

Original article

Long-term outcomes in paediatric asthma

Over the years the aims of asthma management have changed markedly from effective prednisolone treatment of symptoms and exacerbations towards more use of continuous prophylactic treatment. With our new understanding of the disease and its management definition of the aims of treatment and assessment of optimal asthma control have become much more complex. Even in times of evidence-based medicine our asthma management is based upon findings of effects on various outcomes in somewhat short-term (< 1 year) controlled studies. However, assumptions about long-term effects upon the basis of findings in such studies should be made with great caution. Good examples of this are studies which assess the risk of systemic effects and clinical adverse effects of inhaled corticosteroids. From such studies it has become clear that systemic effects detected in short-term trials may have no predictive value of long-term adverse effects. Thus steroid-induced changes in lower leg growth rates assessed by knemometry do not predict long-term statural growth. Moreover, steroid-induced changes in statural growth over 1 year are not predictive of effects upon attained adult height. In contrast, reduced growth caused by uncontrolled asthma disease also seems to affect attained adult height adversely. These findings suggest that long-term outcomes should play a larger role when future asthma management strategies are decided. Some important long-term outcomes of asthma management in children include cure or remission of the disease, prevention of complications of the disease (airway remodelling, adverse effects upon growth/adult height, peak bone mineral density, physical impairment and psychosocial development) or its pharmacological management (adverse effects upon adult height, peak bone mineral density). More controlled long-term studies (several years) are needed to provide a better understanding of how these outcomes are best achieved.

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Twenty years ago, the majority of children with asthma received only intermittent anti-asthma treatment in association with exacerbations of the disease. Evolution of treatment since that time has included the use of continuous treatment with theophylline, β_2 -agonists or sodium cromoglycate for children with moderate or severe, persistent asthma; some patients with very severe disease were also given daily or alternate-day prednisolone or inhaled corticosteroids. During the last decade, asthma therapy has included early introduction of anti-inflammatory medications, especially inhaled corticosteroids. This means that at many clinics inhaled corticosteroids are now given to patients with mild and moderate asthma severity, rather than reserving this therapy for only the most severe cases. This change in treatment strategy, together with new knowledge about the pathophysiology of the disease, has provided useful information supporting a more aggressive introduction of inhaled corticosteroids into the treatment regimens of both children and adults. While this change in therapy seems justified both upon pathophysiological findings and

efficacy data it is often questioned whether it is also justified from a safety viewpoint. Thus, many paediatricians are still concerned about potential adverse effects of long-term treatment with inhaled corticosteroids, particularly on growth.

The widespread use of inhaled corticosteroids for all disease severities has also made treatment with inhaled corticosteroids more complex. Thus it seems that conclusions obtained in trials in patients with a certain age and asthma severity may not always be valid for patients with a different age or disease severity. Therefore, clinical and adverse effect outcomes of inhaled corticosteroids must be based upon the knowledge about beneficial and adverse effects obtained in controlled clinical dose-response trials in patients with a similar age and disease severity as the group in which the drug is going to be used.

In the following the influence of the asthma disease itself and the use of inhaled corticosteroids on growth will be discussed in some detail, as growth has been used as an outcome in several studies of varying duration. As a

consequence growth can be used as a model for discussing the complexity of the relationship between findings in short- and long-term safety studies. In addition the relationship between short-term and long-term clinical effect outcomes will be discussed briefly.

Systemic effects and clinically important adverse effects

The safety and occurrence of systemic effects of inhaled corticosteroids in children have been studied extensively over the past 20 years without a clear definition of the various terms used to describe these issues. Often no distinction is made between a *measurable systemic effect* and a *clinically relevant adverse effect* of an inhaled corticosteroid. This distinction is important for a correct interpretation of the long-term clinical importance of a study measuring systemic effects. Whether a systemic effect is measurable or not depends entirely upon the sensitivity of the method used for the measurement: When more sensitive methods are utilized, more systemic effects become measurable.

All inhaled corticosteroids are absorbed systemically to some extent. Whether the absorbed drug leads to a measurable systemic effect depends on the amount of drug that is absorbed, the potency and pharmacokinetics of the drug and the sensitivity of the method used for measuring the systemic effect. Thus, for a given drug or inhaler, there will always be a dose below which no systemic effect can be detected, no matter which method is used. As the dose increases, there will be a dose range within which systemic effects are measurable in one or more systemic effect models. More often than not, however, these measurable effects merely reflect small changes within the normal range of the normal biological feedback system; even if they do not they may have no clinical relevance.

With regard to growth, the clinical relevance of detectable systemic effects must sometimes be questioned. This does not apply only to the effects of inhaled corticosteroid therapy. For example, sodium cromoglycate treatment has been found to have a significant effect on urinary excretion of growth hormone (1) and markers of bone metabolism (2), and treatment with inhaled β_2 -agonists has been found to adversely affect the secretion of growth hormone (3, 4). Although statistically significant, these findings are probably not clinically relevant although, as yet, there have been no thorough clinical studies to assess this.

Another problem with studies that assess measurable systemic effects is that they are often short-term, single dose, standardized or cross-over in design and are carried out on healthy volunteers or patients with very mild disease, who will tolerate treatment with placebo for a certain period. The clinical relevance of the findings from such studies to patients with more severe asthma is not known. Recent studies suggest that the systemic effects of

an inhaled corticosteroid may be markedly higher in healthy volunteers than in patients (5, 6). Similar differences may be seen between patients with mild disease and those with more severe disease (7–9). Finally, little is known about how long a measurable effect will persist. There are some indications that the effect is more pronounced at the start of treatment, after which it may be attenuated to some extent (10–14).

Our knowledge about the dose level at which *measurable systemic effects* of inhaled corticosteroids are seen in short-term controlled laboratory studies in healthy volunteers or patients with mild disease is good. It varies with different steroid/inhaler combinations (15, 16), and conclusions from one drug/inhaler combination cannot be extrapolated to other drug/inhaler combinations. Although the clinical relevance of the findings in such studies may be questioned, it can probably be assumed that doses of an inhaled corticosteroid which are not associated with any measurable systemic effects in sensitive laboratory test systems are also clinically safe.

Clinically relevant systemic side-effects should be studied in controlled, long-term clinical trials, using clinically relevant doses in groups of patients with a disease severity and age similar to the groups in which the drugs would normally be prescribed. Such studies require large numbers of patients and are difficult to conduct.

Adverse effect outcomes

Growth

When assessing the effects of corticosteroids on growth in children, it is important to appreciate that growth may be divided into three distinct stages (17).

- 1) Growth during the first 2–3 years of life is both rapid and rapidly decelerating. This phase is probably controlled by the same factors that are important for fetal growth, the main one being nutrition.
- 2) Childhood growth occurs from approximately 3–11 years of age. This phase is influenced mainly by the endocrine system, particularly growth hormone.
- 3) Pubertal growth largely depends on a combination of growth hormone and sex corticosteroids.

