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REVIEW

Evaluating the effects of asthma therapy on childhood growth: what can be learnt from the published literature?

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Evaluating the effects of asthma therapy on childhood growth: what can be learnt from the published literature? J. Price, P. Hindmarsh, S. Hughes, J. Efthimiou. ©ERS Journals Ltd 2002.

ABSTRACT: The difficulties of assessing the effects of asthma therapy on childhood growth were explored in the first part of this review. In this part of the review growth studies with inhaled corticosteroids were selected that included a control group, measured height by stadiometry and were of ⩾1 yr duration. The studies were classified as type 1 (placebo control), type 2 (nonsteroidal therapy control), type 3 (comparator inhaled corticosteroid control) or type 4 ("real-life" studies with dose adjustment). The design attributes of these studies were then compared with the recommendations described in the first part of this review. Of the 18 studies identified, 17 were susceptible to one or more important confounding factors. Nevertheless, the outcomes of all 18 studies were mostly consistent.

At recommended doses, beclomethasone dipropionate and budesonide demonstrated a small degree of growth suppression over 1–2 yrs (study types 1 and 2), but there was little evidence of such an effect with fluticasone propionate. Studies comparing different inhaled corticosteroids at recommended doses indicated more rapid growth with fluticasone propionate than with beclomethasone dipropionate or budesonide. However, none of the inhaled corticosteroids appeared to affect final height.

In conclusion, the results from the majority of published growth studies with inhaled corticosteroids must be interpreted with a degree of caution owing to their potential susceptibility to important confounding factors. Further well-designed studies are needed to establish whether different inhaled corticosteroids have different effects on growth in the long term.

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Inhaled corticosteroids are widely recommended as first-line treatment for children with persistent asthma, and there is a wealth of evidence indicating their long-term efficacy in controlling this disease [1]. While it is known that treatment with oral corticosteroids attenuates childhood growth [2, 3], the effect of inhaled corticosteroid therapy, which results in reduced systemic exposure, is less clear. Debate regarding their potential impairment of growth continues. In 1998, the food and drug administration (FDA) reviewed most of the studies that had attempted to address this issue, although no systematic analysis was performed. As a result, they recommended that all inhaled corticosteroids should carry a warning regarding potential effects on childhood growth [4].

Assessing the effects of inhaled corticosteroids on growth in children with asthma is fraught with difficulties and requires carefully designed and controlled clinical trials. Reduction in final adult height is the principal concern of patients and their parents, but difficulties in obtaining high-quality final height data have led to the adoption of surrogate markers. Growth velocity is the most commonly used surrogate, as it is a sensitive measure of impaired growth, although there is no correlation between growth velocity and final height [5]. Most studies attempting to evaluate the effects of asthma therapy on growth in children with asthma are further complicated by the fact that asthma itself impairs growth [6–8]. Comparisons of inhaled corticosteroids with placebo or nonsteroidal asthma therapy are medically and ethically justified only in patients with mild-to-moderate asthma, making it difficult to measure directly the absolute effect of high-dose inhaled corticosteroid therapy in children with severe disease.

In the first part of this review [9], recommendations were developed regarding study duration, age/sexual maturity of patients, exclusion criteria for height and growth velocity, permitted therapy during the study, protocol for height measurement, number of patients for adequate statistical power and methods for statistical analysis. In addition, a simple classification system for growth studies with inhaled corticosteroids was developed, separating medium-term randomized controlled trials (classified according to the comparator treatment: Type 1: placebo; Type 2: nonsteroidal asthma therapy; Type 3: inhaled corticosteroid) from "real-life" final height studies where the treatment in both study groups is more flexible (these studies may

not be randomized or prospective). To ensure quality, only growth studies with a minimum duration of 1 yr and involving measurement of height with a stadiometer qualify for classification by this system. These criteria were recommended by the FDA to avoid the effect of seasonal variation and because stadiometry is widely acknowledged as being one of the most reliable means of measuring height [4].

The aim of this paper is to apply this classification system to all published studies assessing the effects of inhaled corticosteroids on growth in children with asthma. Subsequently, the design of these studies will be compared with the more detailed trial design recommendations, as a means of assessing the validity of the results and the effect of treatment on growth in those studies meeting the recommendations. As part of this assessment, patient numbers will be compared with the estimates of sample sizes required to establish superiority or noninferiority. However, it is important to note that the estimated patient numbers cannot be used to judge definitively whether a study was adequately powered. Three major caveats to be considered are: changes in variability of the data (the calculations were based on a specific estimate of variability from two good quality studies and increased variability would imply an increase in the required sample size); changes in required power (*e.g.* 80% instead of 90%); and changes in the minimum detectable difference (*e.g.* the selection of 0.7 $cm \cdot yr^{-1}$ rather than 0.4 $cm \cdot yr^{-1}$ as the equivalence limit in a noninferiority study). Overall, the assessment process should facilitate informed interpretation and appraisal of the literature and offer some explanation for apparently contradictory data.

Literature search

Relevant randomized controlled trials published in all languages were identified by systematically searching four databases for studies on growth/height with inhaled corticosteroids in children with asthma. The databases were Medline (1966–March 2001), Embase (1974–March 2001), Derwent Drug File (1983–March 2001) and Biosis Previews (1970–March 2001). Both free-text and indexing strategies were used to attain maximum recall of relevant references. Four keywords were used in the search: "asthma", "inhaled", "steroids" and "growth/height". "Steroids" encompassed the following: glucocorticoids, corticosteroids, fluticasone, mometasone, budesonide, beclomet(h)asone and triamcinolone. "Growth/height" encompassed the following: growth, leg, height, knemometry, collagen, bone development. Articles were limited to human studies only, while editorial and review articles were excluded. Duplicates between the databases were removed using the DataStar "Drop Duplicate" feature, which identifies exact title matches.

Each title and abstract was reviewed by one reviewer and annotated as either potentially meeting the minimum entry criteria [9] for the classification system or clearly not meeting the criteria. Full papers were obtained for all publications potentially meeting the minimum criteria and classified as appropriate. Randomized prospective studies meeting the minimum entry criteria were classified as type 1, 2 or 3 if the comparator treatment was placebo, nonsteroidal asthma therapy or another inhaled corticosteroid, respectively. "Real life" studies, typically longer than 12 months in duration and where the doses in both study groups were flexible, were classified as type 4 studies.

