Lack of Long-term Effects of High-dose Inhaled Beclomethasone for Respiratory Syncytial Virus Bronchiolitis

A Randomized Placebo-controlled Trial

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Background: Previously, we showed that high-dose early initiated inhaled corticosteroids during respiratory syncytial virus bronchiolitis partially and transiently prevents subsequent recurrent wheeze. Here, we study treatment effect on lung function at age 6.

Methods: This is a 6-year follow-up report of a randomized placebo-controlled trial, in which 185 infants hospitalized for respiratory syncytial virus bronchiolitis were treated with early initiated, high-dose inhaled beclomethasone (n = 86) or placebo (n = 99) for 3 months. The primary outcome was forced expiratory volume in 1 second as percentage predicted. Secondary outcomes were bronchial hyperresponsiveness, physician-diagnosed asthma, hay fever and eczema. Possible toxicity was assessed by linear growth measurements.

Results: At age 6, no significant differences were found in mean forced expiratory volume in 1 second percentage predicted between beclomethasone-treated and placebo-treated patients (91.4 vs. 93.4, mean difference 2.05 [95% confidence interval: −1.98 to 6.08]). The proportion of bronchial hyperresponsiveness, physician-diagnosed asthma, parent reported hay fever and eczema was comparable between groups. There were no differences in linear growth.

Conclusions: Early initiated prolonged treatment with high-dose inhaled beclomethasone during hospitalization for respiratory syncytial virus infection during infancy did not improve the long-term respiratory outcome, but was safe.

Key Words: respiratory syncytial virus, asthma, children, lung function

PEDIATR INFECT DIS J 2014;33:19–23

Respiratory syncytial virus (RSV) infection is the most common cause of severe bronchiolitis in infants. In the United States, bronchiolitis is the leading cause of hospitalization for lower respiratory tract infections in infants. Recently, we showed that RSV bronchiolitis is causally related to recurrent wheeze in the first year of life in late preterm infants. Additionally, several longitudinal studies have shown an association between viral bronchiolitis and the development of asthma during childhood and adolescence.

Steroids have been thought to modulate the immune system during the acute phase of infant wheeze and thereby prevent asthma development. Assuming viral bronchiolitis contributes to asthma through an immunologic cascade, modulation of the immune system may prevent asthma. In the previous report of the current trial, we have shown that early initiated high-dose inhaled beclomethasone did not have a major effect on recurrent wheeze during a 1-year follow-up period. The purpose of the current study was to investigate the effect of inhaled beclomethasone for RSV bronchiolitis on lung function and risk of asthma at the age of 6 years.

Daily use of inhaled steroids has been associated with reduced linear growth in childhood, and until recently this effect was thought not to accumulate into adulthood. However, a recent large study has shown that this reduction in height did persist into adulthood. Effects of high-dose steroids on linear growth in infancy are lacking. Therefore, we also aimed to evaluate the long-term safety of high-dose inhaled beclomethasone in infants on linear growth at the age of 6.

MATERIALS AND METHODS

Participants

Patients

We did the study within the framework of a randomized, placebo-controlled, double-blind trial on the effectiveness of extra-fine hydrofluoroalkane (HFA) beclomethasone dipropionate on the occurrence and severity of recurrent wheeze after RSV-related lower respiratory tract infections. In the current study, we investigated the long-term effect of inhaled beclomethasone for RSV bronchiolitis on lung function and risk of asthma.

Between 2004 and 2006, 243 previously healthy infants aged <13 months were admitted to the hospital with a RSV infection, as described earlier in detail. Summarized, hospitalized patients with a proven RSV bronchiolitis by a positive immunofluorescence test for RSV in epithelial cells from nasopharyngeal aspirates were randomly assigned to receive either high-dose extra-fine HFA beclomethasone dipropionate, hereafter called inhaled beclomethasone, or placebo. The intervention, in a dosage of 200 mg twice daily for a period of 3 months, is equivalent to 200% of the highest advised therapeutic dose for children between 5 and 11 years of age. This treatment was started within 24 hours of RSV being detected and was continued for 3 months. These infants were invited to participate in the follow-up study visit at 6 years of age (see below). From April 2010 to November 2011, 185 (76%) children attended this study visit. The medical ethics committee of
the University Medical Centre Utrecht approved the study. Written informed consent was obtained from all parents.

