Inhaled corticosteroids used for the control of asthma in a "real-life" setting do not affect linear growth velocity in prepubertal children

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: Recent guidelines recommend inhaled corticosteroids as the first-line treatment for persistent asthma. However, long-term corticosteroid treatment in children has raised concerns about potential growth rate deceleration. We aimed to assess the association of growth velocity with the use of inhaled corticosteroids in prepubertal children with asthma in a "real-life" setting.

Material/Methods: This study included 844 children aged 4–9.5 years coming to the hospital for regular check-ups between October 2006 and February 2009 for asthma with/without allergic rhinitis and no other known constraints of growth. Out of the 844 children, 790 had all data needed for analysis – 245 children were not treated with ICS, 545 children received ICS (fluticasone, budesonide) with/without INCS (fluticasone, mometasone or budesonide). During the study period, 48 children with/without ICS received short SCS courses.

Results: Mean (SE) height at the first check-up was 123.1 (0.31) cm; range (100.0–147.8 cm). Mean (SE) linear growth velocity (LGV) of the included children was 0.185 (0.0035) mm/day between 2 check-ups. No significant difference was found in LGV between the group not treated with ICS (0.180 mm/day±0.0055) and the group treated with ICS (0.187±0.0044 mm/day). Also, there was no statistical difference between subgroups according to additional therapy with INCS and SCS. No significant correlation was found for LGV and daily dose of ICS (r=0.086, p>0.05).

Conclusions: In our retrospective study using electronic hospital database, ICS and combined use of corticosteroids did not show any association with LGV in prepubertal asthmatic children in a "real-life" setting.

key words: asthma • inhaled corticosteroids • linear growth velocity • electronic patient database • "real-life setting"

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BACKGROUND

Asthma affects approximately 300 million individuals worldwide and it is the most common chronic disease of childhood [1]. The goal of asthma treatment is to achieve and maintain clinical control [2]. Medications to treat asthma can be classified as controllers and relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control, mainly through their anti-inflammatory effects. Inhaled corticosteroids (ICS) are the most effective controller medications currently available. ICS are the first-line anti-inflammatory treatment for asthma, and have been used with success for more than 2 decades in mild to severe persistent asthma, reducing hospital admissions, visits to emergency department, oral corticosteroids (OC) usage, bronchodilator usage and frequency of symptoms. Major safety concerns about long-term ICS therapy include suppression of adrenal function, bone development and growth. Asthma itself also can affect growth, as can other chronic disease [3–5]. However, alternating or irregular patterns of high and low velocities may occur in successive periods, even in the absence of morbidity [6]. There have been many clinical trials designed to assess the influence of ICS treatment on growth. Randomized controlled trials (RCTs) are the gold standard by which the benefit and harm of treatments have been established because this approach greatly minimizes the risk of confounding and avoids selection bias.

Only a small percentage (<10%) of patients with asthma seen in primary care are eligible for enrolment in typical double-blind randomized controlled trials [7,8]. Comparisons in RCTs are often selected to provide the greatest contrast between treatment strategies, most commonly by using inactive controls (eg, placebos or shams) [9,10]. There is less of an emphasis on head-to-head comparisons (active controls) between different interventions, although recent trials have increasingly adopted use of active controls [11,12]. Poor patient and clinician adherence to different asthma treatment options is common, probably because multiple supports to promote treatment fidelity in research environments are generally absent in "real-life" practice setting [13,14]. These are the reasons why we need trial results that can be applied to real world patients. The aim of this retrospective study was to assess the association of linear growth velocity with the use of inhaled corticosteroids in prepubertal children with asthma in a "real-life" setting.

MATERIAL AND METHODS

This was a retrospective observational study using anonymous individual patient clinical and prescribing data (patient digital medical record) contained in the electronic database of the Children's Hospital Srebrnjak (CHS). The Children's Hospital Srebrnjak Database (CHSD) covers more than 40,000 patient records. The CHSD was assessed for the period between October 2006 and February 2009.