A total of 362 publications were identified by the literature search, of which 344 were rejected as not meeting the minimum criteria (*i.e.* $\geqslant$12 months duration, used stadiometry, included a control group) for the classification system, or as abstracts from studies subsequently published as full papers. Three studies were classified as type 1, five as type 2, three as type 3 and nine as type 4 (two studies met the criteria for classification as two different study types).

Type 1 growth studies (control: placebo)

Three studies meeting the initial selection criteria of the study classification system compared growth in children with asthma treated with either an inhaled corticosteroid or placebo. Each study was randomized and used stadiometry to measure patient height (table 1). Two were of 12 months duration [10, 11], whereas the third was performed over 27 months [12].

Only one study analysed patients who were prepubertal [11]. The inclusion of pubertal patients in the studies of JONASSON *et al.* [12] and SIMONS *et al.* [10] is likely to have increased the variability of growth data and more importantly could have confounded the results if the distribution of pubertal patients between treatment groups had been unequal. Only one of the three studies excluded patients at the extremes of the normal ranges for height and growth velocity [11]. Apparently, therefore, this was the only study to eliminate the potential confounding effect of abnormally high or low growth velocities.

No more than four short courses of oral corticosteroids per year were permissible in any of the studies, so oral therapy was unlikely to have substantially confounded the results [13]. Nevertheless, at least 50% more courses were administered to patients receiving placebo compared with the inhaled corticosteroid group [10–12]. Thus even in well-designed studies, it is questionable whether the absolute effect of inhaled corticosteroids on growth is measurable.

By definition, stadiometry was used to measure height in all of the studies (although in the study of SIMONS *et al.* [10] stadiometry was only used at "most" study sites). Height was measured at the recommended frequency (*i.e.* every 3 months) in two studies; in the third study, height was only measured every 6 months during the second year [12]. From the information available in the publications, it is not clear whether height measurements in any of the type 1 studies were made in triplicate or at a consistent time of day, or whether different observers measured height.

In the first part of this review, it was suggested that type 1 studies should be designed to establish noninferiority [9], but this was not the case for any of

Table 1. – Summarized design and outcomes of type 1 growth studies (*i.e.* inhaled corticosteroids compared with placebo)

First author [ref. no.]	Treatment groups and number of patients	Severity of asthma	Age and sexual maturity of patients at baseline	Inclusion criteria for height and growth velocity	Permitted therapy (other than study treatment)	Main study outcomes
ALLEN [11]	FP 100 μg·day^{-1} (n=85); FP 200 μg·day^{-1} (n=96); PBO (n=87)	Mild-moderate (FEV_1 ⩾60% pred)	Boys 4–11 yrs, girls 4–9 yrs; prepubertal	Height centiles 5–95; growth centiles 10–97	⩽2 courses of oral CS, as-needed albuterol	No significant intergroup differences in GV: p=0.380 overall. Treatment differences in GV were -0.21 cm and -0.42 cm for FP 100 and 200 μg·day^{-1} respectively, compared with PBO
JONASSON [12]	BUD 100 μg·day^{-1} or 200 μg·day^{-1} (n=68); PBO (n=21)	Mild	7–16 yrs	Not specified	As-needed terbutaline, ⩽2 courses of oral CS in any 6-month period	Significantly reduced GV with BUD than PBO after month 12 in 7–11 yrs old (inter-group differences 1.09–1.49 cm·yr^{-1}, p<0.001)
SIMONS [10]	BDP 400 μg·day^{-1} (n=67); salmeterol 100 μg·day^{-1} (n=58); PBO (n=55)	Mild-moderate (FEV_1 ⩾70% pred)	6–14 yrs	Not specified	Cromones, theophylline, as-needed salbutamol	Significantly reduced GV with BDP (3.96 cm·yr^{-1}) *versus* PBO (5.04 cm·yr^{-1}, p=0.018)

FP: fluticasone propionate; BUD: budesonide; BDP: beclomethasone dipropionate; PBO: placebo; FEV_1: forced expiratory volume in one second; CS: corticosteroid; GV: growth velocity.

the three studies listed. The results of the study that found no difference between corticosteroid treatment and placebo [11] should be interpreted with the focus on the confidence intervals (CI) for estimated treatment difference rather than p-values, but these are not available from the publication. Based on the sample size calculations presented in the first part of the review (>165 patients per group for 90% power) [9], this study may have been underpowered to conclude noninferiority within the range 0.3–0.5 cm·yr^{-1}. Nevertheless, the study does provide some useful information about the potential absolute effect of inhaled corticosteroids on growth. The remaining type 1 studies detected considerably slower growth with the inhaled corticosteroid (*i.e.* beclomethasone dipropionate and budesonide) than with placebo, by >1 cm·y^{-1} [10, 12]. In this context, the discussion of patient numbers for noninferiority becomes trivial, and these studies can be viewed as reasonably reliable.

Only two of the studies provide information on the statistical method used to analyse the growth data [10, 11]. In each case, only a limited number of covariates were included in the analysis, reducing the opportunity to correctly allocate differences due to either the drug or other factors.

One of the type 1 studies indicated that growth was similar in children with mild asthma treated with either placebo or an inhaled corticosteroid [11]. Conversely, the other two studies reported significant differences between study groups, patients receiving placebo growing faster than children treated with the inhaled corticosteroid [10, 12]. The drug used in the study showing no significant difference from placebo was fluticasone propionate at doses of 100 μg and 200 μg·day^{-1} [11], which is of interest because this inhaled corticosteroid has been shown to have a higher efficacy-to-risk ratio than other inhaled corticosteroids [14, 15]. It has been reported in a meta-analysis that growth in the fluticasone propionate 200 μg·day^{-1} group was slower than with placebo (mean difference of -0.43 cm·yr^{-1} (95% CI: -0.01–-0.85)) [16], although the validity of such a *post hoc* analysis is questionable, since this group only contained data from one study, that of ALLEN *et al.* [11]. In summary, none of these studies met all of the design recommendations detailed in the first part of this review [9], although the study by ALLEN *et al.* came closest to fulfilling the most important criteria.