The importance of the various factors affecting growth seems to differ between these three phases. Two recent studies found that the growth-retarding effect of an inhaled corticosteroid administered for 1 year was more marked in prepubertal than in pubertal schoolchildren (13, 18), and was statistically significant only in prepubertal children. The FDA normally recommends that growth studies are conducted in prepubertal children, aged 6–9 years. This increases the likelihood of detecting possible unwanted effects, because this age group seems to be most sensitive to the adverse effects of inhaled corticosteroids (13). However, the general applicability of these results is questionable, because of the possibility of

a lower sensitivity in other age groups (13, 18). The long-term predictive value of such studies must be questioned.

Influence of disease

The asthma disease itself may influence the growth of a child in two ways.

(1) *Direct effects of disease severity.* Asthma and its level of control may affect growth directly in the same way as most chronic diseases of childhood. The most commonly observed effect of asthma on growth is a reduction in growth rate, usually towards the end of the first decade of life (19–25). This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of puberty. The prepubertal deceleration of growth velocity resembles growth retardation. The delay in pubertal growth is, however, also associated with a delay in skeletal maturation so that the bone age of the child corresponds to the height. Ultimately, there is no decrease in attained adult height, although it is reached at a later age than normal (19–25). This difference in growth pattern seems to be unrelated to the use of inhaled corticosteroids and is more pronounced in those children with the most severe asthma. The deviant growth pattern seen in many children with asthma complicates the interpretation of results from cross-sectional studies comparing the heights of asthmatic children treated with inhaled corticosteroids with those of normal children or children with asthma who are not treated with inhaled corticosteroids.

Recent studies confirm that poorly controlled asthma may itself adversely affect growth. Thus, height standard deviation scores before treatment with inhaled corticosteroids were found to correlate significantly with lung function (13, 26) and degree of asthma control (27, 28); the poorer lung function or asthma control are, the lower will be the height standard deviation score. Furthermore, a retrospective study of a cohort of children with different degrees of asthma suggested that severe asthma adversely affects final height (29) and a large population-based study of more than 3000 children with asthma also suggested that severe asthma affects growth adversely (30). The exact mechanisms by which severe or poorly controlled asthma affects growth adversely are unclear, but there may be similarities with the factors operating in poor socioeconomic conditions, which have been shown to have an adverse effect on growth equivalent to that of high-dose inhaled corticosteroids (30). These observations are important and must be considered when assessing the general applicability of the findings of various controlled growth studies.

(2) *Effects of disease severity on systemic availability of inhaled drugs.* The level of lung function in asthma may affect the systemic availability of inhaled corticosteroids. Several studies have suggested that the systemic bio-availability and effects of an inhaled drug are more

pronounced in patients with mild asthma than in patients with more severe disease (5, 7–9). This is due probably to differences in deposition pattern caused by a smaller airway diameter in patients with more severe disease. Thus, children with mild disease are more likely to experience adverse growth effects from a given dose of inhaled corticosteroid than children with more severe disease. The clinical relevance of the findings of studies using inhaled corticosteroid, 400 µg/day or more, in patients with mild asthma should therefore be questioned because such doses are rarely needed by patients with disease of this severity. These doses would normally be used in children with moderate or severe asthma, in whom the systemic absorption of drug would be less and who would also be at greater risk of growth retardation caused by uncontrolled asthma.

Design and analysis of growth studies

Studies evaluating the effect of exogenous corticosteroids on growth are traditionally divided into the following (Fig. 1).

- 1) Growth marker studies, which measure corticosteroid-induced changes in various serum markers that are thought to reflect bone and collagen formation/degradation or growth.
- 2) Short-term studies, which assess growth over periods of 3 months or less.
- 3) Intermediate-term studies, which evaluate growth over periods longer than 3 months, but which do not assess final adult height.
- 4) Long-term studies, which assess growth for many years and also include final adult height in relation to predicted adult height.

It is important to remember these characteristics when assessing the clinical relevance of the results of clinical

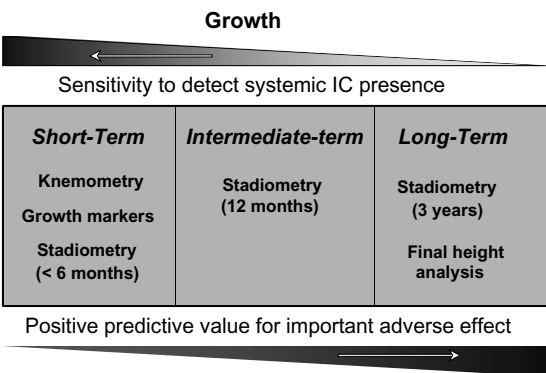


Figure 1. Different designs of studies assessing growth in children. The clinically most important growth outcome is achieved adult height. Although other designs are very good at detecting a systemic activity of an inhaled corticosteroid, their predictive value for long-term growth outcome or adult height is small. Studies on clinically relevant effects of inhaled corticosteroids on growth should be long-term and use doses of inhaled corticosteroids that are tailored to the disease severity.

trials. Several studies have demonstrated poor correlations between short-term height velocity and annual height velocity (31–35), and between corticosteroid-induced changes in short-term lower leg growth rate and statural growth over the subsequent year. Lower leg length velocity over 1 month does not correlate with the variation in annual statural height velocity (34, 35). In addition, the correlation between two consecutive annual height velocity measurements for normal prepubertal children is very poor. A low gain over 1 year is not necessarily followed by a low gain the next year and vice versa (34). There is only a partial correlation between 1-, 2-, 3- and 4-year values (34), and height velocity over a 3- or 4-year period in childhood explains only 34% and 38% of the variation in final height, respectively. Therefore, a change in growth markers or a significant effect on growth found in short- or intermediate-term studies is not necessarily equivalent to an effect on long-term growth or adult height.

Normal growth is nonlinear in the long term and unpredictable in the short term. Furthermore, growth in asthma is influenced by a host of factors including disease severity, social and psychological factors, nutrition, age, puberty, genetic factors, exposure to smoking and treatment. It is therefore extremely difficult to carry out an optimal study on the influence of inhaled corticosteroids on growth. Of course, the design of the study depends on the research question asked. In this respect, it is important to differentiate between:

- 1) studies designed to detect systemic effects of inhaled corticosteroids; and
- 2) studies designed to assess clinically relevant effects of inhaled corticosteroids on growth.

Assessment of measurable systemic effects of inhaled corticosteroids. Most studies into possible effects on growth to date have been designed to evaluate the systemic effects of inhaled corticosteroids. Typically, these studies are parallel group studies of short duration (1 year or less). They include only children with mild asthma and in a limited age range (6–9 years), and use a fixed dose of inhaled corticosteroid that is not adjusted to disease activity or severity. As discussed earlier, these factors all increase the likelihood of detecting an adverse effect on growth (children with mild asthma have a greater systemic exposure to the inhaled drug, children aged 6–9 years are the most susceptible to the effect of exogenous corticosteroids, and the effect of an inhaled corticosteroid on growth seems to be more pronounced at the beginning of the treatment). Also, the growth-inhibiting effect of mild disease is minimal and therefore the likelihood of a possible beneficial effect on growth by improved asthma control is small.