The study was conducted according to the principles of the Declaration of Helsinki (version 2000) and in accordance with the Dutch Medical Research Involving Human Subjects Act. Good clinical practice guidelines were followed.

Outcomes

Questionnaire

The questionnaire contained standardized questions about atopic diseases from the International Study of Asthma and Allergies in Childhood questionnaire, medication use (eg, antihistamines, inhalation steroids and beta-mimetics) in the last 12 months and known risk factors for atopic diseases (ie, positive family history). All questions were answered by the parents of the RSV patients. A positive history of parental allergy was defined as questionnaire-reported allergy to pollen, house dust mite, pets or food. Smoke exposure was defined as smoking by 1 of the parents in the first 5 years of life, and data from the first year of life were used to obtain information about smoke exposure in the first year of life to prevent recall bias. A nonwestern origin was defined as “country of birth in Asia (including Turkey), Africa, Latin America, excluding Indonesia and Japan”. In the Netherlands, children regularly visit child healthcare centers for standardized anthropometry. These measurements are recorded in a personal file, which every child owns. Parents were asked to use this file to report these anthropometric measures in the questionnaire.

From each child, we obtained the recorded asthma diagnoses from the general practitioner after a primary care visit (R03 wheezing, R96 asthma), according to the international Classification of Primary Care. Physician-diagnosed asthma was defined as a history of physician-diagnosed asthma plus asthma symptoms or medication use in the last 12 months (beta-mimetics or inhaled corticosteroids).

Lung Function

The primary outcome of this study was lung function at age 6. Spirometry was performed using a calibrated spirometer (Zan 100 pulmonary spirometer system, nSpire, Oberthulba, Germany). Maximal flow-volume curves were measured according to American Thoracic Society/European Respiratory Society standards. The largest forced expiratory volume in 1 second (FEV1) was measured using a calibrated spirometer (Zan 100 pulmonary spirometer system, nSpire, Oberthulba, Germany). In addition, a challenge with nebulized metacholine was performed to assess bronchial hyperresponsiveness (BHR) according to the ATS/ERS guidelines. All children withheld their rescue medication for at least 12 hours before the test. If the child had suffered from a respiratory tract infection in the last 2 weeks, the test was postponed. BHR was defined as a decrease in FEV1 of ≥20% from baseline at a cumulative dose of ≤0.61 mg methacholine bromide during the challenge.

Allergic Sensitization

Serum IgE antibodies to inhaled allergens (sIgE) were measured using a screening test with a combination of the most prevalent inhaled allergens (Pharmacia Diagnostic, Uppsala, Sweden). A positive test result was defined as a sIgE-level above 0.35 kU/L for 1 of the aero-allergens.

Adverse Effects

To estimate whether groups differed in linear growth, we measured the height (in centimeters during the study visit). Height was converted into gender-specific z-scores, which describes the number of standard deviations (SD) from the population mean. The population norms were derived from the database of the Netherlands organization for Applied Scientific Research.

Statistical Analysis

We analyzed the effect of inhaled beclomethasone on lung function, the proportion atopic diseases and height. Mean differences and associated 95% confidence intervals (95% CI) of the predicted values for lung function between the inhaled beclomethasone and placebo group were calculated. In case of a nonparametric distribution, a median difference and associated 95% CI were calculated. Risk differences and associated 95% CI were calculated for the risk on a physician-diagnosed asthma and atopic diseases between the inhaled beclomethasone and placebo group. In the first instance, we looked only at risk and mean difference and did not adjust for potential confounders, as we reported on the long-term effects of a randomized placebo-controlled trial. To be sure that confounding was not a problem in the post-randomization period, we also studied the following potential confounders of lung function using linear regression analysis: smoke exposure, allergic family history, ethnicity, height and sex.

Height was converted into gender-specific z-scores, adjusted for the exact age using linear regression, and compared between groups using the independent samples t tests. To prevent bias caused by missing data, missing data in the questionnaire were imputed using multiple imputations. We did all analyses with SPSS 18.0 (version 18.0.0, SPSS Inc., 2009, Chicago, IL) on an intention to treat basis.