Children aged 4–9.5 at baseline visit with a history of asthma and receiving asthma medication in the period studied were identified and analyzed. Anti-asthma medication in this study was defined as inhaled corticosteroids, intranasal corticosteroids (INCS), leukotriene receptor antagonists (LTA) and systemic corticosteroids (SCS). In this study, doses

of all ICS were expressed as beclomethasone dipropionate (BDP) equipotent doses. Ethics approval for the study was obtained from the CHS Ethics Committee before the start of the study. Individual informed consent was not needed. A total of 844 children aged 4–9.5 years with persistent asthma, with/without allergic rhinitis, were identified from our digital medical records based on the following criteria: diagnosis of asthma according to ICD 10 (J45) at least 6 months prior to baseline visit; baseline visit between October 2006 and February 2009; age at baseline visit 4–9.5 years; and age at second visit <10.5 years. Patients with missing data for height on each of the visits (missing height at baseline visit or missing height at second visit) and/or no data on usage of prescribed medication were excluded (n=54).

We analyzed the time interval between 2 regular check-ups. Body height was measured at each check-up by the same trained personnel and the same stadiometer (SECA, Germany) according to standard operating procedure (SOP) used in our hospital. Recorded body height, daily dose of ICS, INCS and SCS (oral and parenteral) taken between regular check-ups were extracted from hospital digital medical records. The records showed that 245 children were not treated with ICS (treated with montelukast), of which 29 were treated with INCS, 545 children were treated with ICS (fluticasone, budesonide) of which 47 were treated with INCS (fluticasone, mometasone or budesonide) and 48 children with/without ICS treatment received short courses of SCS (oral or parenteral methylprednisolone, prednisone).

Statistics

Statistical analyses were performed using STATISTICA ver. 7.1 (StatSoft Inc., Tulsa, OK, USA). Basic descriptive summaries of the data were obtained (mean, standard deviations, standard errors of mean) for variables with quantitative data together with number and proportions (%) for categorized data variables. Differences between investigated groups and subgroups were calculated with cross-tabulation and the chi-squared test for categorized data and using factorial analysis of variance (ANOVA) for quantitative data variables. Linear regression analysis was used for association analyses between variables. Sample size was calculated according to previously published studies using an expected difference in LGV between groups of 0.5 cm/year (0.0137 mm/day) with SD of 2 cm/year (0.0548 mm/day) and a group ratio of 2:1 (ICS: non-ICS) with alpha=0.05 and a statistical power of 80%, giving a minimal sample size of 378 for the ICS group and 189 for the non-ICS group. P<0.05 was considered as statistically significant.

RESULTS

Descriptive statistics for treatment, sex, and age are presented in Table I. The time interval between 2 regular check-ups had a median of 162 days (range 32–657 days). Mean age at the baseline visit was 6.67 (SE, 0.04; range, 4–9.4) years. There was a significant difference in baseline age between subgroups according to the ICS drug (budesonide 7.16±0.20 yrs. $vs.$ fluticasone 6.53±0.05 yrs; p=0.034). Mean body height at baseline was 123.1 (SE, 0.31; range, 100.0–147.8) cm. There was a significant difference in body height at baseline between treatment groups (mean ±SE; ICS, 122.5±0.39 cm $vs.$ non-ICS, 124.3±0.55 cm; F=6.901, p=0.009) comparable

Table 1. Descriptive statistics for treatment, sex and age (N=790).

All patients	All	MONT	ICS	FLU	BUD	SCS
N	790	245	545	502	43	44
Boys/girls	527/263	161/84	366/179	340/162	26/17	31/13
Age (yrs, mean ±SE)	6.67±0.04	6.87±0.06	6.53±0.06	6.53±0.05	7.16±0.20	6.69±0.16

Table 2. Linear growth velocity (LGV; mean ±SE) for different subgroups (non-ICS, total ICS and different ICS – fluticasone and budesonide).