The results of these studies conducted during a “narrow window of childhood growth” cannot be used to predict growth during long-term treatment in a clinical setting, when the dose of inhaled corticosteroid is titrated

to disease severity and all age groups are treated for asthma (36). They are, however, suitable for:

- 1) assessing the relationship between dose and the growth-inhibiting effects of individual inhaled corticosteroids or inhalers;
- 2) comparing the growth-inhibiting effects of different inhaled corticosteroids or inhalers;
- 3) comparing growth during treatment with an inhaled corticosteroid with that of and another class of drug; and
- 4) defining the dose of inhaled corticosteroid that is most unlikely to be associated with any detectable adverse effects on growth.

Assessment of clinically relevant effects

Studies designed to assess the clinically relevant effects of inhaled corticosteroids on growth are conducted over several years and include children of all ages. In addition, the dose of inhaled corticosteroid is titrated to the severity of the disease at regular intervals.

If children with only mild disease are included, such studies can be used to compare growth during treatment with an inhaled corticosteroid with growth during treatment with another class of drug or placebo, or with another inhaled corticosteroid. If children with more severe disease are included, only the last option is feasible because inhaled corticosteroids are clinically markedly more effective than other classes of drugs or placebo. Attempts to compare inhaled corticosteroids with other drugs in these patients would lead to differences in drop-out rates during the study and, by the end of the study, the groups would no longer be comparable with respect to disease severity. Poor asthma control is a common reason for withdrawal from clinical trials and, because children with uncontrolled asthma grow more slowly, such withdrawals may cause an upwardly biased estimate of the mean growth rate for the control group. Finally, this study design also allows more accurate predictions about possible effects on final adult height and assessments of growth effects at different ages.

Effect of inhaled corticosteroids on markers

Several placebo-controlled cross-over studies have assessed markers of bone and collagen resorption and formation. All the studies found that high daily doses of inhaled corticosteroids ($>400 \mu\text{g}$) had a statistically significant effect on some of these markers in children. All studies were short term and involved patients with relatively mild disease. Lower doses of inhaled corticosteroids did not affect the levels of the various markers adversely in most studies. Thus, inhaled corticosteroids at standard paediatric doses ($<400 \mu\text{g/day}$) have no reported adverse effects on markers of bone formation and degradation or on markers of growth. Higher doses

may, however, cause significant changes, which suggest a reduced bone turnover rate.

The clinical relevance and predictive value of treatment-induced changes in growth markers remains unknown. A recent study found no correlation between the levels of various markers and corticosteroid-induced changes in these markers and statural growth during budesonide treatment for 1 and 2 years (37), indicating that the predictive value of corticosteroid-induced changes in these markers is low and that assessment of changes is not clinically useful. This is in good agreement with the observation that growth markers have been found to correlate poorly with growth rate in healthy children (38). Furthermore, a study to assess the clinical usefulness of the various markers in children suspected of corticosteroid-induced growth retardation and children with normal growth during treatment with inhaled corticosteroids found no clinically useful differences in GH secretion, serum cortisol, osteocalcin and IGF-1 levels, or bone mineral density between the two groups (39). Thus, the relevance of changes reported from short-term studies to long-term clinical outcomes remains to be demonstrated (40).

Changes in growth markers may also occur with other forms of treatment for asthma. Sodium cromoglycate has been found to be associated with significant effects on the excretion of GH in the urine (1) and markers of bone metabolism (2), and inhaled β_2 -agonists have been found to adversely affect GH secretion (3, 4, 41). Although statistically significant, these findings are probably not clinically relevant.

Short-term growth studies

Knemometry measures changes in short-term linear growth of the lower leg within weeks and may be a valuable adjunct/alternative to traditional methods, because it enables the study design to be well controlled. To date, all children participating in placebo-controlled, double-blind knemometry studies have had mild asthma, which has not required continuous treatment with inhaled corticosteroids (42–51). The results have shown that the effect of inhaled corticosteroids on lower leg growth rate is dose-dependent with no detectable effect at low doses. Moreover, the dose-response curves for growth inhibition seem to differ between the various inhaled corticosteroids.

As with growth markers, the clinical implications of the findings of knemometry studies still need further assessment, since lower leg growth velocity over 1 month and short-term corticosteroid-induced changes in lower leg growth rate do little to explain the variation in annual statural height velocity (34, 35). Treatment for 2 weeks with oral prednisolone, 2.5 mg/day or 5 mg/day, or inhaled BDP, 400 μ g/day, has been found to stop lower leg growth completely (52, 53). This suggests that knemometry is a very sensitive tool, which probably

exaggerates the growth-stunting effects of exogenous corticosteroids. On the other hand, it also suggests that if an exogenous corticosteroid has no adverse effect on lower leg growth in a properly performed knemometry study, it is unlikely that such treatment will be associated with any growth suppression during long-term treatment. This assumption is supported by the finding that, so far, none of three well-powered growth studies that have been carried out has found any adverse effects of inhaled corticosteroids on statural growth at doses found not to adversely affect lower leg growth in well-designed knemometry studies.

Intermediate-term studies

A large number of intermediate-term studies have evaluated the effect of inhaled corticosteroids on statural growth (13, 19, 20, 26–28, 54–79). Most have been carried out in schoolchildren and none of those carried out before 1993 included a control group. None of these studies, comprising more than 3500 children treated for mean periods of 1–13 years, found any adverse effect of the inhaled corticosteroid on growth. In agreement with this, a meta-analysis of 21 studies representing 810 patients has to some extent corroborated these findings. The analysis compared the attained height with the expected height of children with asthma treated with inhaled or oral corticosteroids (80). Significant, although slight, growth impairment was found in children receiving oral corticosteroids, whereas children treated with inhaled corticosteroids attained normal height. Furthermore, there was no statistical association between inhaled corticosteroid therapy and growth impairment either at higher doses or during extended therapy.

A recent follow-up in family practices of a cohort of 3347 children with asthma corroborated these findings, but also highlighted the complexity of the growth process. This study found that most children had normal growth rates and only those receiving daily doses of inhaled corticosteroids of 400 μ g or above showed growth impairment. This effect on growth was, however, smaller than the effect of poor socioeconomic status or severe asthma (30). This study illustrates how important confounding factors may be in growth studies and such factors must therefore be accounted for in the analysis of the data.

In contrast to these findings, several parallel-group studies conducted over the last few years have found significant growth retardation in children with mild asthma treated continuously for 9–12 months with a fixed daily dose of BDP of 400 μ g (10, 18, 78, 79, 81, 82). The magnitude of the growth reduction in these trials has been consistent, ranging from 0.9 to 1.5 cm/year of treatment.

In at least two of the studies with BDP, the difference in growth rate between BDP and placebo was due mainly to a markedly lower growth rate in the BDP-treated children

during the first 3 months of the study. After this, the growth rate in the BDP group was similar to that in the placebo group (10, 79).

Fluticasone propionate, 100 µg/day or 200 µg/day, was found not to affect growth adversely (83, 84) in two 1-year growth studies.

The growth studies with budesonide have all been longer than 1 year and the asthma disease in the children in the studies seems to have been somewhat more severe than that in the patients in the previously mentioned 1-year growth studies. Over the 3–6 years, the annual increase in height was not affected adversely by the budesonide treatment in 216 children (26). Because the dose of budesonide varied in each individual child during the treatment period, the influence of the budesonide dose on growth could not be assessed accurately. However, when high doses were used (> 400 µg/day), both growth rate and lung function were lower than during run-in and during treatment with 400 µg/day, indicating that either high doses or poor asthma control (or both) adversely affected growth.