RESULTS

Lung Function

Of the 243 children that underwent randomization, 185 participated in the follow-up study (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B683). After the initial study, 21 caregivers refused participation in the follow-up study. For the current study, we attempted to include the remaining 222 infants. Of these, follow-up data were available from 185 (83.3%) children. The median age of the RSV group was 5.9 years (interquartile range: 5.8–6.3) and 50.3% were boys. Baseline characteristics of the 185 participants did not differ between the beclomethasone and placebo group (Table 1), nor between participants and nonparticipants (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B684).

Table 2 shows the results of the spirometry performed at the age of 6 years. In 135 patients a successful baseline spirometry was performed. No differences in lung function, resistance (R03) or FeNO were found between the beclomethasone and placebo group (Table 2). Adjustment for potential confounders did not alter the relationship between treatment and lung function. Challenge tests were successfully performed in 101 children and again, results were comparable between both groups (Table 2). BHR was present in 25.0% of the beclomethasone group and in 34.7% of the placebo group [risk difference −9.7% (95% CI: −27.4 to 8.1%)]. BHR plus current wheezing, obtained from the International Study of Asthma and Allergies in Childhood questionnaire, was present in 3.8% (2/52) of the beclomethasone group and in 6.1% (3/49) of the placebo group [risk difference −2.3% (95% CI: −10.8 to 6.2%)].
Asthma Diagnosis and Allergic Diseases
In the RSV group, allergy tests were performed in 96 RSV patients (48 beclomethasone, 48 placebo). Seventeen children had detectable serum IgE against 1 of the aero-allergens, but proportions between groups were not significantly different (beclomethasone 16.6%, placebo group 18.8%) (RD −2.1 (95% CI: −17.4 to 13.2). Physician-diagnosed asthma was present in 24.4% of the beclomethasone group versus 21.2% of the placebo group, RD 3.2 (95% CI: −8.9 to 15.3). Proportions of other atopic diseases were also comparable between both groups (Table 3).

Linear Growth
Patients treated with prolonged high-dose inhaled beclomethasone had similar linear growth as patients treated with placebo. Both groups did have a slightly lower height for age and sex (z-score −0.16 in the placebo group and −0.18 in the treatment group), compared with the normal population.20

DISCUSSION
Early initiated high-dose extra-fine HF a beclomethasone administered to infants (<13 months) for 3 months after RSV-related lower respiratory tract infection did not improve lung function at the age of 6 years. It did also not affect the development of BHR, physician-diagnosed asthma or other atopic diseases. No adverse effect on linear growth at the age of 6 years was found.

To our knowledge, we are the first to study long-term effects of high-dose inhaled beclomethasone in children with RSV bronchiolitis using a randomized placebo-controlled trial. Our study was designed to study whether treatment of RSV bronchiolitis with early initiated, high-dose beclomethasone prevents the development of recurrent wheezing in infancy.10 In the original study, the total number of wheezing days in the year following the RSV bronchiolitis was not different between the beclomethasone and the placebo group. In the current study, we have also found no differences in lung function and BHR between both groups.

### TABLE 1. Baseline Characteristics for 185 RSV Patients Hospitalized < 13 Months of Age, Presented in Relation to the Randomly Assigned Treatment, Measured at the Age of 6 Years. Data are Numbers (Percentages) Unless Stated Otherwise

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Beclomethasone (n = 86)</th>
<th>Placebo (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (IQR)</td>
<td>5.83 (5.7–6.2)</td>
<td>6.00 (5.8–6.3)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>42 (48.8)</td>
<td>51 (51.5)</td>
</tr>
<tr>
<td>Mother born in western country†</td>
<td>83 (96.5)</td>
<td>97 (98.0)</td>
</tr>
<tr>
<td>Father born in western country†</td>
<td>84 (97.7)</td>
<td>96 (98.0)</td>
</tr>
<tr>
<td>Atopic mother</td>
<td>35 (40.7)</td>
<td>39 (39.4)</td>
</tr>
<tr>
<td>Atopic father</td>
<td>44 (51.2)</td>
<td>42 (42.4)</td>
</tr>
<tr>
<td>Smoke exposure</td>
<td>26 (30.2)</td>
<td>25 (25.3)</td>
</tr>
<tr>
<td>Premature birth†</td>
<td>15 (17.4)</td>
<td>14 (14.1)</td>
</tr>
<tr>
<td>Mean height in cm (SD)</td>
<td>118.4 (5.3)</td>
<td>119.0 (6.4)</td>
</tr>
<tr>
<td>Mean weight in kg (SD)</td>
<td>21.9 (3.3)</td>
<td>22.6 (3.9)</td>
</tr>
</tbody>
</table>

