Evidencias en Pediatría

Critically Appraised Article

# Early introduction of inhaled corticosteroids in preschool children at high risk for asthma does not modify the evolution of the disease

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# Early introduction of inhaled corticosteroids in preschool children at high risk for asthma does not modify the evolution of the disease

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**Reference:** Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006; 354: 1985-97

## Structured abstract:

**Objective:** to determine if inhaled corticosteroids (IC) in preschool children with high risk for suffering asthma on the long run modify the natural history of the disease.

**Design:** multicenter clinical trial (RCT), randomized, double blind, controlled with placebo and parallel groups. The treatment was administered during 2 years. The study was continued during the third year, so as to evualuate the results.

**Location:** five university hospitals of the United States of America and the homes of the patients.

**Study population:** two hundred and eighty five children with ages ranging from 2 to 3 years and at high risk of asthma, based on the Castro-Rodriguez predictive index. To be eligible they should not have used inhaled corticosteoids in the previous 4 months, nor need to use them in the preinclusion period of the study. 8% of the treatment group (TG) and 12 % of the placebo group (PG) discontinued the study.

**Intervention:** after being randomly distributed in blocks with stratification according to clinic and age group,143 children were treated with fluticasone (2 puffs = 88 mcg every 12 hours) and 142 placebo (2 puffs every 12 hours) by means of an AeroChamber spacer device with face mask. Moroever the children were given an educational program to favour adherence to treatment. During all the study period other medications were allowed:

1.-Inhaled albuterol as a rescue therapy indicated through written instructions.

2.-Prednisolone during 4 days in case of exacerbation.

3.-Montelukast: 4 mg/day if criteria for treatment failure were met.

4.-Fluticasone:110 mcg/day in case of failure of previous treatments.

Children were followed up at the clinic every 4 months and telephone contact was made with their caregivers every 2 months during the treatment period and every month in the observation period.

**Outcome measures:** principal variable of the study: proportion of days without symptoms of asthma in the year of follow-up. This information was gathered in the periodic clinical visits and the telephone contacts based on the recall of the past 2 weeks. Secondary variables: proportion of symptom free days during the treatment period, number of oral corticosteroid treatments, number of treatments with baseline medication (montelukast, fluticasone),impulse oscillometry results, number of eosinophiles, results of prick test and mean increase in height.

**Principal results:** during the observation year no differences between both groups in the proportion of symptom free days (86.8% versus 85.9%; P = 0.78), number of exacerbations (85.5/100 child-year versus 82.5/100 child-year ; P = 0.78) and pulmonary function measured by impulse oscillometry were detected.

During the treatment period, the fluticasone treated group had a greater proportion of symptom free days (93.2 % versus 88.4%; P = 0.006), less exacerbations (57.4 versus 89.4; p<0.01) and less need of baseline medication, either montelukast (11.4 days/year versus 24,2 days/year; p<0.001) or supplementary fluticasone (8.3 days/year versus 17.6 days/year; p<0.001).The mean increment in height was lower in the TG than in the PG at the end of the second treatment year (12.6 cm, standard deviation [SD]:1.9 cm versus 13.7 cm (SD: 1.9 cm; p<0,01).This difference was smaller at the end of the third year (19.2 cm; SD: 2.2 cm versus 19.9 cm; SD: 2.2 cm; p = 0.008).

**Authors conclusion:** inhaled fluticasone reduces symptoms of asthma and altered pulmonary function in preschool children with high risk of asthma during the two years of treatment. However the protective effect disappears after ending the treatment.

**Competing interests:** authors declare having cooperated as counsellors for several pharmaceutical companies. The article specifies that several pharmaceutical companies have cooperated with material and medications, but not in the development of the study.

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## Commentary:

**Justification:** asthma is the most prevalent chronic disease in children. Diagnosis at early ages is based primarily on clinical judgement and it is not easy to differentiate those children with intermittent bronchospasms from those with asthma[1,2]. To aid the diagnosis several predictive indexes that take account of clinical data, family history of atopy in the patient and in the parents, have been used[3]. In this study the hypothesis that early introduction of

prolonged inhaled corticosteroid treatment in children with high risk of asthma can modify the natural history of the disease, for the better is evaluated.

**Validity:** this study is an RCT. However the method of blinding of the sequence of randomisation is not specified. The groups were comparable at the beginning of the study except for the eosinophil count and the frequency of eczema. Losses were 8 % in the TG and 12 % in the PG. A possible cause of bias could be the co interventions, even though they probably do not affect the conclusions of the study. The use of other medicines such as montelukast or fluticasone at greater doses was possible in both groups as needed. This may have produced a contamination of the control group, due to the fact that extra use of medication was more frequent in it, thus influencing the results with a better prognosis. The authors state that an analysis by intention to treat was made, but this is not clearly specified in the article. Since the losses of patients have been small probably this has not altered the conclusions of the study.

**Clinical relevance:** in a previous study by the Childhood Asthma Management Program where children of ages 5 to 12 with mild persistent or moderate asthma were treated with inhaled budesonide[4], the conclusions were similar to this study. This spurred the need of other studies to see if the treatment at earlier ages could be beneficial on the long run. Bisgaard et al[5] has published a study where children of asthmatic mothers were treated with inhaled budesonide after the third day of a wheezing episode, starting from the first episode. His results also disprove any positive effect of innhaled corticosteroids on the natural evolution of the disease. The study that we are commenting here and done on children with intermediate ages to those of these other studies, has not demonstrated the efficacy of IC after the interruption of treatment.

**Applicability in clinical practice:** children participating in this study are children of 2 to 3 years of age, with four or more episodes of wheezing and family or personal history of atopy[3].These type of patients are frequent in primary care. The present study, done with inhaled fluticasone, has not proved the effectiveness of this treatment on the natural history of the disease after being interrupted. As a conclusion, these results favour the use of inhaled corticosteroids for the control of wheezing, but not with the final purpose of changing the natural history of the disease.

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