velocity (-0.48 cm/year, 95% CI -0.65 to -0.30) and the mean increase in height (-0.61 cm, 95% CI -0.83 to -0.38) during a one-year treatment period (Figure 1 A and B). There was evidence of a dose-response relationship, with medium doses (HFA-beclomethasone or equivalent, 100 to 200 μg/day,) producing a statistically significant greater reduction than low doses (HFA-beclomethasone or equivalent, 50 to 100 μg/day,) in the mean increase in height, but not in linear growth velocity [9]. There was also evidence of a difference in the effects between six molecules

(beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone and mometasone). Some first-generation drugs had a slightly larger suppressive effect on growth than newer drugs, with a mean reduction in linear growth velocity of -0.91, -0.59, -0.08 and -0.39 cm/year for beclomethasone, budesonide, ciclesonide and fluticasone, respectively [9]. Another Cochrane review identified three randomized trials that compared the effects of ICS at low (50 to 100 μg) versus low to medium (200 μg) doses of hydrofluoroalkane (HFA)-beclomethasone equivalent in 728 prepubescent school-aged children with mild to moderate persistent asthma [19]. A small (0.20 cm/year) but statistically significant difference in linear growth was observed over 12 months, with a lower growth velocity in the higher ICS dose group.

A limited number of head-to-head trials compared the effects of ICS on growth between different molecules (beclomethasone vs. fluticasone, budesonide vs. fluticasone, and budesonide vs. ciclesonide) [4, 20-24]. These trials have confirmed the findings from the Cochrane review, that first-generation drugs have slightly larger suppressive effect on growth than newer drugs. However, the implications of these findings for clinical practice remain uncertain.

Only five RCTs examined the effects of ICS on growth beyond one year. Three had follow-up of two years [16,25,26], one of three years [27], and one four to six years [28]. ICS-related reduction in linear growth velocity during the second year of treatment (-0.19 cm/year, 95% CI -0.48 to 0.11) was smaller than that in the first year of treatment (-0.58 cm/year, 95% CI-0.77 to -0.44). During the third year of treatment, one trial [28] showed no statistically significant difference in linear growth velocity between ICS and placebo, and another trial [27] revealed a smaller difference than that observed in the first year of treatment (-0.33 cm, 95% CI -0.52 to -0.14 vs. -0.58 cm, 95% CI -0.76 to -0.40). It remains unclear why ICS-induced growth suppression is less pronounced during subsequent years of treatment than during the first year of treatment. Decreased adherence to treatment with ICS over time has been postulated to contribute to this phenomenon, but a recent observational study [29] did not confirm this hypothesis. An increased additional use of inhaled and systematic corticosteroids over time in the control group due to poor asthma control may also attenuate long-term effects of ICS on growth in the intervention group.

Four trials monitored growth after treatment cessation for periods ranging from two to 12 months. Three trials [13,15,30] failed to find significant catch-up growth two to four months after treatment with ICS (beclomethasone, ciclesonide or mometasone) was stopped. One trial [16] showed accelerated linear growth velocity 12 months after cessation of

treatment with fluticasone, but the difference of 0.7 cm in height between the fluticasone and placebo groups remained at the end of the three-year trial.

The main concern of parents and health care practitioners is whether ICS use in childhood may have a negative impact on final adult height. An extended follow-up of the CAMP trial [28] provides information on this issue. Although statural growth was not the primary outcome of this trial, height was measured regularly and precisely with a stadiometer during the 4-6 years of the study. Follow-up of the trial participants to the age of 25 (SD 3) years showed that children treated with budesonide 400 μg/day for a mean duration of 4.3 years during prepubertal age had a mean reduction of 1.20 cm (95% CI -1.90 to -0.50) in adult height compared to those treated with placebo. The effect size was similar as that observed after two years of treatment in prepubertal age (-1.3 cm, 95% CI -1.70 to -0.90). These results from a single valid and well-designed large RCT suggest that the initial decrease in height associated with ICS use in prepubertal children results in a small reduction in final adult height which was already present after 1 year of treatment. The effect of ICS on growth appears to be neither progressive nor cumulative, therefore.