Type 2 growth studies (control: nonsteroidal therapy)

Of the five studies meeting the criteria for classification as type 2 (*i.e.* inhaled corticosteroid *versus* nonsteroidal asthma therapy), one was also a type 1 study, while another was also classed as type 3. The design aspects and main outcomes of all published type 2 studies are summarized in table 2 [10, 17–20].

Only one of the type 2 studies included only prepubertal children [18], thus maintaining a predictable level of variability in the data. The remaining four studies all included pubertal patients. Another potential source of variability in all these studies stems from the apparent lack of exclusion criteria for

Table 2. – Summarized design and outcomes of type 2 growth studies (*i.e.* inhaled corticosteroids compared with nonsteroidal asthma treatment)

First author [ref. no.]	Treatment groups and number of patients	Severity of asthma	Age and sexual maturity of patients at baseline	Permitted therapy (other than study treatment)	Main study outcomes
KANNISTO [19]	FP 200 μg·day^{-1} (n=11); BUD 400 μg·day^{-1} (n=12); cromones (n=9)	No requirement for oral or inhaled CS therapy during the previous 12 months	5.5–14.7 yrs	Not specified	Height SDS decreased significantly with BUD (-0.23, p<0.01) *versus* baseline, but not with FP (-0.03) or cromones (-0.09). BUD greater change over time *versus* FP (p<0.05)
PRICE [18]	FP 100 μg·day^{-1} (n=34); sodium cromoglycate (n=26)	Persistent asthma inadequately controlled with as-required salbutamol	4–10 yrs, prepubertal	Control medication only	Adjusted GV 0.5 cm·yr^{-1} lower in the FP group (95% CL: -1.0, 0.1, p=0.08); no significant difference in height velocity SDS; height centiles similar at beginning and end of study
SIMONS [10]	BDP 400 μg·day^{-1} (n=67); salmeterol 100 μg·day^{-1} (n=58); PBD (n=55)	Mild-moderate (FEV_1 ⩾70% pred)	6–14 yrs	Cromones, theophylline, as-needed salbutamol	Significantly reduced GV with BDP (3.96 cm·yr^{-1}) than with salmeterol (5.40 cm·yr^{-1}, p=0.004)
TINKELMAN [17]	BDP 336 μg·day^{-1} (n=77); theophyline (n=68)	Mild-moderate (FEV_1 >50% pred)	6–17 yrs	As-needed β-agonists, oral CS (up to 10 days in any 90-day period)	Lower GV with BDP *versus* theophylline (4.2 *versus* 5.5 cm·yr^{-1}, p=0.005). Estimated treatment difference= -1.6 cm·yr^{-1}
VERBERNE [20]	BDP 400 μg·day^{-1} (n=32); salmeterol 100 μg·day^{-1} (n=25)	Mild-moderate (FEV_1 55–90% pred)	6–16 yrs	As-needed salbutamol, oral CS (⩽3 courses in any 3-month period)	Smaller height increase with BDP *versus* salmeterol (4.7 *versus* 6.1 cm, p=0.007), larger decrease in height SDS with BDP (-0.28 *versus* -0.03; p=0.001).

FP: fluticasone propionate; BUD: budesonide; BDP: beclomethasone dipropionate; PBO: placebo; CS: corticosteroid; FEV_1: forced expiratory volume in one second; SDS: standard deviation score; GV: growth velocity; CL: confidence limits. The duration of growth assessment for all studies was 12 months (plus a prevlous 12-month period in the KANNISTO *et al.* [19] study). Inclusion criteria for height and growth velocity were not specified for any of the studies.

subjects with very high or low centiles for height or growth velocity.

Annual use of oral corticosteroids was confined to ⩽4 courses in two of the five studies, minimizing the risk that oral corticosteroid treatment might confound their findings [10, 18]. However, in one study [17] oral corticosteroids were permitted for up to 10 days in any 90-day period and in another [20] up to 12 courses were allowed during the 1-yr study period. In the remaining study, permitted oral corticosteroid use was not specified [19]. In three of the studies, therefore, administration of more than four courses of oral corticosteroids in 1 yr could have confounded the results. In four of the five studies, more courses of oral corticosteroids were administered to patients receiving nonsteroidal asthma therapy than to those receiving inhaled corticosteroids, although the intergroup difference in this regard varied between studies. Although this imbalance would have favoured corticosteroid treatment, a significantly larger reduction in growth rate was still seen in corticosteroid-treated patients. As with the type 1 studies, therefore, some doubt is cast over the ability of these type 2 studies to estimate the absolute effects of inhaled corticosteroids. In the other study [18], five courses of oral corticosteroids were administered to both the nonsteroidal and the inhaled corticosteroid group.

Height was measured at least every 3 months in four of the five studies [10, 17, 18, 20]. In the other study, however, height was not measured between months 6–12 in the inhaled corticosteroid group, or between months 4–12 in the cromone group, reducing the accuracy of annual growth velocity calculations performed by linear regression [19]. Interobserver variability in height measurement was eliminated in three of the five studies by ensuring that the same observer measured patients' height at each visit [10, 18, 19]. In one study, the data were strengthened further by specifying that readings were made in triplicate, and always at the same time of day [18].

Applying the principles discussed in the first part of this review, type 2 studies should be designed to demonstrate noninferiority. However, none of the five studies appeared to be designed in this manner and the same points made previously for type 1 studies are also relevant here. From assessment of the patient numbers, none of these studies were likely to be sufficiently powered to establish noninferiority using a noninferiority margin of 0.3–0.5 $cm \cdot yr^{-1}$. One must therefore exercise a degree of caution when interpreting the two studies reporting no difference between an inhaled corticosteroid and a nonsteroidal comparator [9, 19]. Therefore it is recommended that the data is assessed, principally by examining the confidence intervals of the estimate of treatment difference, rather than focusing on the p-values. The studies provide valuable information, but cannot be viewed as conclusive in proving noninferiority to the nonsteroid comparator on the basis of the margin mentioned earlier.

Four of the five studies [17–20] specified a per-protocol population for analysis, although none clarified whether pubertal patients were excluded from this population. All of the studies provide some information on the statistical method used to analyse the growth data. Only one study included age and sex as covariates in the analysis, which are arguably the most important factors in predicting growth [18]. Nevertheless, as for the type 1 studies, in each of these five studies only a limited number of covariates from the recommended list defined in first part of this review were included in the analysis, thereby reducing the opportunity to correctly allocate differences due to drug and those due to other factors.