†Defined as a gestational age < 37 weeks.

### TABLE 2. Lung Functions of RSV Patients at the Age of 6 Years. Values Are Expressed as Absolute Values and the Percentage of the Predicted Values (Mean ± SD) Unless Stated Otherwise

<table>
<thead>
<tr>
<th></th>
<th>Beclomethasone (n = 66)</th>
<th>Placebo (n = 69)</th>
<th>Mean difference * (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (l)</td>
<td>66 1.21 (0.19)</td>
<td>91.4 (12.1)</td>
<td>69 1.26 (0.22)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>66 1.33 (0.22)</td>
<td>96.8 (13.7)</td>
<td>69 1.37 (0.28)</td>
</tr>
<tr>
<td>FEV/FVC (%)</td>
<td>66 91.6 (8.0)</td>
<td>96.7 (8.6)</td>
<td>69 92.4 (8.3)</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>55 2.72 (0.38)</td>
<td>94.3 (17.1)</td>
<td>61 2.91 (0.56)</td>
</tr>
<tr>
<td>Rint (kPa L/s)</td>
<td>54 0.76 (0.23)</td>
<td>124.2 (37.2)</td>
<td>53 0.77 (0.25)</td>
</tr>
<tr>
<td>FeNO (ppb), median (IQR)</td>
<td>44 8.5 (6.0–12.0)</td>
<td>—</td>
<td>45 10.0 (6.0–14.9)</td>
</tr>
<tr>
<td>BHR present (n, %)</td>
<td>52 13 (25.0)</td>
<td>—</td>
<td>49 17 (34.7)</td>
</tr>
</tbody>
</table>

*Between absolute values.
†Two-tailed P < 0.05.
‡Median difference (95% CI).
§Risk difference (95% CI).

### TABLE 3. The Prevalence of Atopic Diseases for RSV Patients at the Age of 6 Years (Questionnaire Based). Values Are Numbers (Percentages)

<table>
<thead>
<tr>
<th></th>
<th>Beclomethasone (n = 86)</th>
<th>Placebo (n = 99)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>21 (24.4)</td>
<td>21 (21.2)</td>
<td>3.21 (−8.9 to 15.3)</td>
</tr>
<tr>
<td>Current asthma symptoms</td>
<td>36 (41.9)</td>
<td>41 (41.4)</td>
<td>0.45 (−13.8 to 14.7)</td>
</tr>
<tr>
<td>Current medication use</td>
<td>5 (5.8)</td>
<td>9 (9.1)</td>
<td>−3.28 (−10.8 to 4.2)</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>10 (11.6)</td>
<td>9 (9.1)</td>
<td>2.54 (−6.3 to 11.4)</td>
</tr>
<tr>
<td>Parent reported allergic diseases</td>
<td>8 (9.3)</td>
<td>14 (14.1)</td>
<td>−4.84 (−14.1 to 4.4)</td>
</tr>
<tr>
<td>Asthma ever</td>
<td>8 (9.3)</td>
<td>14 (14.1)</td>
<td>−4.84 (−14.1 to 4.4)</td>
</tr>
<tr>
<td>Hayfever ever</td>
<td>7 (8.1)</td>
<td>6 (6.1)</td>
<td>2.08 (−5.4 to 9.5)</td>
</tr>
<tr>
<td>Eczema ever</td>
<td>26 (30.2)</td>
<td>33 (33.3)</td>
<td>1.94 (−15.5 to 11.6)</td>
</tr>
</tbody>
</table>

