Paediatric Respiratory Reviews 16 (2015) 51–52

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Cochrane Corner

Inhaled corticosteroids in children with persistent asthma: is there a dose response impact on growth? - an overview of Cochrane reviews

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WHY DO WE NEED THIS REVIEW?

Because of their efficacy, inhaled corticosteroids (ICS) are the preferred first-line treatment for children with persistent asthma of all ages [1]. Their potential for growth suppression in children remains a concern for parents and physicians. Consequently, international guidelines recommend the use of inhaled corticosteroids at the minimally effective dose [1]. Yet, the impact of increasing or decreasing doses of ICS on children's linear growth is poorly described. The aim of this Cochrane Review [2] was to assess whether increasing the dose of ICS is associated with a slower linear growth, weight gain and skeletal maturation in children with asthma.

WHAT COMPARISONS DID WE MAKE IN THE REVIEW?

We selected for inclusion parallel-group, randomised trials evaluating the impact of different doses of the same ICS, using the same device in both groups, for a minimum of three months in children aged one to 17 years with persistent asthma. The primary outcome was linear growth velocity, that is, the pattern of growth measured repeatedly over time and adjusted for relevant covariates. Secondary outcomes included change over time in growth velocity, height, weight, body mass index and skeletal maturation.

Using the rigorous Cochrane methodology, we identified 22 eligible trials, yet only 10 of them measured growth or other measures of interest. The aggregated data provided 17 group comparisons (3394 children with mild or moderate asthma) because some trials compared three ICS doses. Trials used different ICS (beclomethasone, budesonide, ciclesonide, fluticasone or mometasone) as monotherapy or as combination therapy with a long-acting ß2-agonist and generally compared low (50 to 100 μg) with low-to-medium doses (200 μg) daily doses (converted to μg HFA-beclomethasone equivalent) over 12 to 52 weeks. Two authors independently assessed the studies and did the data extraction. Additional unpublished data and information was obtained through collaboration with the study authors and pharmaceutical groups from six trials.

It was originally intended to undertake subgroup analyses on age, baseline severity of the airway obstruction, ICS dose and concomitant use of non-steroidal anti-asthmatic drugs. However, the similarity across trials or inadequate reporting prevented such analyses.

WHAT DID WE FIND?

Three industry-funded trials with high methodological quality (resulting in four dose comparisons) contributed data to the main outcome [3–5]. They pertained to 728 school-aged children measured by stadiometry, who had mild or moderate asthma and were treated with one of three ICS molecules (fluticasone, ciclesonide or mometasone) in whom a dose difference $\leq$ 150 μg was compared over 52 weeks. A very small (0.20 cm/y) but statistically significant group difference in linear growth was observed over 12 months, with a lower growth velocity in the higher ICS dose group (Figure 1). Because the three trials lasted one year, the long-term impact of different ICS doses on growth velocity could not be explored beyond this period. The

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http://dx.doi.org/10.1016/j.prrv.2014.10.002
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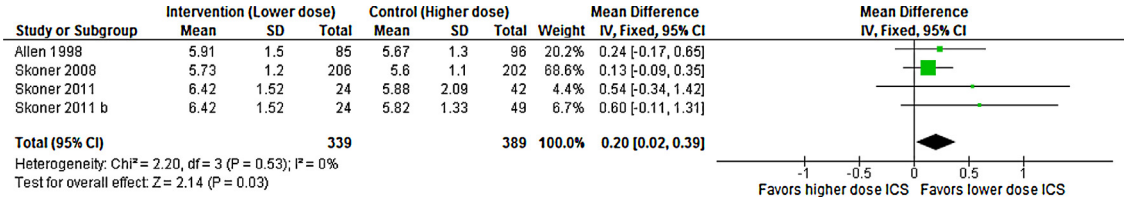

Figure 1. Growth velocity (cm/y) by stadiometer from 0 to 12 months.

three different molecules did not influence the magnitude of effect (P value of 0.33). This is of interest as another Cochrane review [6], evaluating the growth-suppressive effect of several ICS molecules compared with placebo, suggested less impact on growth of fluticasone, mometasone and ciclesonide compared with budesonide and beclomethasone. Our findings revealed that the ICS molecules believed to have little or no suppressive effect do have a small statistically significant effect on growth when used at low-to-medium doses compared with a lower dose. In the absence of supporting data, one could hypothesise that the small observed group difference of 0.2 cm in growth velocity over the first year of treatment with the use of most recent molecules could translate as greater impact when used at higher dose and or with older molecules (budesonide and beclomethasone), which have well-documented growth-suppressing effects [7].

No statistically significant group difference was observed in most of the secondary outcomes, namely, change from baseline in weight, change in SD scores (height) and body mass index. Of interest, a change in height between baseline and three months showed a significant decrease of 0.15 cm in the opposite direction, that is not favouring a lower ICS dose, emphasising the impact of neglecting important covariates influencing growth and the impact of the timing of measurement on the effect size. Of note, a statistically significant group difference in skeletal maturation of a quarter of a year was observed, not favouring a higher dose (200 μg/d), with an ICS group difference of 100 μg/d HFA-beclomethasone equivalent [3]; as this observation is derived from a single study, replication is required.

The review provides evidence of a small, but statistically significant, lower linear growth over 12 months between prepubescent school-aged children with mild to moderate persistent asthma treated with low or moderate ICS dose; the difference was observed with a daily dose difference $\leq$ 150 μg HFA-beclomethasone equivalent. There is insufficient power due to the small number of trials to explore if various molecules have a different dose response impact on annual linear growth.

IMPLICATIONS FOR PRACTICE AND RESEARCH?

Clearly, the ICS should be reduced to the lowest effective dose in children with asthma and their growth should be systematically monitored during any ICS treatment.

The lack of, or incomplete, reporting of annual growth velocity in more than 86% (19/22) of eligible paediatric trials is a matter of concern. Future paediatric ICS trials should systematically measure growth and report growth velocity rather than other metrics. In the absence of relevant trials, there is a need to quantify growth impact in groups of children treated with ICS doses differing by more 150 μg/day, specifically with medium and high ICS dose, and explore the potential differential impact on growth velocity of specific ICS molecules. Long-term (>1 year) trials of high methodological quality with adequate documentation of linear growth velocity in children with asthma treated with ICS are needed to provide a fair comparison of the long-term safety of different ICS dose options.

In collaboration with the Cochrane CF and Genetic Disorders Group' http://cfgd.cochrane.org/.

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