A randomized study compared growth over 2 years in children treated with a fixed dose of budesonide, 600 µg/day via pMDI or placebo (77). Budesonide treatment was found not to affect growth adversely.

The largest (approximately 1000 patients aged 5–12 years) and longest randomized growth study conducted so far compared growth over 4.3 years during treatment with budesonide, 400 µg/day via Turbuhaler, nedocromil, sodium and placebo (14). In the first year of treatment, the mean growth rate in the budesonide group was significantly lower (around 1 cm/year) than in the two other groups. The growth rate during the last 3 years of the study was similar in all three groups and, at the end of the study, bone age, projected final height and Tanner stage in the two active treatment groups were similar to those in the placebo group. The authors concluded that extrapolating the findings of 1-year growth studies to subsequent years is inappropriate.

Conclusions from short- and medium-term growth studies in children receiving inhaled corticosteroid therapy for asthma.

- 1) Controlled studies have not reported any statistically or clinically significant adverse effect on growth with orally inhaled corticosteroids at the usual childhood doses of 100–200 µg/day (16, 37, 82, 85).
- 2) Growth retardation may be seen with all inhaled corticosteroids when a sufficiently high dose is administered without any adjustment for disease severity and control.
- 3) Growth suppression in both short- and intermediate-term studies is dose-dependent.
- 4) Important differences seem to exist between the growth-retarding effects of various inhaled corticosteroids and inhalers (16, 86).

- 5) Different age groups seem to differ in their susceptibility to the growth-retarding effects of inhaled corticosteroids; children aged 4–10 years are more susceptible than pubertal children (13, 18).
- 6) The growth-retarding effect of inhaled corticosteroid treatment seems to be more marked at the beginning of treatment and, in some way, becomes attenuated with continued treatment (10–14).
- 7) There seems to be a discrepancy between the findings in the placebo controlled studies in well-defined patient groups and the findings in less controlled, more “real world” studies (the former studies finding an effect whereas the latter normally do not).

Long-term studies and studies of final adult height

Most physicians consider attained adult height to be the most important growth outcome and the key question with regard to effects on growth is whether the slowing in short-term growth rates leads, ultimately, to a diminished adult height. At present, few prospective long-term studies of attained adult height have been conducted. Because the number of studies is low, and the design and methods of the various studies vary, each study will be summarized briefly.

Retrospective studies. One study (87) comparing the adult heights of all pregnant women born in Sweden between 1960 and 1974 with the heights of all pregnant women with asthma ($n = 2738$) born during the same period. The authors concluded that asthma may itself adversely affect adult height and that this effect may be more marked if the asthma is severe. This is in good agreement with the findings of other studies in children with asthma (13, 29), and the observations in children with other chronic diseases (88, 89).

Other studies (29, 90–92) have compared the measured adult heights of corticosteroid-treated children with their target adult heights. One study found that the adult height of children with asthma treated with inhaled corticosteroids was not significantly different from that of adults with asthma who were not treated with corticosteroids (90). Another study (29) found that mean attained adult height in patients who took inhaled corticosteroids during childhood was the same as that in those who had never received such treatment. However, the difference between adult height and target height was significantly lower in corticosteroid-treated patients than in those who had never received inhaled corticosteroids. Furthermore, the difference between adult height and target height was lower in patients who had been hospitalized for asthma than in those who had never been hospitalized, indicating that asthma severity negatively influenced attained adult height. A third study (91) compared the measured adult heights of 97 children treated with inhaled corticosteroids during childhood with the adult heights of 70 noncorticosteroid-treated

patients with asthma and 136 healthy controls. Use of inhaled corticosteroids did not affect adult height adversely. Similar results were reported in a study which assessed the longitudinal growth of 97 children treated with BDP in daily doses of 300–800 µg for more than 8 years (92).

Prospective studies. Balfour-Lynn (19, 20) followed 66 children with asthma for an average of 13.1 years. Final adult heights were reported to be within the expected range in the children treated with BDP. No data on predicted height estimated from parental height were given.

Recently, the findings of all these studies were corroborated by a 14-year prospective, long-term study in which asthmatic children were treated with inhaled budesonide for several years in doses tailored to disease severity (13). One hundred and forty-two children attained adult height after a mean of 9.2 years of budesonide treatment at a mean daily dose of 412 µg. Eighteen control children with asthma, who never received any inhaled corticosteroids, and 51 healthy siblings were also followed until adult height was attained. The budesonide-treated children attained their expected adult height to the same extent as their healthy siblings and the control children. Height standard deviation scores (SDS) before treatment with budesonide correlated positively with percentage of predicted FEV₁, indicating that asthma severity influenced growth. Furthermore, adult height depended significantly upon height SDS before budesonide treatment. Growth rates were reduced significantly during the first 2 years of budesonide treatment but the reduction in annual growth rate did not persist and the changes in growth rate during this period showed no relation to the differences between measured and target adult height.

The authors concluded that long-term treatment with inhaled budesonide did not affect adult height adversely, whereas poorly controlled asthma did. Furthermore, changes in growth rate during the first year of budesonide treatment were not useful in predicting adult height (Fig. 2). These conclusions are in good agreement with the findings in the largest and longest randomized growth study conducted so far (14).

Although prospective studies of several years' duration and retrospective analyses may be criticized for being less controlled than prospective, short-term studies, some conclusions from them about the effect of inhaled corticosteroids on adult height seem to be justified.

- 1) Uncontrolled or severe asthma seems to affect growth and attained adult height adversely.
- 2) Corticosteroid-induced changes in growth rate during the first 1 or 2 years of treatment do not predict adult height.
- 3) Children with asthma treated with inhaled corticosteroids have been found consistently to attain normal final adult height.

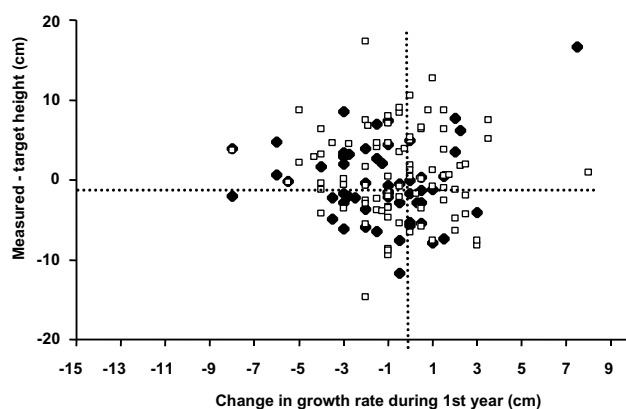


Figure 2. Association between changes in growth rate during first year of budesonide treatment and the difference between measured and target adult height in 142 children with asthma treated with inhaled budesonide for a mean of 10 years. The changes in growth rate during the first year of treatment were not correlated with the differences between measured and target adult height ($P = 0.44$), emphasizing that inhaled corticosteroid-induced changes in growth rate during 1 year of treatment are unrelated to the attained adult height even if the inhaled corticosteroid treatment is continued for several years. So, even if a child grows 3 cm less during the first year of treatment with an inhaled corticosteroid this will not influence adult height.