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No treatment during RSV bronchiolitis has been convincingly shown to decrease the risk of long-term airway morbidity. Leukotriene receptor antagonists were suggested to be effective in reducing long-term wheeze, but this conclusion could not be confirmed in a large double-blind study.\textsuperscript{31} Previous studies have shown that treatment of bronchiolitis in patients with inhaled steroids may decrease the risk of developing asthma.\textsuperscript{22,23} Our early report showed that the number of wheezing days in the year following the RSV bronchiolitis did not differ between the beclomethasone and placebo group.\textsuperscript{22,24} In line with our initial report, we have found no differences in the proportion patients with physician-diagnosed asthma, the presence of BHR or differences in lung function between the beclomethasone and placebo group. Previous studies have shown that RSV bronchiolitis is associated with a lower lung function at school age.\textsuperscript{7,25–27} Our results are in line with those results, as the percentage predicted values of the lung-function measurements are all below the expected values for age and sex. These results give rise to the question which strategy is required to prevent RSV-related loss of lung function. The answer depends on the causal relationship between RSV bronchiolitis and loss of lung function.\textsuperscript{28} If the lower lung function in RSV patients is preexisting, as shown in preterm infants\textsuperscript{29} and high-risk infants,\textsuperscript{30} attempts to alter the natural course of disease during RSV bronchiolitis will prove to be futile. Alternatively, if RSV infection is a major factor in the pathogenesis of loss of lung function, attempts to prevent RSV infection or dampen the host response during early course of disease may beneficially impact on RSV-related development loss of lung function.

Long-term safety of high-dose inhaled glucocorticosteroids during infancy was an important outcome of our study. A recent study by Martinez et al\textsuperscript{11} shows that daily use of normal dose inhalation steroids in asthmatic children negatively affects linear growth. Intermittent administration in this study does not lead to a reduction of linear growth on short term. However, a recent large study has shown that the reduction in height did persist into adulthood.\textsuperscript{31} We used a high-dose inhalation steroids, equivalent to 200% of the highest advised therapeutic dose in The Netherlands for children between 5 and 11 years of age.\textsuperscript{15} We did not find an effect of a 3-month course of high-dose inhaled steroids on linear growth in children at the age of 6 years.

The strengths and limitations of this study deserve further discussion. First, we were able to retain 76% of patients in this 6-year follow-up study. Because we have found no differences in baseline characteristics, we conclude there is no selection bias. Second, to prevent bias that might result from a complete case analysis, our missing data in the questionnaires were imputed using multiple imputations.\textsuperscript{35} Our study also has limitations. First, we were not able to measure BHR in all patients. International guidelines describe asthma as a disease characterized by a triad of specific symptoms (cough, wheeze and dyspnea), reversible airway obstruction and BHR.\textsuperscript{32} Consequently, we could only evaluate asthma based on lung function in a subset of the RSV group. Secondly, our study was powered to demonstrate a treatment effect on our primary outcome, that is, wheezing days in the first year after end of therapy. Our study was underpowered to show smaller but potentially relevant treatment effects on asthma diagnosis or lung function. Third, the initial study was designed as a randomized, double-blinded controlled trial and was unblinded 1 year after the end of therapy. The current study was single blinded as the researchers measuring outcome, including spirometry, were blinded to the treatment. This minimizes the potential effect of information bias on the lung-function measurements. Because parents were informed about treatment allocation, this may have influenced the presentation of the symptoms of their child.

ACKNOWLEDGMENTS

The authors thank all the parents and children who participated, the lung-function analysts Mrs. R. Bekkema, Mrs. H. Faber, Mrs. V. Haneveer-van Maanen, and Mrs. Tersmette from the Department of Pediatric Pulmonology for collecting the data and Mrs. E.M. Bloemen-Carlier in assisting in recruiting the subjects and collecting the data.

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16. Zomer-Kooijker K, van Erp FC, Balemans W, et al.; Expert Network for Pediatric Pulmonology for collecting the data and participating, the lung-function analysts Mrs. R. Bekkema, Mrs. H. Faber, Mrs. V. Haneveer-van Maanen, and Mrs. Tersmette from the Department of Pediatric Pulmonology. 