Although RCTs are considered to be the gold standard of studying treatment effects, concerns have been raised on the external generalizability of RCT results. First, ICS-induced suppressive effects on growth are likely to be inflated in most one-year growth trials due to enrollment of prepubertal children with mild persistent asthma who may be more sensitive to the growth-suppressive effect of ICS than children with moderate or severe asthma. Second, long-term trials such as CAMP use fixed dose of ICS, which is not representative of long-term clinical practice in which ICS dose is being tapered off once asthma control has been achieved. Therefore, results from long-term observational studies in which children with asthma on long-term ICS treatment in normal clinical practice provide useful additional information on the long-term growth effects of ICS in clinical practice.

Insert Figure 1 A. Effects of ICS on linear growth velocity (cm/year) during a one-year treatment period

Insert Figure 1 B. Effects of ICS on mean increase in height (cm) during a one-year treatment period

4.2 *Evidence from "real life" observational studies*

We identified 11 prospective "real life" observational studies [29-31], that assessed the effects of ICS on growth in children with asthma (Table 1). Two studies [37,39] were population-based, and the remaining studies were hospital or clinic-based. Most studies [29-32, 34, 35,38,40] did not show significant suppressive effects of ICS on long-term growth or adult height, and some studies found an initial growth reduction related to ICS which did not persist in subsequent years [33,36]. Only one study took electronically assessed adherence into account [29] which is critically important as ICS adherence is usually low. These results corroborate the findings of randomized trials. However, confounders, lack of data on adherence to treatment, high withdrawal rate, asthma severity, and poor control are the main limitations of "real life" observational studies. One prospective observational study [32] showed that children with asthma who had received long-term treatment with budesonide attained normal adult height. This study followed the participants of another prospective controlled study in which 332 (270 budesonide, 62 controls) prepubertal children with asthma were enrolled. However, caution should be taken in interpreting the findings of this study because only 48% (142 budesonide, 18 controls) of original enrolled patients were included in the final analysis of adult height.

Insert Table 1

5. A short case report

A male presented as at 6 months of age with his first episode of wheezing when diagnosed with bronchiolitis. He was then hospitalized several times due to acute asthma, with unequivocal responsiveness to inhaled bronchodilators. At the age of two, beclomethasone (1,000 mcg beclomethasone) was given and due to the asthma severity, during the four following years received combined therapy (salmeterol + fluticasone, 500 mcg). Apart from several courses of oral corticosteroid, until six years, he was hospitalized eight times in intensive care unit, one with mechanical ventilation. It was only, from the age of six, that his stature was systematically monitored and he started to use formoterol + budesonide (800 mcg) and, from that moment the adherence rate was systematically assessed through the counter coupled to the inhaler and was always higher than 80%. In order to obtain better control between seven and eight years, he used 1,200 budesonide daily. His growth curve (see below, Figure 2) shows that initially it falls from 0.6 to 0.3 Z-score (probably related to the cumulated effect of high doses of inhaled and courses of oral corticosteroid) then, the fall is interrupted and, nowadays, at 11 years, pubertal growth spurt is clearly featured. Finally, it is worth noting that basal cortisol assessed several times under inhaled corticosteroid and during some of the oral corticosteroid courses revealed adrenal suppression and bone densitometry showed no abnormalities.

6. Effects of uncontrolled asthma on growth

As is the case with any chronic disease, asthma itself may reduce growth. Although this attenuation of growth is highly variable between individual patients, it appears to be related to the severity of the disease, being most pronounced in chronic, poorly controlled asthma [3]. Studies on the effects of asthma on growth have shown that the most perceived growth failure is caused by pubertal delay and that adult height in asthmatic patients is no different from non-asthmatic patients [41]. Chronically uncontrolled asthma, however, can affect growth by itself by decreasing the prepubertal spurt, delaying puberty, and slowing down the catch-up phase of adult final height [42].

7. Final remarks

The effects of ICS therapy on growth over a period of weeks to months are dose dependent. Thus, even if ICS is used for many years, they are unlikely to cause permanent growth retardation or reduced adult height in asthmatic children [3].

Although the risk of this suppression of growth is greatest when high doses of ICS are used, clinically significant growth suppression can occur in any dose of ICS in any patient. This suggests that reduced growth during ICS therapy is an idiosyncratic event - the result of increased individual patient sensitivity in particular to the systemic side effects of corticosteroids [3].