The outcomes of three of the five type 2 studies indicated that children treated with inhaled corticosteroids grew a little more slowly than those treated with nonsteroidal therapy (treatment difference 1.3–1.4 $cm \cdot yr^{-1}$). In the other two studies, no significant differences in growth velocity were reported between children treated with fluticasone propionate and those treated with sodium cromoglycate [18, 19], although growth was slower in children treated with budesonide than in those treated with cromones [19]. Reduced growth velocity was reported in all studies of beclomethasone dipropionate [10, 17, 20]. However, none of the type 2 studies met all of the principal design criteria and further well-designed studies to compare inhaled corticosteroids with nonsteroidal therapy would be useful.

Type 3 growth studies (control: comparator inhaled corticosteroid)

Table 3 presents the main design aspects and outcomes of the three growth studies comparing different inhaled corticosteroids that were classified as type 3 [19, 21, 22].

Two of the type 3 studies included only prepubertal children [21, 22], and thereby avoided possible confounding by the unpredictability of pubertal growth. The inclusion of patients in the pubertal age range in the other study increases the difficulty of establishing a genuine treatment effect [19]. No exclusion criteria according to height or growth velocity were specified for two of the three studies [19, 22], introducing a potential source of variability in the results. In the remaining study [21], children with a disorder likely to affect growth were excluded.

In one study, patients who received treatment with systemic corticosteroids were excluded from the growth analysis, removing any potential for additional steroid use to confound the results [21]. In the other two studies, use of oral corticosteroids was not specified. In one, no permissible therapy other than study medication was mentioned [19], and in the other, sodium cromoglycate was permitted [22].

All the recommendations made to optimize the accuracy of growth measurement were implemented in one study: measurements were made every 3 months, using the same observer throughout to eliminate interobserver variability, and all measurements were made at a similar time of day to avoid inaccuracies due to circadian variability in height [21]. For the remaining two studies, height was measured less often than recommended during the second half of the treatment period [19, 22]. Nevertheless, the number of

Table 3. – Summarized design and outcomes of type 3 growth studies (*i.e.* inhaled corticosteroids compared with another inhaled corticosteroid)

First author [ref. no.]	Treatment groups and number of patients	Duration of growth assessment	Severity of asthma	Age and sexual maturity of patients at baseline	Permitted therapy (other than study treatment)	Statistical analysis for growth	Main study outcomes
DE BENEDICTIS [21]	FP 200 μg·day^{-1} (n=137); BDP 200 μg·day^{-1} (n=140)	12 months	Moderate (requirement for FP 100–200 μg·day^{-1} or equivalent)	Boys aged 4–11 yrs, girls aged 4–9 yrs; prepubertal; Tanner stage sexual maturity rating of 1	Cromones, xanthines and β-agonists; as-needed oral CS	GV calculated for each patient using linear regression; analysis by ANCOVA (terms for baseline height and age, country, sex and race)	GV significantly greater with FP *versus* BDP (5.01 *versus* 4.10 cm·yr^{-1}, p<0.001)
KANNISTO [19]	FP 200 μg·day^{-1} (n=11); BUD 400 μg·day^{-1} (n=12); cromones (n=9)	12 months (plus previous 12 months)	No requirement for oral or inhaled CS therapy during the previous 12 months	5.5–14.7 yrs	Not specified	Student's t-test	Height SDS decreased significant with BUD (-0.23, p<0.01) *versus* baseline, but not with FP (-0.03) or cromones (-0.09). BUD great changer over time *versus* FP (p<0.05)
RAO [22]	FP 200 μg·day^{-1} (n=15; 7 received PBO for the first 10 weeks); BDP 400 μg·day^{-1} (n=8)	20 months	Moderate (steroid-naïve)	5–10 yrs, prepubertal	Sodium cromoglycate	Not specified	"Highly significant" difference in GV for BDP *versus* (4.94 *versus* 5.75 cm·yr^{-1} a treatment difference of 0.81 cm·yr^{-1} (95% CL: 0.45, 1.16)

FP: fluticasone propionate; BDP: beclomethasone dipropionate; BUD: budesonide; PBO: placebo; CS: corticosteroid; GV: growth velocity; ANCOVA: analysis of covariance; SDS: standard deviation score; CL: confidence limits.

observers was limited to one or two in both studies, and in one of them [22] all measurements were taken at the same time of day.

As discussed in the first part of the review, type 3 studies may be designed to establish either noninferiority or superiority [9]. The aim of each of the three studies listed was to evaluate whether one inhaled corticosteroid, fluticasone propionate, was superior to another inhaled corticosteroid. The sample size tables provided in the first part of the review [9] indicate that even to detect a difference as large as 1 $cm \cdot yr^{-1}$ between treatment groups, with 90% power, approximately 42 patients per treatment group would be required. It is likely that only one of the three type 3 studies listed was adequately powered to establish superiority with a minimum detectable between-group difference of this order [21]. The remaining two studies were probably not adequately powered to detect between-group differences in growth velocity of $\leqslant 1$ $cm \cdot yr^{-1}$, since none of the treatment groups contained more than 15 patients [19, 22].

All three studies specified a per-protocol population for analysis although only one study [21] stated that pubertal patients were excluded from this population. Only one study included covariates in the analysis for key factors such as age, sex, race, country and baseline height [21]. Thus, for the other two studies, it is impossible to correctly allocate differences due to drug and those due to other factors, such as demographic, baseline, study and environmental characteristics. A notable weakness of the study by RAO *et al.* [22] is the lack of information upon which statistical analysis was based. Fluticasone propionate was compared with either budesonide or beclomethasone dipropionate in all three type 3 studies, and both these comparators had a significantly greater detrimental effect on growth velocity in children. Although two of these studies [19, 22] were apparently underpowered to detect a difference in growth of 1 $cm \cdot yr^{-1}$ [19, 22], judged according to the recommendations on minimum patient numbers in Part I of this review [9], it is likely that the variability (SD) of the growth measurements in these studies was much smaller than the value on which the current author's recommendations were based. Only one study of the three [21] appears to have been well designed, with no major weaknesses.

Type 4 growth studies (long-term, "real-life")

Final height studies

Whatever the short- to medium-term effects, the principal concern of patients, their parents and physicians is the effect of inhaled corticosteroids on final height. The five type 4 studies that assessed the effects of anti-asthma therapy on final height and met the present authors' criteria for inclusion are summarized in table 4 [5, 23–26].