Drugs	LGV, mm/day (mean±SE)		
	All	Boys	Girls
All groups (N=790)	0.185±0.0035	0.183±0.0043	0.189±0.0099
Montelukast (n=245)	0.180±0.0055	0.180±0.0066	0.181±0.0098
ICS total (n=545)	0.187±0.0044	0.184±0.0055	0.194±0.0071
Fluticasone (n=502)	0.187±0.0046	0.186±0.0058	0.189±0.0072
Budesonide (n=43)	0.194±0.0158	0.167±0.0141	0.236±0.0283
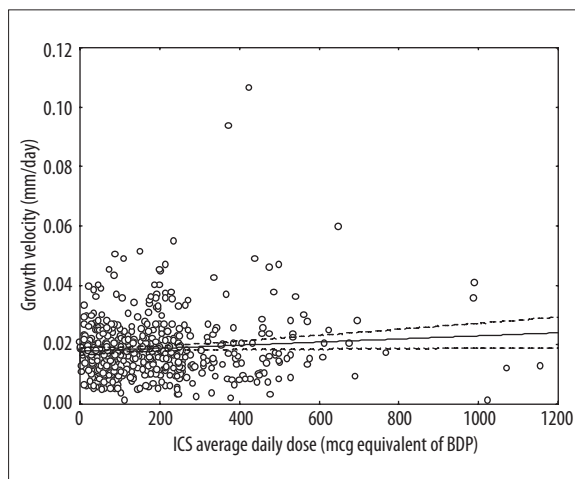
Figure 1. Scatterplot for association between average daily dose of used inhaled corticosteroids (doses presented as beclomethasone equipotent dose) and linear growth velocity (r=0.086; p=0.055).

to age differences (Table 1). Data of LGV related to treatment and sex are presented in Table 2.

More patients in the ICS group used SCS than in the non-ICS group (7.34% *vs.* 1.63%) (chi-squared=12.697; df=2, p=0.00179), but no significant difference was found according to sex (chi-squared=0.294, df=1, p=0.587). No significant difference was found for the coexisting INCS treatment between ICS and non-ICS group (p>0.05).

No significant differences between different treatment subgroups (ICS, non-ICS, INCS, SCS) according to sex or age were found (p>0.05 for all comparisons; ANOVA). Mean (SE) LGV of included children was 0.185 (0.0035) mm/day between 2 check-ups. No significant difference for LGV

between the non-ICS group (0.180±0.0055 mm/day) and the ICS group (0.187±0.0044 mm/day) was found.

No significant difference for LGV between treatment groups (montelukast, fluticasone, budesonide) according to sex was found (F(2,784)=0.991; p=0.372; ANOVA; Table 2). Use of ICS as well as combining CS in different forms with inhaled corticosteroids (intranasal corticosteroids, systemic corticosteroids) during the observed period also had no influence on LGV (F(1, 782)=0.247; p=0.619; ANOVA). No significant association (correlation) between average daily dose of ICS and LGV (r=0.086; p=0.055; Figure 1), age and LGV (r=–0.058; p=0.102), height and LGV (r=–0.041, p=0.252), as well as body weight and LGV (r=0.0295, p=0.411), was found.

DISCUSSION

Our study showed no effect of ICS treatment on growth retardation in prepubertal children. This was the same throughout the treatment subgroups (different types of ICS, concomitant use of SCS and/or INCS). The only significant difference found between subgroups showed slightly older children on treatment with budesonide (7.16 yrs) compared to fluticasone (6.53 yrs). This difference was generated by the labeling of these drugs in Croatia (budesonide has an indication for treating asthma in children >6 years, in comparison to fluticasone, which has an indication for children of >1 year) (15). Short courses of SCS were used significantly more in the group on ICS compared to the montelukast treated group, reflecting that more severe patients were treated with ICS based on treatment options according to GINA guidelines.