Higher doses should be used with caution in any patient as they only slightly improve efficacy but substantially increase the risk of side effects (including reduced growth). It is important to emphasize that the general evidence that argues against a clinically relevant and persistent retarding effect of ICS growth on childhood asthma does not exclude a clinically relevant effect of slowing the growth of ICS in an individual case.

Thus, if a patient grows well during the first 6 months of ICS therapy, it appears that the risk of this subsequent development of this patient's development is small. However, it is important to continue monitoring growth in all asthmatic children using ICS. Only then can individual cases of delayed onset of puberty or significant growth retardation be identified. If the growth chart shows reduced height growth of > 0.25 SD/year, or > 1 SD overall, , further investigation is required.

The most common cause for suppression of prepubertal growth in asthmatic children using inhaled corticosteroids is the late onset of puberty; this can be easily diagnosed by physical examination and when delayed puberty is suspected a determination of bone age [3].

Finally, even in the rare case of truly clinically relevant growth suppression due to inhaled corticosteroid therapy, the reasons for continuing therapy (well controlled asthma) almost always outweigh the reasons for withdrawing treatment (slower growth) [3].

Take home messages

Use of ICS in prepubertal children with asthma is associated with a small but dose-dependent suppression in growth in the first year of treatment, but the well-established benefits of ICS may outweigh the potential risk of this small growth reduction in children with persistent asthma.

It remains unclear to what extent long-term ICS use in childhood has an effect on final adult height. Awaiting additional long-term prospective "real life" studies, it appears that the deleterious effects of ICS on adult height, if any, are small (max 1.2 cm).

Clinicians are recommended to use the minimally effective ICS dose in children, and to monitor growth regularly during treatment.

First-generation drugs may have larger suppressive effect on growth than newer drugs, but the clinical implications of these findings remain uncertain. Selection of ICS should be based on the efficacy, overall safety profile, cost, ease of use, and availability.

Future research directions

More real life studies (it's unethical having a group without ICS, the first line medicine for asthma), ideally with data analysis on adherence, different molecules, blind and independent assessment of height, daily dose, treatment duration.

Studies protocol and/or statistical analysis shouldn't look not only for the prescribed dose of ICS but also on the role of asthma severity/symptom control.

Special attention should be given on studies assessing growth among patients suffering from severe asthma whose generally use highest doses of ICS.