Of the five final height studies, three measured final height only [23, 25, 26], and only one long-term prospective study has been published. This is not surprising, given the logistical difficulties of performing a long-term, prospective clinical trial in children, with final height as the principal end point. For the prospective study, care was taken to obtain complete datasets for all the patients [5]. However, two-thirds of patients in the control group transferred into the corticosteroid group due to worsening asthma symptoms. A further nine were lost to follow-up, four were excluded because they took prednisolone for more than 2 weeks, and height data were missing for one patient. Thus, the number of patients with final height data in the nonsteroidal therapy group was almost eight-times smaller than the number in the budesonide group. One final height study with long-term growth data was performed retrospectively, facilitating a better balance in the numbers of patients who received nonsteroidal or steroidal therapy [24].

None of the final height studies specified exclusion criteria for children with high or low centiles for height or growth velocity. As a result, the data may be susceptible to greater variability than might have occurred had such exclusion criteria been employed. Another potential source of variability for final height studies is the age at which final height measurement is made. Since asthma has been associated with delayed puberty, it is important to ensure that final height is measured only after completion of the growth process. Three robust methods used to ensure this are to specify one of the following: growth rate <0.5 $cm \cdot yr^{-1}$ for two consecutive years; achievement of adult skeletal bone maturity or height measurement at age $\geqslant 23$ yrs. Table 4 indicates that of the five final height studies, only one (INOUE *et al.* [24]) was likely to have measured patients' final height too early (measurement at the age of 20 yrs does not rule out subsequent growth).

Use of oral corticosteroids was permitted as required in four studies [23–26], and limited to 2 $weeks \cdot yr^{-1}$ in the remaining study [5]. In two studies where oral corticosteroids were permitted as required [24, 26], all patients received less than the recommended four courses per year, reducing the risk of confounding the outcomes. In the study of VAN BEVER *et al.* [26] oral corticosteroid use was limited to one course for two children in the inhaled corticosteroid group (data on oral corticosteroid use by each treatment group was not presented in the study of INOUE *et al.* [24]). In another of the studies, the mean number of courses of oral corticosteroids during childhood was 2.4, also minimizing the chance of confounding the results [23]. In one study, however, oral corticosteroid use was not specified [25].

Three observers measured all of the children's heights throughout the long-term prospective final height study, minimizing the potential for interobserver variability [5]. In one of the retrospective studies where height was only measured in patients who had already attained final height, the same observer made all height measurements [26]. However, there was no evidence of any measures to optimize the accuracy of height measurements in the other final height studies.

As suggested, type 4 final height studies should be designed to establish noninferiority of the inhaled corticosteroid to nonsteroidal comparator treatment [9]. This was not the case for any of the five studies listed and therefore a degree of caution should be

Table 4. – Summarized design and outcomes of type 4 growth studies (*i.e.* "real life" studies)

First author [ref. no.]	Treatment groups and number of patients	Duration of growth assessment	Severity of asthma	Age and sexual maturity of patients at baseline	Permitted therapy (other than study treatment)	Frequency and specified protocol for stadiometry	Statistical analysis for growth	Main study outcome
AGERTOFT [5]	BUD 110–877 $\mu g \cdot day^{-1}$ (n=142); no steroids (n=18); healthy controls (n=51)	3–13 yrs (prospective, until attainment of final height) (run in period of 1–2 yrs)	No requirement for continuous inhaled CS	3–13 yrs	As-needed β-agonists, oral CS $\leqslant$ 2 weeks$\cdot yr^{-1}$ (BUD group only)	Every 6 months, same three observers throughout	Measured adult height minus calculated target height; paired t-test	*Final height*. Actual minus target final heights: BUD, +0.3 cm, 95% CL -0.6, 1.2; no steroids, -0.2 cm, 95% CL -2.4, 2.1; healthy controls +0.9 cm, 95% CL -0.4, 2.2. significant reductions in GV (1.0 and 0.6 $cm \cdot yr^{-1}$) with BUD during 1st and 2nd years compared with run-in
INOUE [24]	BDP 100–800 $\mu g \cdot day^{-1}$ initiated either before pubertal growth (n=32) or after (n=29); nonsteroidal therapy (n=36)	8–10 yrs (retrospective)	Moderate-severe	10–12 yrs	Oral CS	Annual	Yearly mean height SDS values at ages 10–20 (final height); unpaired t-test	*Final height*. No significant intergroup differences in height SDS (males or females). Evidence of delayed pubertal growth in all three groups
LARSSON [25]	Inhaled or oral CS (n=113); no steroids (n=82); healthy controls (n=151)	Adult height measurement only (duration of asthma therapy $\leqslant$12 yrs)	Not specified	Not applicable; height measured at age 23 (mean)	Not specified	Not specified	Measured adult height (males and females analysed separately)	*Final height*. No significant intergroup differences in final height (men or women)

Table 4 continued on next page.

Table 4. Continued

First author [ref. no.]	Treatment groups and number of patients	Duration of growth assessment	Severity of asthma	Age and sexual maturity of patients at baseline	Permitted therapy (other than study treatment)	Frequency and specified protocol for stadiometry	Statistical analysis for growth	Main study outcome
SILVERSTEIN [23]	Inhaled and/or oral CS (n=58); no CS (n=95); healthy controls (n=153)	Adult height measurement only (mean time from first to last CS exposure= 7.3 yrs)	Not specified	Not applicable (height measured at mean age of 25.7 yrs)	Oral CS	Not specified	Relationship between final height (adjusted for midparental height) and CS exposure; ANCOVA.	*Final height*. CS group=1.2 cm shorter than no CS (95% CL -3.1, 0.6). No significant difference between patients with asthma and controls
VAN BEVER [26]	Inhaled CS (n=42); Nonsteroidal therapy (n=43)	Adult height measurement only (mean age at first CS exposure= 13.3 yrs)	Not specified	Not applicable (height measured at mean ages of 23.6 yrs (inhaled CS) and 22.1 yrs (nonsteroid)	Oral CS	One observer throughout	Final height minus calculated target height; nonpaired t-test and ANOVA	*Final height*. Adult minus target height: inhaled CS -0.003± 5.9 cm; no CS, 2.54±4.8 cm; p=0.03. No significant intergroup difference in adult height SDS
AGERTOFT [27]	BUD ⩽800 μg·day^{-1} (n=216); no steroids (n=62)	2–6 yrs (prospective) (run-in period or 1–3 yrs)	Mild-moderate	3–11 yrs	As-needed β-agonists, oral CS ⩽ 2 weeks·yr^{-1} (BUD group only)	Every 6 months, same two observers throughout	GV calculated by linear regression. Measured height converted to SDS for intergroup comparison	No significant difference in GV between BUD (5.48 cm·yr^{-1}; 95% CL: 5.31, 5.65) and control (5.62 cm·yr^{-1}; 95% CL: 5.07, 6.17)

Table 4 continued on next page.