Discrepancies between intermediate- and long-term growth studies

The reason for the apparent discrepancy between the findings of some intermediate-term studies and the conclusions of the studies on adult height is not clear. Intermediate studies with BDP have found a growth retardation of 1.5 cm per year. An annual growth retardation of 1.5 cm, if persistent, would be expected to result in a cumulative mean reduction in measured adult height of 15 cm were the treatment given continuously for 10 years. Such marked effects would be difficult to miss in the day-to-day clinic or in long-term prospective studies. Some possible explanations for the discrepancy are as follows (Fig. 1).

- 1) As mentioned earlier, the correlation between two consecutive annual height velocity values for normal prepubertal children is poor. A low gain in one year is not necessarily followed by a low gain the next year and vice versa (34). The correlation between 1-, 2-, 3- and 4-year growth velocities is only partial (34) and growth rate computed over a period of 3 or 4 years in childhood explains only 34% and 38% of the variation in final height, respectively.
- 2) The growth retarding effect of exogenous corticosteroids is most pronounced during the first year of treatment (10–14). Therefore, conclusions from short-term studies of 1 year should not be extrapolated to the long-term situation (36).
- 3) Corticosteroids seem to retard bone maturation. If this occurs to the same extent as the retardation of growth then final height should not be adversely

affected (because bone age will correspond to height age). Such children will grow for a longer period than their peers and eventually attain normal final height.

- 4) The results obtained in prepubertal school children may not be valid in other age groups because prepubertal children may be more sensitive to the growth retarding effect of inhaled corticosteroids (13, 18). If the pubertal growth spurt is not affected adversely the effect on final height may be small.
- 5) In a real-life situation children with mild asthma are not treated continuously with a high, fixed dose of inhaled corticosteroid. The dose is adjusted to the severity of the disease. Only children with moderate or severe asthma would require continuous treatment with daily doses of 400 µg or more. The systemic effects in these children may be lower than in children with mild disease (5, 7, 8). Many clinics would also use spacers when administering inhaled corticosteroids with low first-pass metabolism.
- 6) Compliance may be lower during long-term “real life” treatment than during a controlled trial with several visits to the clinic, although when compliance was assessed in two studies it did not seem to explain the findings (13, 14).

More prospective studies are needed to assess the relative importance of these possibilities.

Bone mineral density

In children the rate of bone modelling or turnover is much higher than in adults. Furthermore, in adults the skeletal mass is decreasing over time, while in children it is increasing over time until peak bone mass/density is reached in early adulthood. The increase in bone mass is not a constant process but varies with age and season of the year. The skeletal modelling/turnover rate and the retention of calcium are highest during spring and summer and during infancy and adolescence. Normally, most of the skeletal mass will be accumulated by late adolescence. Just as adult height in relation to predicted adult height is the most important outcome measure of growth in children, so fracture or maximal peak bone mass/density is probably the most clinically relevant outcome measure for assessing the influence of steroids on bones in children. In addition to nutrition (including calcium intake), heredity (both parents), endocrine factors (sexual development), poor asthma control and physical activity appear to have profound effects on peak bone mass formation (93–101). Some chronic diseases have also been reported to be associated with reduced peak bone mass in children (102, 103). The finding that delayed puberty in itself is associated with a significantly lower peak bone mass/density (104, 105) is particularly important in the clinical management of children with asthma as this condition is seen in many children with asthma and atopy, independent of treatment. Obviously,

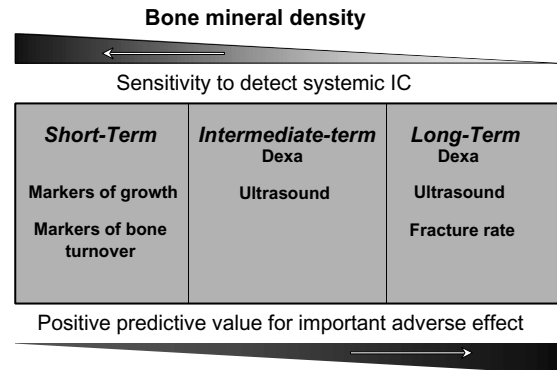


Figure 3. Different designs of studies assessing adverse effects of inhaled corticosteroids on bones. The clinically most important outcome is risk of fracture. The remaining outcomes are surrogate markers for the main outcome: risk of fracture. The long-term predictive value for changes in short-term outcomes is very poor. The predictive value of bone mineral density (BMD) increases with the duration of the study period. Studies on clinically relevant adverse effects of inhaled corticosteroids on BMD and risk of fracture should be long-term and use doses of inhaled corticosteroids that are tailored to the disease severity.

these confounding factors must be considered when the effects of steroids on bone metabolism are assessed. Finally, children show a remarkable ability to repair steroid induced bone loss. Children <3 years with synacten-induced compression fractures of the spine had normal X-rays of the spine 5–10 years later (106). Such remodelling and repair are not seen in adults. The different designs used to assess adverse effects of corticosteroids on bones are summarized in Fig. 3.

Bone densitometry has been applied to assess the bone mineral density (BMD) in children receiving inhaled corticosteroids in two long-term trials. The findings have been consistent. A long-term, prospective study found that total body BMD of children treated with 3–6 years of continuous inhaled budesonide at an average daily dose of around 500 µg was not different from the BMD of 112 children with asthma, who had never received inhaled or oral steroids (107) (Fig. 4). Furthermore, bone density did not correlate with years of budesonide treatment or current or accumulated dose of budesonide. These findings were corroborated in a prospective, randomized, double-blind study on 1000 children, which compared the changes in BMD over 4 years in three groups of children with mild asthma. No differences were found in increases in BMD between the group which received inhaled budesonide at a daily dose of around 400 µg, and the groups of children treated with nedocromil or placebo (14). Several cross-sectional studies and prospective, longitudinal studies on much smaller groups of children treated for shorter periods of time with inhaled steroids have reported similar results (103, 108–111).

In summary, low doses of inhaled corticosteroid are not associated with any changes in biochemical markers

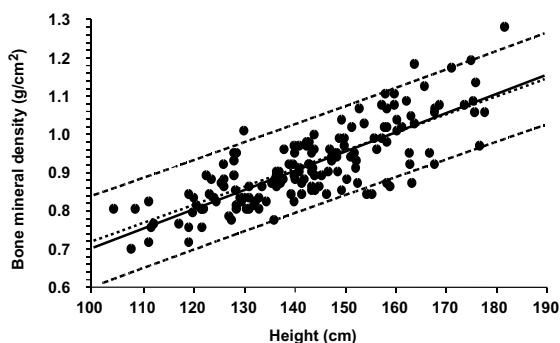


Figure 4. Individual bone mineral density (BMD) as a function of height and age in 157 asthmatic children treated continuously for 3–6 years with the inhaled corticosteroid budesonide at a mean daily dose of 504 μg . For comparison, the 95% prediction interval and mean regression lines from measurements in 111 children with asthma who had never received continuous treatment with exogenous steroids are given.

of bone formation or degradation, whereas low doses of prednisolone (2.5–5 mg/day) and high doses of inhaled corticosteroids affect some of these markers adversely. Even if short-term studies show effects on markers of bone turnover, 4–5 years treatment with inhaled budesonide at an average daily dose of 400 μg is not associated with an increased risk of reduced bone mineral density, osteoporosis or fracture in children. Further controlled prospective studies are needed to assess the effect of long-term treatment on peak bone mass/density.