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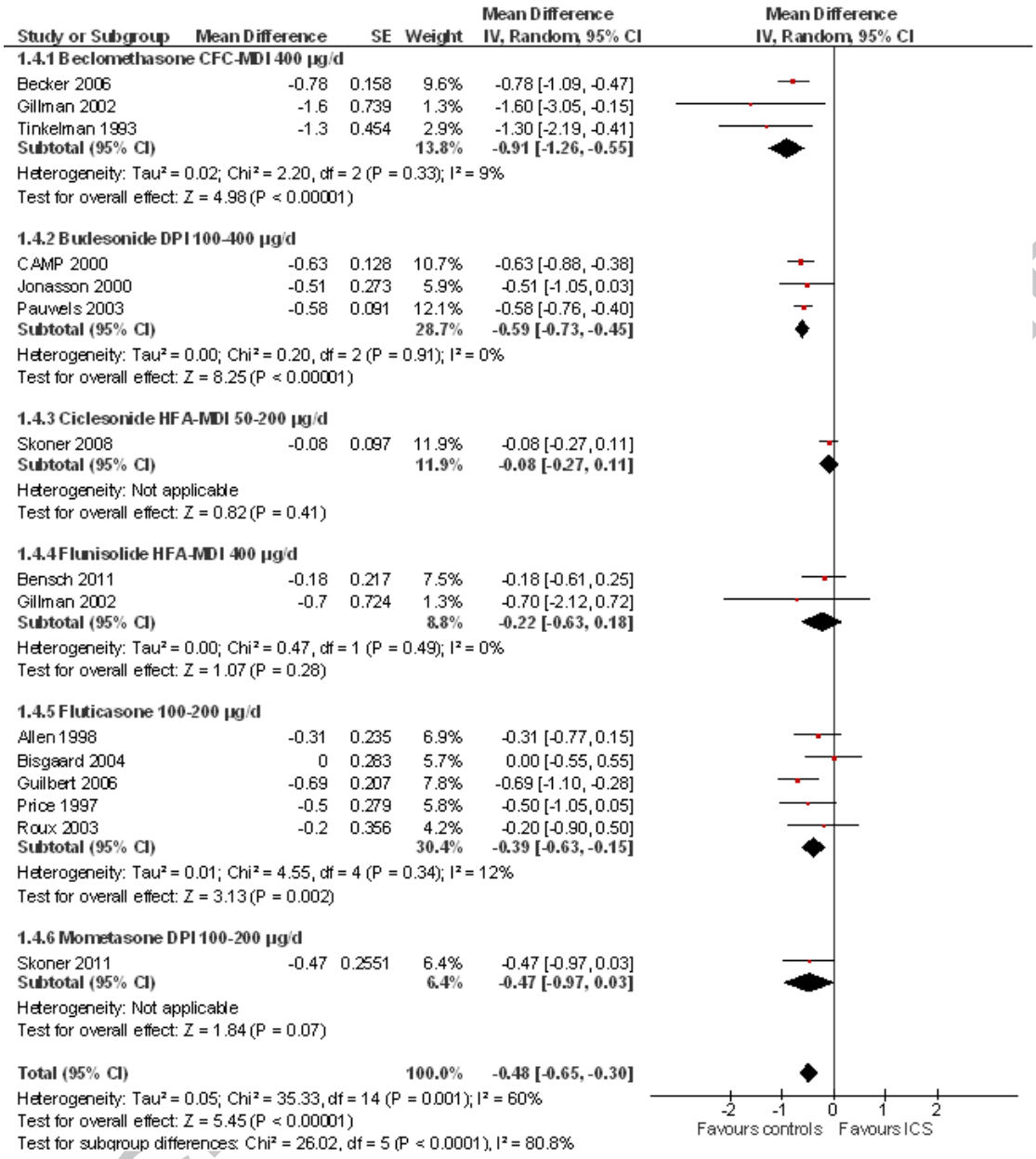
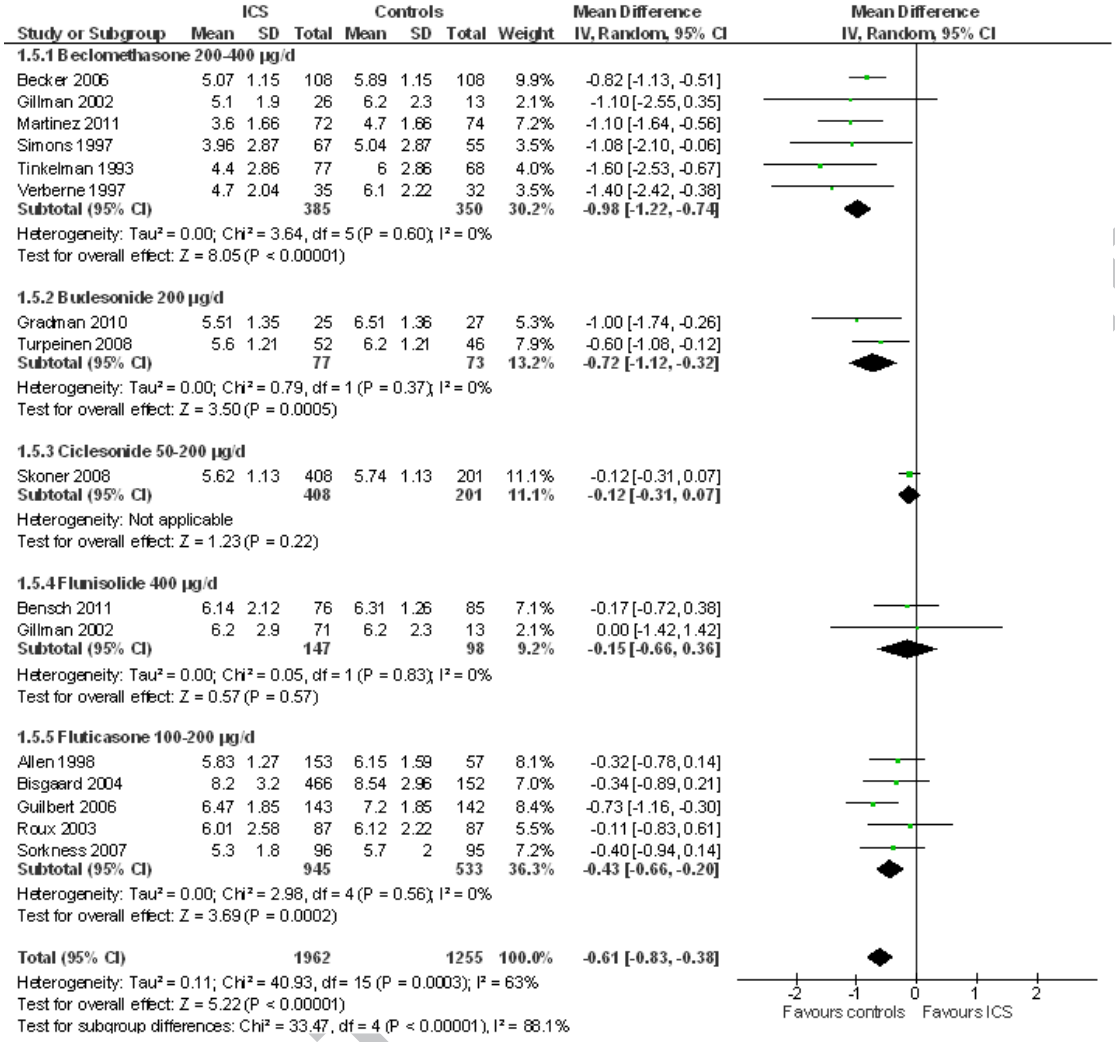