Table 4. Continued

First author [ref. no.]	Treatment groups and number of patients	Duration of growth assessment	Severity of asthma	Age and sexual maturity of patients at baseline	Permitted therapy (other than study treatment)	Frequency and specified protocol for stadiometry	Statistical analysis for growth	Main study outcome
Childhood Asthma Management Program Research Group [29]	BUD 400 μg·day^{-1} (n=280); nedocromil 16 mg·day^{-1} (n=271); PBO (n=379) (all doses reduced to zero if asthma well controlled)	4.3 yrs (prospective)	Mild-moderate	5–12 yrs	Oral CS; addition of BDP 336 μg·day^{-1} as needed	Every 2 months for the first 4 months, and every 4 months thereafter	Multiple regression, with covariates for age, sex, race, clinic, duration of asthma and skin-test reactivity	Change in height from baseline. Significantly smaller increase in height with BUD *versus* PBO (22.7 *versus* 23.8 cm, p=0.005), due to lower GV during the first yr (GVs were similar thereafter)
SKONER [28]	TAA 600 μg·day^{-1} mean (n=119); nonsteroidal therapy (n=12)	12 months (prospective)	Moderate	6–11 yrs	Not specified	Not specified	Not specified	GV significantly lower with TAA *versus* no CS therapy (5.3 *versus* 6.1 cm·yr^{-1}, p<0.001)
SKONER [30]#	BUD 500–1000 μg·day^{-1} (n=371); "Conventional asthma therapy" (n=156) (all doses reduced to zero if asthma well controlled)	12 months (3 studies) (prospective)	Mild	1–9 yrs	As-needed β-agonists, oral CS	Week 4 and every 8 weeks thereafter	Changes in height SDS (general linear model); GV (linear regression); intergroup differences (general linear model)	No significant intergroup differences for pooled data. In all of the three studies, GV was significantly reduced in the BUD group (-0.8 cm·yr^{-1}, p=0.002)

BUD: budesonide; BDP: beclomethasome dipropionate; CS: corticosteroid; PBO: placebo; TAA: triamcinolone acetonide; SDS: standard deviation score; ANCOVA: analysis of covariance; ANOVA: analysis of variance; GV: growth velocity; CL: confidence limits. Inclusion criteria for height and growth velocity were not specified for any of the studies. The population used for the growth analysis was unspecified in all but 2 studies (AGERTOFT *et al.* [5] and SKONER *et al.* [28]; per protocol for both). #: also published as a full paper in 1999 [31].

exercised when interpreting studies reporting no difference between an inhaled corticosteroid and nonsteroidal treatment. Focus should be placed on the confidence intervals of the treatment difference rather than the p-values (table 4).

Only one of the five studies provided details of the populations analysed [5]; the other four studies provided no information in this regard. Three of the five studies either provided no information on the statistical method used to analyse the data, or analysed the data using a t-test which does not allow for adjustment of important covariates, thus making it impossible to correctly allocate differences due to drug and those due to demographic or environmental factors [5, 24, 25]. The remaining two studies allowed for adjustment of covariates by performing analysis of variance on the data, but details of which covariates had been included were unclear [23, 26].

All five final height studies compared the effects of inhaled corticosteroids with nonsteroidal therapy. None of the studies reported significant between-group differences in adult height [5, 23–26], and the difference was <1 cm in the study that did record a difference (1.4 cm for patients receiving oral as well as inhaled corticosteroids (95% CI: -3.5–0.7 cm)) [23]. A weakness of a number of these studies is the lack of information on the estimates of treatment difference with associated confidence intervals in order to be able to make a noninferiority assessment. Lack of evidence of a difference is not evidence of no difference, and may simply be due to insufficient patient numbers or poor study design. Final height data are only available for two corticosteroids: budesonide [5] and beclomethasone dipropionate [24]. Both studies included long-term height measurements and, interestingly, both suggested that inhaled corticosteroid treatment may affect growth in the short-term, but not in the long-term. The study with budesonide indicated that growth was reduced during the first 2 yrs of treatment, while the study with beclomethasone dipropionate suggested growth impairment during the early period of puberty. The study by AGERTOFT and PEDERSEN [5], which showed no effect of budesonide on final height, is the only prospective study conducted to date.

Growth velocity studies

As well as final height, four type 4 ("real life") studies have compared the effects of treatment strategies on growth velocity (table 4) [27–30]. Note that one of these publications reported pooled results from three distinct clinical trials [30].

Although none of the four growth velocity type 4 studies specifically excluded children entering puberty, the age range for one of the studies implied that all patients would have been prepubertal [30]. For the other three studies [27–29], the possibility of the older patients entering puberty during the study increases the likely variability of the data, and the potential for confounding interpretation. This is most relevant for studies by the Childhood Asthma Management Programme Reasearch Group [29] and by AGERTOFT and PEDERSON [27]: although the mean ages of subjects at baseline were 9 and 6.2 yrs, they were treated for mean durations of 4.3 and 5.3 yrs, implying that many patients entered puberty during the studies.