Discussion of adverse effect outcomes

The literature on growth and bone mineral density in children emphasize clearly the poor long-term predictive value of changes in markers of growth or bone turnover or reductions in growth velocity in short-term studies (studies shorter than 3 years). This questions the clinical relevance of the findings in such studies. The observed changes seem to be more a marker of the systemic activity of the inhaled corticosteroid (as a 10% reduction in cortisol excretion in the urine is a marker of a systemic activity) rather than a clinically important finding which will predict long-term outcome. Most people would agree that to be clinically important the reduction in growth rate or change in markers should be either persistent and predictive of the long-term growth or increase in BMD of the patient (or group of patients) or predictive of achieved adult height or peak BMD of the patient (or group of patients). It seems that neither of these criteria is fulfilled for the reductions in growth rate found in short- or intermediate-term growth studies or markers or for the changes in markers of growth and bone turnover. This is supported by the findings of the two longest and most comprehensive growth studies conducted so far. Although inhaled budesonide in these studies led to a reduced growth rate during the first year of treatment,

attained adult height was not affected adversely, even if these doses were used for several years. Furthermore, changes in growth rate during the first year of treatment were not useful in predicting long-term growth or adult height. This would also explain the paradox that several short-term studies have found marked reductions in growth rate during 1 year of treatment, whereas long-term treatment with inhaled corticosteroids has been found consistently not to adversely affect adult height. Although the data are not so strong for BMD it has become clear that changes in markers of bone turnover do not predict long-term changes in BMD. Furthermore, it seems that the effect of oral steroids on bone may be more marked during the first year(s) of treatment than later on: just as the effect on growth is more marked in the beginning of treatment. These findings emphasize the importance of undertaking long-term studies to assess long-term safety outcomes. These outcomes cannot be assessed upon the findings in short-term trials.

Clinical effect outcomes

In modern asthma management both short-term and long-term outcomes must be considered. The immediate aim is to produce the maximum achievable effect on *all* known outcome parameters. The long-term aim is to prevent clinical progression of the disease and/or prevent complications of the disease or its pharmacological treatment. If the immediate aim is not achieved the risk of also missing the long-term aim is increased.

Undoubtedly, the majority of both short and long-term outcome parameters are related to some extent to the degree of airway inflammation. However, at present we do not have the tools to measure all aspects of airway inflammation in day-to-day management and it is not clear to what degree the inflammatory process must be suppressed or which aspects of inflammation need to be controlled to influence the various outcome parameters.

Immediate aims

Over the last decade, a number of well-conducted dose-response or dose titration studies with inhaled corticosteroids have been carried out in children, mainly in groups with moderate and severe asthma (112–117). The findings of these studies have been consistent and in good agreement with the findings of dose-response studies in adults (16). All studies have demonstrated marked and rapid clinical improvement and changes in symptoms and lung function at very low daily doses of about 100 μg . Additional improvement in these parameters with increasing doses is small, often requiring an additional fourfold increase in dose to produce a further statistically significant (but clinically very small) effect. In patients with mild disease, low doses have also been found to normalize exhaled nitric oxide (eNO) and to offer full

protection against exercise-induced asthma (117, 118), whereas children with more severe asthma may require 4 weeks' treatment with budesonide, 400 µg/day via a pressurized metered-dose inhaler (pMDI) plus spacer, to achieve maximum protection (113). Low doses are so effective clinically that even very large, well-conducted studies normally fail to show any statistically significant or clinically relevant additional effect on symptoms and lung function when the dose is increased above 100 µg/day (16). The marked effect of low doses may be even more pronounced in children with mild disease but, at present, no studies have used doses below 100 µg/day.

It seems clear from these data that the majority of asthma patients will be well controlled on rather low doses of inhaled corticosteroid. However, certain outcomes, such as maximum control of airway inflammation, exacerbations or bronchial hyper-responsiveness or exercise-induced asthma in patients with more severe disease may require higher doses of inhaled corticosteroids (or add-on treatment with another drug). The concern therefore is that low doses of inhaled corticosteroid may produce good *subjective control without optimal disease control*, i.e. achieving the short-term aim only. The results of a recent study supports this assumption indirectly because inclusion of bronchial hyper-responsiveness (surrogate marker of inflammation) as an outcome in the daily clinical management led to the use of higher doses of inhaled corticosteroid, improved asthma control, less airway remodelling and fewer exacerbations (119) (Fig. 5). Further studies are needed to address this question.

Long-term aims

In addition to maintaining the short-term aims throughout childhood the long-term aims are also to prevent clinical progression of the disease and/or prevent complications of the disease such as interference with normal psychosocial development and airway remodelling and its clinical consequences.

Psychosocial development. At present no long-term studies have assessed the psychosocial development of optimally treated and under-treated children. Several studies have found that under-treated or nontreated children with asthma are physically and socially impaired in their daily living and often have to markedly adjust their lifestyle. The question is what the long-term consequences of this are – if any – and, if present, whether they are preventable by continuous optimal treatment? Several studies have shown that asthma severity and its impact of disease on daily life are often greatly underestimated because of the difficulty in correctly assessing symptoms and the extent to which the patient has adapted his or her lifestyle to avoid symptoms (120–122). As a consequence many patients are under-treated, optimal asthma control is not achieved and

effective treatment is either not prescribed or prescribed after the asthmatic condition has progressed for a number of years, when the effect may be less than if it had been prescribed early in the course of the disease. Unfortunately we do not have well-defined objective ways at present of assessing a patient's physical activity or impairment under daily living conditions. Until we have such tools it will be very difficult to assess accurately the long-term consequences of the disease imposed change in lifestyle.

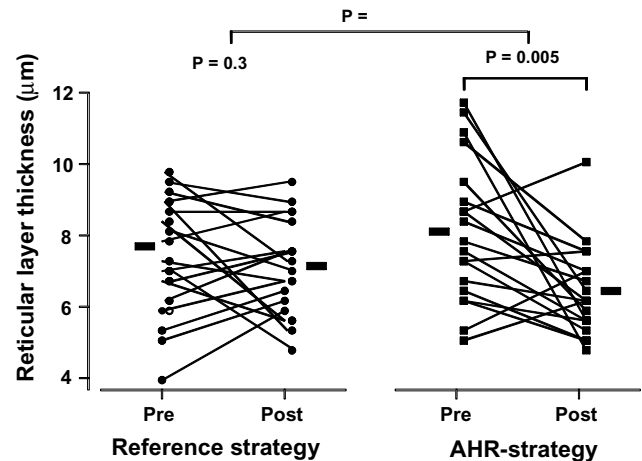


Figure 5. Changes in reticular layer thickness (airway remodelling) over 2 years in two groups of patients treated with different doses of inhaled budesonide. The inclusion of bronchial hyper-responsiveness (surrogate marker of inflammation) as an outcome in the daily clinical management led to the use of higher doses of inhaled corticosteroid, improved asthma control, less airway remodelling and fewer exacerbations (119).