Squares represent point estimates and *horizontal lines represent 95%* CIs of the weighted mean difference between ICS and control. Diamonds represent pooled estimates.



Squares represent point estimates and *horizontal lines represent 95%* CIs of the weighted mean difference between ICS and control. Diamonds represent pooled estimates.

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FIGURE LEGENDS

Figure 1 A. Effects of ICS on linear growth velocity (cm/year) during a one-year treatment period

Squares represent point estimates and *horizontal lines represent 95*% CIs of the weighted mean difference between ICS and control. Diamonds represent pooled estimates.

Figure 1 B. Effects of ICS on mean increase in height (cm) during a one-year treatment period

Squares represent point estimates and *horizontal lines represent 95*% CIs of the weighted mean difference between ICS and control. Diamonds represent pooled estimates.

Figure 2. Growth curve of the reported case

Table 1. Characteristics and main findings of prospective "real life" observational studies

Insert Table 1. Characteristics and main findings of prospective "real life" observational studies

Study	Participants	ICS and dose	Statural growth assessment	Main findings
Agertoft 1994	Children (3-11 yr) with mild and moderate asthma (216 ICS, 61 no ICS)	Budesonide at mean daily dose decreasing from 710 to 430 µg according to guidelines for 3 to 6 years	Height was measured by the same two nurses at 6 months interval during study period	Compared with run-in (1-2 yr corticosteroid-free period) and with the control group, budesonide did not cause any statistically significant changes in growth rate.
Agertoft 2000	Participants of Agertoft 1994 study (142 ICS, 18 no ICS) and 51 healthy siblings	Budesonide at a mean (range) daily dose of 412 (110 to 877) µg for a mean of 9.2-year treatment (3 to 13 years)	Height was measured by the same three nurses at 6 months interval until attainment of adult height	The mean differences between measured and target adult heights were +0.3 cm (95% CI -0.6 to +1.2) for the budesonide group, -0.2 cm (95% CI -2.4 to +2.1) for asthmatic controls, and +0.9 cm (95 % CI -0.4 to +2.2) for healthy controls. The adult height depended significantly on the child's height before budesonide treatment.
Anthracopoulos 2007	Prepubertal children with mild to moderate asthma (322 budesonide, 319 fluticasone)	The median initial daily dose was 400 µg for budesonide and 200 µg for fluticasone; the median maintenance daily dose was 200 µg for budesonide and 100 µg for fluticasone, for at least 6 months	Height was measured according to standardized techniques at 6, 12, 24, and 36 months of treatment, and 6 months after cessation of treatment	During the first 6 to 12 months, a decrease in height SD score of approximately 18% below baseline values was noted that was restored to almost baseline average levels by 24 months, and slightly increased to above baseline during the third year. No differences were found between budesonide and fluticasone regarding height SD score and height velocity SD score at any time point.
Arend 2006	124 children (3-16 yr) with persistent asthma taking ICS (62 beclomethasone, 43 budesonide, 9	Mean (SD) daily beclomethasone equivalent dose was 594 (264) µg for ICS plus INC, and 494 (314) µg for ICS alone, for at least one year	Height was measured by the same three investigators at one to three months interval during one year	Compared to NCHS growth curves, there was no significant reduction in the height of children and adolescents with asthma taking ICS for more than one year at doses recommended by guidelines.