Oral corticosteroid use was permissible in three of the four growth velocity studies [27–29], although in one this was limited to 2 weeks·yr^{-1} and to the budesonide group only [27]. In the SKONER *et al.* [30] publication, oral corticosteroid use was generally balanced between patient groups, with 53–63% of patients in the conventional asthma treatment groups receiving this therapy compared with 46–56% of those in the budesonide group. This publication presented pooled data from three studies, and the control group ("conventional asthma therapy") was allowed treatment with inhaled corticosteroid in two of the studies. Since the extent of this treatment was unspecified, it could have confounded growth outcomes. In the Child Asthma Management Program Research Group study, use of oral corticosteroids was significantly lower in the budesonide group (0.70 courses per patient per year) and nedocromil group (1.02 courses per patient per year) compared with the placebo group (1.22 courses per patient per year) [29]. In this study, it is notable that additional beclomethasone dipropionate therapy was administered to children receiving placebo on 18.7% of days, compared with 17.1% for nedocromil and 6.6% for budesonide. Thus, the use of additional corticosteroid therapy probably affected the results of the Childhood Asthma Management Program Research Group [29] and SKONER *et al.* [30] studies; the comparison actually achieved was one of treatment strategies rather than fixed-dose therapy with specific drugs. In the remaining study, there was no information on the use of oral corticosteroids [28].

For two of the type 4 growth velocity studies, the interval between each height measurement was more than every 3 months [27, 29]. However, both studies were long-term, and the number of measurements for each patient was adequate to prevent introduction of substantial inaccuracy. Height was actually measured more often than recommended in one of the studies [30], but the frequency was not stated in the remaining study [28]. Unfortunately, only one study [28] described evidence of measures to optimize the quality of height measurements (the same two observers measured height throughout).

As for the type 4 final height studies, it was suggested in the first part of this review that these studies should be designed to establish noninferiority of the inhaled corticosteroid treatment strategy to nonsteroidal comparator treatment strategy [9]. This was not the case for any of the four studies listed.

Only one of the four studies provided information on the populations analysed [30]; the other three studies provided no detail in this regard. One of the studies provided no information on the statistical method used to analyse the data [28] but the remainder all analysed the data using a model-based approach, which allows for the adjustment of important covariates. One study specified the covariates adjusted for, and the list appears to cover many of the important factors [29].

All four growth velocity studies classed as type 4 compared a specific inhaled corticosteroid with

nonsteroidal asthma therapy, although inhaled corticosteroids were administered to the control groups in two of the studies [29, 30]. In one study, there were two control groups, treated with nedocromil and placebo, respectively [29]. The findings of the four studies were somewhat contradictory, in that the study by AGERTOFT and PEDERSON [27] detected no significant difference between budesonide and nonsteroidal therapy, but growth velocity was reduced with budesonide compared with placebo and nedocromil in the Child Asthma Management Program Research Group study. In the third publication comparing budesonide with a control ("conventional asthma therapy"), there was no significant between-group difference for the pooled data from three studies, but there was a difference in one of the individual studies, where inhaled corticosteroid therapy was not used in the control group. In the remaining study, triamcinolone acetonide was found to attenuate growth in comparison with nonsteroidal therapy [28]. The different outcomes could have arisen from design heterogeneity, inadequate statistical power, inadequate allowance in the statistical analysis for factors affecting growth, or differences in the systemic activity of the inhaled corticosteroids [15, 32]. Of the four studies of this type, the Child Asthma Management Program Research Group Study appeared to have the fewest design weaknesses, although an assessment of the impact of puberty on the results of this study would be helpful.

Discussion

With the exception of one type 3 study [21], none of the growth studies identified in the comprehensive literature search performed in the present study fulfilled all of the trial design recommendations defined in the first part of this review. The most common shortcoming, for all but the type 3 studies, was the fact that they were not designed to assess noninferiority of the inhaled corticosteroid therapy compared with either placebo or nonsteroidal asthma therapy, and without more complete information on the confidence interval of treatment difference, it is difficult to infer noninferiority conclusions. Many studies also failed to fulfil several other recommendations. Overall, the level of quality was similar across the different growth study types, with one or two studies in each classification approaching fulfilment of the key design criteria.

Despite the flaws identified in the full list of studies, there were few direct contradictions in the outcomes of these trials. In summary, the evidence indicates impaired growth velocity with budesonide and beclomethasone dipropionate in comparison with placebo, nonsteroidal therapy and fluticasone propionate during 1–2 yrs of treatment, but no impact on final height. Children treated with low-dose fluticasone propionate for 1 yr grow similarly to those receiving placebo or nonsteroidal therapy, but there are no data on this drug's effect on medium-term growth, particularly on the timing of puberty and final height. One study with triamcinolone acetonide treatment for 1 yr indicated that this drug impaired growth in comparison with nonsteroidal therapy.

There is evidence of a dose-response relationship for growth impairment with fluticasone propionate [11], but none of the studies which met the criteria for the classification system compared different doses of budesonide or beclomethasone dipropionate. In type 1 and type 2 studies, the most commonly investigated dose of both budesonide and beclomethasone dipropionate was 400 $\mu g \cdot day^{-1}$. There was a consistent reduction in growth with this dose of either drug compared with placebo or nonsteroidal therapy, while similar reductions in growth were reported with lower doses of budesonide.

These are the results from those studies deemed to meet the criteria for the classification system outlined in the first part of this review. Some of the other publications identified by this report's literature search were also of interest. Evidence of potential growth impairment with inhaled beclomethasone dipropionate is provided by a randomized, double-blind study of 177 children [33]. Those treated with beclomethasone dipropionate 800 $\mu g \cdot day^{-1}$ for 1 yr grew significantly more slowly (3.6 cm increase; 95% CI: 3.0–4.2) than children treated with half this dose (5.1 cm increase; 95% CI: 4.5–5.7); height standard deviation score (SDS) decreased by 0.27 cm (95% CI: -0.34–-0.19) and 0.16 cm (95% CI: -0.24–-0.07), respectively during the study. This study was excluded from the classification system because there was no control group receiving only placebo, nonsteroidal therapy or a different inhaled corticosteroid. Another randomized double-blind study compared beclomethasone dipropionate 400 $\mu g \cdot day^{-1}$ with placebo for 7 months in 94 children, and those in the beclomethasone dipropionate group grew significantly less than those in the placebo group (2.66 *versus* 3.66 cm, $p<0.0001$) [34]. This study was excluded because it was <12 months in duration and growth was measured using a Raven Minimeter rather than by stadiometry. A 12-month study in 56 children with asthma compared the effects on growth of budesonide, beclomethasone dipropionate, nonsteroidal therapy, and inhaled plus oral corticosteroids (all doses administered according to clinical requirements) [35]. Growth velocity SDS was significantly reduced among children receiving beclomethasone dipropionate (-1.04) and oral corticosteroids (-1.58) compared with nonsteroidal therapy (0.03) and budesonide (-0.20; $p<0.001$). A 2-yr study indicated that growth among children treated with budesonide 600 $\mu g \cdot day^{-1}$ plus salbutamol was no different from that in children treated with salbutamol alone [36]. Neither of the previous two studies specified stadiometry as the method for measuring height and hence they were excluded from the list of studies.