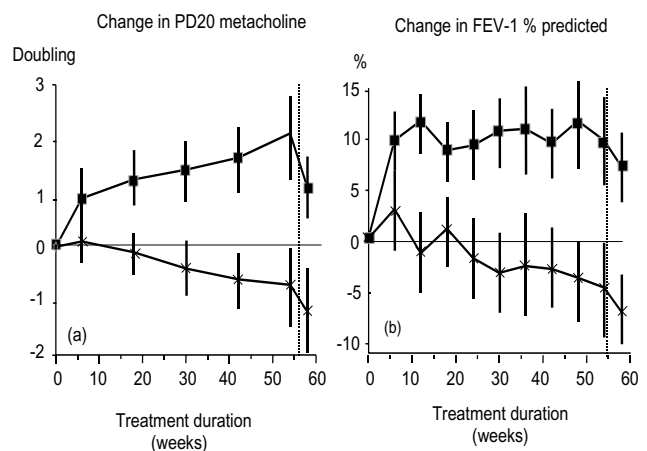


Figure 6. (a) Changes in airway responsiveness (PD_{20}) in doubling doses (mean, 95% CI) from baseline during treatment with salmeterol (closed squares) or beclomethasone (crosses). (b) Changes in FEV_1 % predicted (mean, 95% CI) from baseline during treatment with salmeterol (squares) or beclomethasone (crosses). A significant fall reduction in FEV_1 and a worsening of airway responsiveness was seen during treatment with salmeterol.

Clinical progression and complications. The adverse effects of treatment have been discussed earlier. Therefore, only prevention of progression of the disease and disease complications will be discussed briefly.

The prevention of airway remodelling and its potential consequences is complex. It has become well established that significant inflammation is present in early asthma as well as in patients experiencing symptoms for only a short period, and in those with only mild disease. Airway remodelling, including increases in airway smooth muscle (hyperplasia and hypertrophy), vascular proliferation, increases in bronchial glands, oedema formation and collagen deposition (123) is also present to some extent in the majority (all?) patients with persistent asthma. Some studies suggest that airway remodelling increases with time and also with disease severity. However, the direct relation of airway inflammation and remodelling is not known. The two conditions seem to be connected to some extent and treatment with inhaled corticosteroids modifies both airway inflammation and remodelling. The question is how inflammation and remodelling are linked to long-term clinical outcomes of asthma such as disturbances of lung function, development of irreversible changes in lung function, progression of clinical disease severity and increased bronchial responsiveness? This is difficult to assess because we have no effective methods of quantifying the degree of remodelling in the small airways or measuring the function of peripheral airways.

There is some indirect evidence that remodelling may have some long-term clinical consequences. A number of studies have found that growth of lung function was compromised in children with persistent asthma compared with healthy nonasthmatic children (18, 26, 124–126). Others have reported a negative correlation between percentage of predicted lung function, bronchial hyper-responsiveness and asthma severity and duration of asthma before treatment was initiated (26, 127), or a poorer growth of lung function or worsening of bronchial hyper-responsiveness with time. Finally, subjects with persistent asthma during childhood continued into adult life with lower levels of lung function (124, 128–133) and increased bronchial reactivity to specific and nonspecific agents (127, 134–136), regardless of the presence of asthmatic symptoms. Finally, several studies have reported patients in whom chronic childhood asthma has been suspected of leading to chronic irreversible airway obstruction to a clinically important extent (124, 125, 128–131, 137, 138). Furthermore, chest deformities due to persistent hyperinflation are not uncommon.

Several of these studies have been cross-sectional, but the findings in longitudinal studies generally seem to support the findings from cross-sectional studies. Few studies have tried to relate lung function measurements to airway inflammation. The data in the various studies

have normally been presented as significant differences in the group mean data. However, the interpatient variation seems to have been marked. Generally, the different studies have used crude outcome measures, such as FEV₁ or FVC, which do not reflect smaller airway function and which may remain normal even in the presence of marked damage of the smaller airways. It is not known whether measurement of other outcomes would have been more sensitive in detecting the consequences of airway remodelling. With these reservations in mind the literature suggests that the chronic inflammation of asthma can influence growth of lung function adversely and the progression of the disease – at least in some patients. None of the studies has examined individual risk factors so it will be difficult to identify in advance those individuals who are likely to develop these complications to a clinically important extent. It seems, however, that the risk is higher in patients with more severe disease.

Can treatment modify long-term disease progression or complications of airway remodelling? Disease progression and complications of airway remodelling may not be totally separate entities; a marked degree of overlap may exist. There is no agreed definition of disease progression. However, several outcomes suggest disease progression:

- Increased severity or frequency of symptoms.
- Development of exacerbations.
- Increased bronchial hyper-responsiveness.
- Increased medication requirement.
- Decline in or reduced growth of lung functions.
- Hospitalization or death.
- Development of chest deformities.

Several controlled studies and epidemiological evidence have shown that regular treatment with inhaled corticosteroids reduces frequency and severity of symptoms, frequency and likelihood of development of an exacerbation, improves bronchial hyper-responsiveness and reduces the need for additional medication, chest deformities, hospitalization and death (Figs. 5–7). Therefore, with the definition of progression outlined above, inhaled corticosteroids can modify the progression of the asthma disease. The effect on these outcomes seems to be maintained as long as the treatment is taken. For some outcomes, such as bronchial hyper-responsiveness, there even seems to be a continuous improvement for years. The same may be the case for some of the other outcomes, but they have not been studied to the same extent. There is no evidence that treatment may “cure” the disease once it has become clinically manifest.

The evidence for a possible long-term effect on decline or growth of lung function is more indirect and comes mainly from trials comparing early and late use of inhaled corticosteroids in the course of the disease.

One study compared two treatment strategies: inhaled corticosteroids as first-line therapy vs β_2 -agonist alone (139, 140). Patients with asthmatic symptoms of less than a

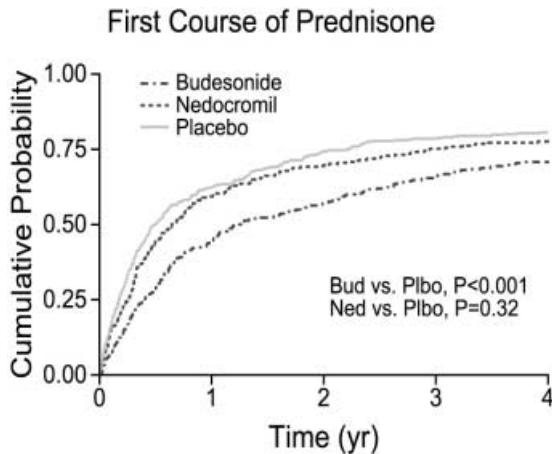


Figure 7. Effect of long-term treatment with inhaled budesonide on exacerbations requiring prednisolone. The probability of receiving prednisolone was significantly lower in children treated with budesonide than in children treated with Nedocromil sodium or placebo, indicating that budesonide reduced the progression of the asthma disease.

year's duration and with no previous history of anti-inflammatory therapy were randomized to treatment with either inhaled budesonide or terbutaline as the first and only regular medication. Two years' treatment with inhaled budesonide resulted in almost complete clinical recovery and normalization of lung function. Furthermore, inhaled budesonide treatment was superior to β_2 -agonist treatment. Bronchial biopsies, taken from a subgroup of patients, revealed that the budesonide-treated patients had a significantly greater reduction in the numbers of inflammatory cells than the terbutaline-treated patients (141). The study was continued for a third year to investigate the effects of discontinuation of steroid treatment and a delayed introduction of inhaled steroid. Most of the patients who switched from budesonide to placebo showed a gradual and slight decline in lung function, which became significant towards the end of the third year, but 20% did not deteriorate at all (140). Those patients who had received terbutaline for 2 years before treatment with budesonide was initiated did not reach the same level of lung function or improvement in bronchial hyper-responsiveness as those who were treated with budesonide during the first 2 years of the disease. This finding suggests that some functional reversibility was lost by delaying the start of inhaled corticosteroid treatment – perhaps due to the failure of a continuous β_2 -agonist to affect the underlying airway inflammation of asthma.