When assessing the effects of corticosteroids on growth in children, it is important to appreciate that growth may be divided into 3 distinct stages [16]. Growth during the first 2 years of life is both rapid and rapidly decelerating. This phase is probably controlled by the same factors that are

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important for fetal growth, the main one being nutrition. Childhood growth occurs from approximately 3 to 11 years of age. This phase is mainly influenced by the endocrine system, particularly growth hormone. Pubertal growth largely depends on a combination of growth hormone and sex steroids. The importance of the various factors affecting growth seems to differ between these 3 phases.

In 1998, the U.S. Food and Drug Administration (FDA) reviewed all inhaled and intranasal corticosteroid growth studies in pediatric patients. All marketed ICS showed evidence of minor effect on growth in studies with major design flaws [17]. Two growth studies found that the growth-retarding effect of an inhaled corticosteroid administered for 1 year was more marked in prepubertal than in pubertal school children [18,19] and was statistically significant only in prepubertal children. As a result, precautionary labeling regarding growth suppression was implemented for the entire class, and a draft guidance for conduct of future growth studies was issued [15]. The FDA normally recommends that growth studies are conducted in prepubertal children. 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 [20].

We used a patient database to identify children with asthma in which we assessed the influence of inhaled corticosteroids on linear growth velocity in prepubertal asthmatic children in a "real-life" setting. Our results showed no growth retardation, which is not fully in line with findings from exploratory trials [18,19,21]. There are several possible explanations for these differences. One of the important factors influencing results of our study is the "real-life" setting. The importance of real world factors in asthma (eg, comorbidities, patient adherence, and inhaler technique) should not be overlooked, as they may explain the wide gap between the level of asthma control that can be achieved in controlled randomized clinical trials (cRCTs) and the frequently disappointing results from observational studies carried out among less selected populations. Classical randomized controlled trials, even though seen as the "gold standard" for medical evidence because of their high internal validity, have certain drawbacks arising from their necessarily strict design limiting their external validity and the ability to extrapolate these data to real world patients [22,23].

As defined by the National Centre for Biotechnology Information, an observational study is a "type of nonrandomized study in which the investigators do not seek to intervene, but instead simply observe the course of events" [24]. As such, observational studies using clinical databases offer another method of studying the comparative effectiveness of outcomes as evaluated in real world patients in a noninterventional, naturalistic setting. They also provide a means to study, characterize, and better understand real world prescribed practices and adherence to guidelines in clinical practice. Observational studies involve accessing, collating, and analyzing information held in patient records. Although they are limited by the lack of treatment randomization and potential bias through subjectivity of treatment choice, their use of routine clinical data gives them high external validity [22]. Thus, observational studies can be a good supplementary research tool with high external validity and can evaluate real world outcomes.

The other limiting factors (besides RCT design) of our study may be connected with the lack of certain data that we are unable to check for, as this lack could be because the data is non-existent or because data was not entered at the time of the check-up (retrospective design). Also, there can be some false entries that we were unable to check for at the time of the analysis, and even though most of our patients are treated for exacerbations in our ER and are formally asked about the control of asthma between regular check-ups, exacerbations, usage of health system resources, comorbidities and adherence to prescribed treatment, there is always a possibility that these data lack precision and completeness, which can influence the final results. On the other hand, if this was the case it would influence data in all subgroups in the same way, minimizing the effect because of the large sample sizes. The same may apply to the possibility of confounding results with irregular pattern of growth velocity. According to that, and the fact that there were no differences between groups in duration of period between check-ups, the probability that irregular pattern of growth velocity could confound our results was minimal.

CONCLUSIONS

This "real-life" study comprising prepubertal asthmatic children, followed in an outpatient setting, did not demonstrate any compromising effect on growth in children using ICS. According to the results of this study, in routine daily practice physicians should use inhaled corticosteroids at conventional doses without fear of growth retardation in children. The routine monitoring of height should be used if prescribed doses are higher than conventional.

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