A large study of >3,000 children with asthma indicated that children receiving high dosages of inhaled corticosteroids (≥ 400 $\mu g \cdot day^{-1}$), and who were attending hospital for asthma care, had reduced height SDS, and those receiving high-dose inhaled corticosteroids also had low growth velocity (SDS of -0.19) [37]. This effect was, however, smaller than that of social deprivation. The "normal" population of

children (*i.e.* those not currently treated with inhaled corticosteroids) with asthma demonstrated no evidence of impaired growth. Unfortunately this 4-yr study did not specify the use of stadiometry to measure height, and no results for specific inhaled corticosteroids were presented. In a primary care-based study, children receiving inhaled budesonide or beclomethasone dipropionate for a year were found to have low growth velocity (SDS scores of -1.0 and -1.7 respectively) [38]. However, switching the 20 children with slowest growth to fluticasone propionate treatment for 1 yr resulted in an increase in growth velocity SDS to +1.6. The method for measuring height was again not described for this study.

A final height study was rejected because height was not measured by stadiometry [39]. Nevertheless, the results were in agreement with the suggestion in the other beclomethasone dipropionate final height study that the drug may delay pubertal growth [24]. Also, in both studies, there were no significant differences in final height between children treated with beclomethasone dipropionate and those treated with non-steroidal therapy.

A slightly different but highly relevant study confirmed the growth-suppressive effects of oral corticosteroids in 163 patients with severe asthma [40]. Height standard deviations of patients receiving intermittent, alternate-day or daily oral corticosteroids were -0.44, -1.22 and -1.95, respectively (the mean dosage of inhaled corticosteroids was 1,675 $\mu g \cdot day^{-1}$). Notably, this study indicated that the introduction of inhaled corticosteroids attenuates asthma-associated growth suppression by allowing reduced use of oral corticosteroids and by improving the control of asthma.

Thus, growth studies that did not meet the criteria for inclusion in the classification system did not contradict the findings of those that did and the evidence overall suggested that budesonide and beclomethasone dipropionate may have a similar effect on growth velocity at dosages of $\geqslant 400$ $\mu g \cdot day^{-1}$.

Two meta-analyses of growth studies have been published. The first of these, published in 1994, only included data on beclomethasone dipropionate (200–875 $\mu g \cdot day^{-1}$) [3]. In light of the results of the present review, it is perhaps surprising that no significant association was found between beclomethasone dipropionate (100–400 $\mu g \cdot day^{-1}$) treatment and impaired growth [3]. However, closer inspection of the results indicates that there was evidence of a short-term reduction in growth velocity, although final height, the principal outcome, remained unaffected. This is compatible with the present findings. Also, this meta-analysis [3] failed to show any association between dose and growth-suppressive effects of beclomethasone dipropionate, again similar to the present authors' findings. One study, however, has demonstrated a dose-related effect of beclomethasone dipropionate; children treated for 1 yr at a dosage of 800 $\mu g \cdot day^{-1}$ grew more slowly than those receiving 400 $\mu g \cdot day^{-1}$ [33]. The more recently published meta-analysis exercised several quality criteria for inclusion: randomized controlled trials only; inhaled corticosteroid compared with nonsteroidal therapy; children aged <18 yrs not using oral corticosteroids at the outset; clinical diagnosis of asthma; and treatment for a minimum of 3 months [16]. Five studies met these criteria: four with beclomethasone dipropionate (328–400 $\mu g \cdot day^{-1}$) and one with fluticasone propionate (200 $\mu g \cdot day^{-1}$). Decreases in growth velocity of 1.51 $cm \cdot yr^{-1}$ were reported for beclomethasone dipropionate (95% CI: 1.15–1.87), and 0.43 $cm \cdot yr^{-1}$ for fluticasone propionate (95% CI: 0.01–0.85). The latter is based on data from the 200 $\mu g \cdot day^{-1}$ group in the ALLEN *et al.* [11] study, but in the original publication the overall treatment effect was calculated and no significant difference was reported ($p \geqslant 0.05$). Overall, the findings from the two published meta-analyses are consistent with the present authors' results.

Conclusions

This review has examined studies assessing the effects of inhaled corticosteroids and other asthma therapies on childhood growth, taking into account key trial design recommendations derived from important physiological, statistical and trial design principles defined in the first part of this review [9]. Many factors potentially confound studies attempting to establish any treatment effects on growth, and almost all of the published trials are susceptible to one or more of these factors. Nevertheless, the outcomes of studies meeting the minimum selection criteria for design quality were largely consistent. Thus, despite the need for caution when interpreting these results, it is probable that the broad findings are correct. All published studies comparing beclomethasone dipropionate or budesonide with placebo or nonsteroidal therapy (*i.e.* study types 1 and 2) indicate that treatment with either drug at recommended dosages appears to carry a risk of a relatively small degree of growth impairment over 1–2 yrs. In contrast, the original publications from study types 1 and 2 with fluticasone propionate $\leqslant 200$ $\mu g \cdot day^{-1}$ concluded that this drug does not impair growth, although a recent limited meta-analysis suggested that growth was slightly slower with fluticasone propionate 200 $\mu g \cdot day^{-1}$ than with placebo. Studies comparing different inhaled corticosteroids also indicate greater growth velocity with fluticasone propionate than with beclomethasone dipropionate or budesonide over 1–2 yrs. None of the inhaled corticosteroids appear to have a significant effect on final height.

Important aims for the future include further growth studies designed to avoid all of the main confounding factors, and long-term prospective 'real life' studies to obtain more precise and conclusive data comparing different inhaled corticosteroids. Both short- and long-term studies need to incorporate the recommendations described in the first part of this review in order to obtain more accurate and consistent estimates of the growth effects due to treatment with inhaled corticosteroids. It is also clear that different steroids should be distinguished as they do not all affect growth in the same way, additional well-designed type 3 studies will aid this assessment.

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