Respiratory Medicine (2007) **101**, 1625–1632

ELSEVIER

respiratoryMEDICINE

No evidence that early use of inhaled corticosteroids reduces current asthma at 10 years of age ☆

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Received 16 December 2006; accepted 28 March 2007
Available online 21 May 2007

KEYWORDS
Birth cohort;
Childhood asthma;
Early intervention;
Inhaled corticosteroids;
Prevalence;
Propensity score

Summary
Background: It is debated whether early treatment with inhaled corticosteroids (ICS) can change the natural course of childhood asthma.
Aim: To assess if ICS treatment before 2 years of age in children with obstructive airways disease reduces current asthma at 10 years of age.
Methods: Children with ($n = 233$) and without ($n = 219$) recurrent (r) bronchial obstruction (BO) attending clinical examination at 2 years of age in the birth cohort Environment and Childhood Asthma study in Oslo, were reinvestigated at 10 years of age. Current asthma (CA) at 10 years was defined as asthma with either symptoms and/or asthma treatment during the last year, and/or $\geqslant$10% fall in forced expired volume in 1 s after standardized treadmill run. The risk of CA was assessed by logistic regression and propensity modelling (including gender, parental atopy and severity score at 2 years) in children with rBO who received ICS or not by 2 years.
Results: CA was found in 97 children, more often among rBO children with (56.9%) and without ICS treatment (30.8%) compared to no-BO children (5.5%) ($p < 0.001$). In rBO children logistic regression analyses (adjusted odds ratio aOR (95% confidence interval)) identified male gender (aOR 1.82 (1.01–3.27), $p = 0.046$) and severity score at 2 years 1.14 (1.03–1.28), ($p = 0.01$), as significant and ICS treatment as non-significant 2.00 (0.98–4.12) risk factors for CA. With propensity modelling adjusting for disease severity,

☆The study is performed within the ORAACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment), a member of the GA²LEN (Global Allergy and Asthma European Network).

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2007.03.011

ICS treatment by 2 years caused a non-significant increased risk aOR of CA of 1.84 (0.89–3.82).
Conclusion: No evidence was found that early use of ICS before age two in children with rBO reduces current asthma 8 years later.

Introduction

Inhaled corticosteroids (ICS) are the preferred long-term controller medication for persistent asthma based on their anti-inflammatory properties and significant evidence of efficacy.[1] Regular use of ICS has been reported, especially during the early stages of asthma, to improve control of symptoms and lung function in children 5–10 years of age,[2] and lung function in early childhood.[3,4] Efficacy has also been shown by stopping medication, as patients frequently experience an exacerbation of their asthma upon withdrawal of ICS, as shown both in pre-school and school children,[5,6] whilst regular use of low dose ICS prevents asthma deaths as shown in a study including subjects from 5 to 44 years of age.[7] It has been stated that about two-thirds of mildly asthmatic children outgrow their disease, while the last third with more severe asthma will have persistent symptoms in adult life.[8] However, a study of bronchial biopsies in subjects with asthma remission for more than 3 years suggests that asthma might persist throughout life.[9]

Recently, two randomized double-blind placebo-controlled studies[5,10] covering different parts of the preschool age reported that symptom control and improved lung function obtained during ongoing treatment with inhaled steroids, were reduced after stopping treatment, and the authors of both papers concluded that use of inhaled steroids did not seem to influence the long-term prognosis of asthma.[5,10] A Danish study reported no influence on the progression from episodic to persistent wheeze, with intermittent treatment during episodes of wheezing from infancy to the age of 3 years.[11]

Randomized controlled trials are generally considered the best study designs to assess treatment efficacy, but are associated with high costs, selected populations and are often logistically difficult to maintain for many years. Thus, an alternative for studying long-term outcome is by use of prospective longitudinal observational cohorts.

Employing propensity score assessment in statistical analyses has been proposed as a method to adjust for bias in treatment assignment that may be present in observational studies.[12] The propensity score provides an estimate of the likelihood that the patient would receive treatment based only on the values of individual covariates (which, for asthma, would include factors such as gender, parental atopy, atopic dermatitis and severity of illness) and adjust for that the use of ICS for childhood asthma serves merely as a marker of asthma severity.

In a recent article, we reported that 21% of children with recurrent (r) bronchial obstruction (BO) received ICS by 2 years of age in the Environment and Childhood Asthma (ECA) study in Oslo, an observational birth cohort study established in 1992/1993.[3] The main objective of the present study was to assess if ICS treatment by 2 years of age influenced current asthma occurrence at 10 years of age.

Methods and subjects

Study design

The present study is a part of the 10-year follow-up of the prospective birth cohort study, the ECA-study in Oslo.[13] Briefly, a cohort of 3754 newborn babies was established at birth in Oslo during 15 months starting from January 1992. Written informed consent was obtained from parents of all subjects upon enrolment. The study was approved by the Regional Committee for Medical Ethics and the Norwegian Data Inspectorate. The overall design of the birth cohort is described elsewhere.[13,14]

To identify children with BO, parents of all children completed half-yearly questionnaires from birth to their child's second birthday. Questions included: health of the child (respiratory, allergic, skin as well as general diseases) and details of all types of medical treatment, family history of allergic and other diseases, parental socio-economic status and environmental exposures as parental smoking habits. Additionally, clinical signs of BO and treatment were recorded in a check-box card by attending doctors at any respiratory illnesses and returned to the study personnel at the latest every 6 months.

A nested case-control study was established[3,13,15] before 2 years of age to compare all children with at least two episodes of doctor confirmed BO or minimum 4 weeks of persistent BO by their second birthday (rBO) ($n = 306$)[14] to control subjects without symptoms or signs of BO (no-BO) ($n = 306$). The 2-year detailed clinical examination was attended by 516 of 612 eligible children, 265 rBO children and 251 no-BO children, respectively (Fig. 1).

The 10-year follow-up study (September 2001–August 2004) included 239 of the rBO and 220 of the no-BO children from the nested case control study at 2 years of age (attendance rate 89%) (Fig. 1).

Subjects

Of the 459 children who attended both 2- and 10-year follow-up visits (Fig. 1), 452 (245 boys and 207 girls) had sufficient data to assess current asthma at 10 years of age. The seven excluded subjects did not differ from the remaining children regarding baseline demographic data and parental atopy, but were significantly heavier at 10 years (data not shown). Mean age (standard deviation (SD)) at the 10-year visit was 10.3 (0.7) years. Demographic data