	fluticasone)			
Camargos 2010	82 prepubertal steroid-naïve children with moderate to severe persistent asthma	Beclomethasone at a mean (range) daily dose of 351.8 (137 to 1140) μg for a mean of 5.2-year treatment (2.3 to 6.1 years)	Height was measured by the same pediatric pulmonologist according to standardized technique at 3 months interval	Height for age Z score was not affected by either duration of treatment or daily dose of beclomethasone. The multivariate analysis showed that severe persistent asthma was associated with lower height/age Z score.
Lasmar 2016	80 prepubertal children (3 to 9.5 yr) with asthma taking daily ICS	Beclomethasone at 3 daily doses: < 500 μg, 500-750 μg, and > 750 μg for a mean (SD) of 3.50 (1.39) years. 24% (19/80) of patients were exposed to both ICS and INC	Height was measured according standardized technique at 3 months interval for at least 2 years	Linear growth velocity was similar between 6 groups: < 500 μg, no INC; < 500 μg plus INC; 500 to 750 μg, no INC; 500 to 750 μg plus INC; > 750 μg, no INC; > 750 μg plus INC. An initial reduction of growth velocity related to use of beclomethasone > 500 μg, particularly combined with INC, did not persist during subsequent years of follow- up.

Table 1. continued

Study	Participants	ICS and dose	Statural growth assessment	Main findings
McCowan 1998	2355 children with asthma or asthma related features, from Tayside growth study and Tayside childhood asthma project, with a mean age of 9.7 yr at the last growth measurement	Distribution of patients based on BTS treatment step: 0 (n=1924), 1 (n=435), 2 (n=61), 3 (n=174), and 4 (n=259)	Tayside growth study accurately measured the height of children every two years	Children who were receiving > 400 μg daily of ICS and who were attending both hospital and general practice for asthma care had lower height than average, independent of the effect of deprivation. Children receiving high doses of ICS also showed lower growth rates.

Ninan 1992	58 prepubertal children with asthma	Budesonide or beclomethasone at a median (range) dose of 800 (200-1600) µg for a median duration of 2.7 (1-5.1) years	Height was measured by nurses according to standardized technique	Good control of asthma correlated significantly with the height velocity SD score, both before and after ICS was started. No evidence was found that use of ICS has an adverse effect on growth.
Protudjer 2015	2746 children and adolescents from a longitudinal, population-based cohort, of whom 182 had asthma	Parent-reported data on asthma and ICS use in the previous 12 months	Height was measured at clinic at 8 years, and child-reported at 12 years	Children with asthma averaged 0.93 cm (95% CI 0.35-1.50) shorter than children without asthma. Children with asthma using ICS were 1.28 cm (95% CI 0.62-1.95) shorter than those with asthma without using ICS.
Volovitz 1993	15 children (2-7 yr) with severe perennial asthma	Budesonide at daily dose of 200 µg for 3 to 5 years. Twice annually, treatment was stopped if the child's clinical condition would permit. Adherence (mean of 82%) was assessed *by counting the number* of remaining doses in the inhaler	Height was measured by a trained nurse at each visit	The mean (SD) height velocity during the first year of treatment with budesonide, which was in the 60th (23) percentile for normal children, did not change throughout the treatment period, 66th (17).
Wardenier 2016	99 prepubertal children (2-13 yr) with asthma taking ICS for ≥ 3 months	Fluticasone at low-to-moderate doses, for at least 3 months before the start of the study, and continued for one year. ICS dose was adjusted based on the degree of asthma control. Adherence (median of 84%) was electronically assessed	Height was measured by trained nurses or pediatricians at each visit	The negative correlation between cumulative ICS dose and height growth velocity became non-significant after adjustment for age and sex in a multiple regression model. One year of ICS treatment in guideline recommended dosages with high adherence did not result in significant or relevant growth suppression.

BTS: British Thoracic Society; INC: intranasal corticosteroids; NCHS: National Center for Health Statistics; SD: standard deviation