Overbeek et al. reported similar results in a more heterogeneous group of patients who had already experienced symptoms for several years before the start of the study. The patients, who were on maintenance β_2 -agonist therapy, were randomized to 2.5 years' additional intervention with either inhaled anticholinergic, inhaled corticosteroid or placebo (142). The addition of inhaled corticosteroid to maintenance treatment with

β_2 -agonists improved symptoms, lung functions and bronchial responsiveness. The study was continued after the first 2.5 years to investigate the effects of adding 800 μg daily inhaled beclomethasone to the patient groups that had not previously received it. Airway hyper-responsiveness showed no significant change after 6 months in these patients, whereas it had shown significant improvement as early as 3 months after starting inhaled corticosteroid among the patients who had received beclomethasone during the initial 2.5-year treatment period. Similarly, the increase in lung function was lower when inhaled corticosteroids were started after 2.5 years delay compared with the early initiation of inhaled corticosteroids.

The protective effect of inhaled corticosteroids on the possible decline in lung function associated with continuous nonspecific obstructive lung disease has also been addressed in a study by Dompeling et al. (143). During the first 2 years of this study, patients were treated with bronchodilator therapy alone. While the patients demonstrated and maintained a bronchodilator response to inhaled β_2 -agonist, lung function (FEV_1) showed a decline greater than that normally associated with ageing. At the end of the first 2 years, inhaled beclomethasone was instituted at 800 $\mu\text{g}/\text{day}$. The initiation of inhaled corticosteroid resulted in significant improvement in pre-bronchodilator lung function and an equivalent improvement in FEV_1 values measured post-bronchodilator. Additionally, the annual decline in lung function noted during the initial 2 years, i.e. during treatment with bronchodilator alone, was lessened during treatment with inhaled corticosteroids.

Verbene and colleagues (18) found that 1 year's treatment with beclomethasone 400 $\mu\text{g}/\text{day}$ had a significantly better effect than salmeterol 50 μg twice daily on lung function, rate of asthma exacerbations, morning and evening PEF rates and symptoms in children with asthma (19). Furthermore, both pre- and post-bronchodilator lung functions grew significantly better during treatment with beclomethasone. Indeed there was a significant trend towards a decrease in lung function over the year and an increase in bronchial hyper-reactivity among the children treated with salmeterol (Fig. 6). These results are similar to those obtained in a similarly designed study in which inhaled budesonide was compared with short-acting β_2 -agonists (144).

Selroos et al. (145) evaluated the correlation between the response to treatment and the duration of symptoms prior to starting inhaled corticosteroids for the first time. A negative correlation between improvement in lung function following inhaled corticosteroid therapy and duration of asthma was found.

In a long-term study in children (26) inhaled budesonide treatment was compared with treatment combinations of other anti-asthma drugs in 278 children over a period of 3–6 years. Marked improvements were seen in lung function, peak flow variability, symptoms

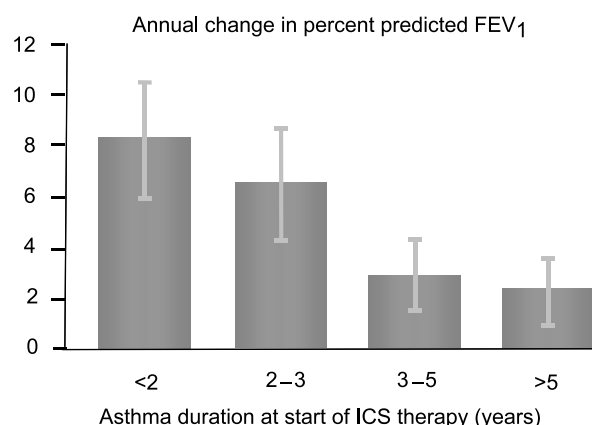


Figure 8. Influence of asthma duration at the start of inhaled budesonide on the mean annual increase in percentage predicted FEV₁ after initiation of budesonide treatment. Children in relation to the duration of asthma at the time when treatment with inhaled budesonide was initiated. Children who started early had a more rapid and obtained significantly better lung functions than children who did not receive budesonide treatment until some years after the onset of asthma symptoms.

and hospitalization rate in the budesonide-treated group. Furthermore, the group treated with budesonide showed significantly increased lung function growth rates compared with the children not receiving inhaled budesonide. Children who started treatment early had a more rapid response and obtained significantly better lung function than the children in whom budesonide was not started until some years after the onset of asthma symptoms (Fig. 8). In addition, the accumulated dose of budesonide taken after 4.5 years of continuous treatment was significantly lower among the children who started budesonide treatment early than in the group of children in whom budesonide treatment was not initiated until after more than 5 years of continuous symptoms.

The long-term implications of these studies are not known. A study of 181 patients aged 13–44 years, which assessed the chance of improving or even becoming symptom-free over a period of more than 25 years, found that the longer the patients went without treatment after

debut of symptoms the less likely they were to show decline in, or normalization of, bronchial hyper-responsiveness (146). The data also indicated that patients who improved or became symptom-free tended to be those who were diagnosed and treated at a younger age or had less severe disease at the time of diagnosis. This corroborates the observation in another study: children who started inhaled corticosteroids early had better lung function at a lower accumulated dose of budesonide after 4.5 years of treatment than children in whom inhaled steroids were not initiated until after more than 5 years of symptoms (26). These studies suggest that early use of inhaled corticosteroids may also have some long-term beneficial effects. However, further studies are needed to confirm this.

Discussion of clinical effect outcomes

These studies provide evidence that treatment with inhaled corticosteroids in addition to excellent effects on the immediate aim of asthma therapy also influences some long-term outcomes of the disease. They also suggest that treatment with inhaled corticosteroids reduces airway remodelling. The question of whether this treatment also improves the growth of lung function in children or reduces the accelerated decline in lung function in adults needs more study. However, such studies are difficult to perform because they should be long-term (several years) and include a large number of patients (several thousands) in order to detect small changes in crude outcomes such as pre- or post-bronchodilator FEV₁. These studies can be performed only in patients with mild asthma disease because they would be unethical in patients with more severe disease. Even in patients with mild asthma the risk of exacerbations and drop-outs in the placebo group might complicate the interpretation of the results, because at the end of the study the two treatment groups would no longer be comparable. At present, no studies have assessed the long-term predictive value on long-term clinical outcomes of the clinical results in short-term trials. This should be included in future long-term studies.

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