

## Early Inhaled Corticosteroid Use in Children at Risk of Asthma

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### Background

Asthma is the most common chronic disease in children, adolescents, and young adults - Canadian data shows prevalence rates of clinical asthma in these populations as high as 14.1%,<sup>1</sup> with disease persisting in adults at a prevalence rate of 5-7%.<sup>2,3</sup> Poorly controlled asthma may lead to life-long limitations in quality of life, missed days of school and work, decreased productivity, hospitalizations, and even death. Consequently, asthma is a very costly disease,<sup>4</sup> both in terms of its direct costs to health care and its indirect costs to society due to decreased productivity and unfulfilled potential. In 1990, total costs due to asthma in Canada were estimated to be between \$504 million and \$648 million.<sup>5</sup>

The underlying pathophysiology of asthma involves reversible hyperresponsiveness and inflammation of airways in response to endogenous or exogenous stimuli, leading to variable and reversible airflow limitation.<sup>6</sup> One of the cornerstones of asthma treatment is the early use of inhaled corticosteroid (ICS) therapy. A 2005 Cochrane review concluded that treatment with inhaled beclomethasone (QVAR®) significantly improves forced expiratory volume in one second (FEV<sub>1</sub>) and morning peak expiratory flow (PEF), while reducing exacerbations and the use of  $\beta$ -agonists.<sup>7</sup> A 2003 prospective study of 3,568 pediatric and adult patients with mild asthma showed that long-term, once-daily treatment with low-dose budesonide (Pulmicort®) in patients with mild persistent asthma decreased the risk of severe exacerbations and improved asthma control (fewer symptoms and improved FEV<sub>1</sub>) within two years of onset.<sup>8</sup>

Since the pathophysiological processes responsible for asthma begin early in life, early initiation of treatment is important. A 1994 controlled prospective study of 216 children diagnosed with asthma showed significant FEV<sub>1</sub> improvements on budesonide treatment, in contrast with annual FEV<sub>1</sub> decreases in untreated children.<sup>9</sup> Furthermore, there were significantly better FEV<sub>1</sub> values in children who began treatment within 2 years after the onset of asthma, when compared to those who began more than 5 years after the onset of asthma.<sup>10</sup> An extension of this idea is that it might be possible to change the course of asthma by interfering with the underlying inflammation at an early stage in the disease process.<sup>10</sup>

### Studies

The hypothesis that the course of asthma might be changed by early ICS therapy was recently tested in two prospective randomized controlled trials that were published in the *New England Journal of Medicine*. The first study by Guilbert et al.<sup>11</sup> was a North American multicentre, double-blind, randomized, placebo-controlled, parallel-group trial of inhaled fluticasone (Flovent®) (88  $\mu$ g twice daily via an Aerochamber) compared with masked placebo. The study was conducted on 285 children, two or three years of age who were at high risk

for asthma (as assessed by a modified version of an instrument known as the "positive asthma predictive index"<sup>12</sup>) but did not have a clinical diagnosis of asthma. One-hundred-forty-three children were treated with fluticasone and one-hundred-forty-two were assigned to placebo. The children were treated for two years, and were followed for an additional observation year after discontinuing the study medication. The two study groups were similar with respect to all baseline characteristics, except that the group assigned to receive the inhaled corticosteroid had a higher percentage of peripheral-blood eosinophils.

In this study, the primary outcome was the difference in the proportions of episode-free days during the year-long observation period between the study groups. Secondary outcomes included the proportions of episode-free days during the treatment period. Other outcomes measured during both the treatment period and the observation period included the subjects' height, percentage of eosinophils, the number of courses of systemic corticosteroids/controller medications, and the time until their use. Impulse oscillometry, which assesses the contribution of resistance and reactance to the total impedance of the respiratory system, was also performed.

The second study by Bisgaard et al.<sup>13</sup> was a Danish single-center, randomized, double-blind, prospective study of three years' duration on a birth-cohort of 411 newborns of women with a history of physician-diagnosed asthma. The purpose of the study was to test the hypothesis that intermittent ICS treatment of wheezing episodes in these infants may prevent or delay progression to persistent wheezing. At one month of age, 301 children were randomized to treatment after every three-day episode of wheezing with two-week courses of inhaled budesonide (400  $\mu$ g per day via MDI and a spacer) or placebo. One-hundred-and-fifty-one infants were assigned to budesonide treatment and one-hundred-and-fifty received a placebo; the two groups were similar in terms of all recorded baseline characteristics at the beginning of the study.

In this study, the primary outcome was the number of symptom-free days. Secondary outcomes included the time to discontinuation due to persistent wheezing and safety, as evaluated by height and bone mineral density (by ultrasonography of the phalanx) at the end of the study. Symptoms and the use of  $\beta$ -2 agonists were recorded in daily diaries by the parents during the infants' first three years of life. Nasal secretions were collected at every episode to allow evaluation for respiratory viruses. In addition, lung function and bronchial responsiveness were also tested at enrollment and at the end of the trial.

### Results

The results of the first study by Guilbert et al.<sup>11</sup> showed that two years of fluticasone treatment, compared with placebo, did not increase the proportion of episode-free days dur-

ing the observation year (86.8 percent [95% confidence interval, 81.2 to 90.9 percent] vs. 85.9 percent [95% confidence interval, 79.9 percent to 90.3 percent],  $p=0.78$ ). In addition, there was no significant difference between the groups in the time to a first course of prednisolone ( $p=0.51$ , from 24 to 36 months, and  $p=0.61$ , from 0 to 36 months). The time to the initiation of any supplementary asthma-controller medication (fluticasone, montelukast (Singular<sup>®</sup>), or other non-assigned asthma medication) was also not significantly different in the fluticasone group, compared to the placebo group, during the observation period. Moreover, there was no significant difference between the study groups in any lung function measure derived from impulse oscillometry at the end of the observation year.

During the two-year treatment period, however, fluticasone significantly increased the proportion of episode-free days (93.2 percent [95% confidence interval, 91.1 to 94.9 percent] vs. 88.4 percent [95% confidence interval, 84.9 to 91.2 percent],  $p=0.006$ ). The time to a first course of prednisolone was longer during the treatment period in the treated group compared to placebo ( $p=0.01$ , from 0 to 24 months).

Treatment with fluticasone was associated with decreased height in both the treatment and the observation period. At the end of the observation year, the mean increase in height, relative to baseline, in the group assigned to inhaled fluticasone was 0.7 cm less than in the placebo group ( $19.2\pm 2.2$  cm vs.  $19.9\pm 2.2$  cm,  $p=0.008$ ). This difference in the mean height increase at the end of the observation year was smaller than the 1.1-cm difference observed at the end of the two-year treatment period ( $12.6\pm 1.9$  cm vs.  $13.7\pm 1.9$  cm,  $p<0.001$ ). The difference in growth was detected during the first 12 months of inhaled-corticosteroid treatment as a difference in growth velocity between the study groups ( $6.6\pm 1.0$  cm per year in the fluticasone group vs.  $7.3\pm 1.0$  cm per year in the placebo group, between months 1 and 8,  $p=0.005$ ). During the last 12 months of the treatment period, however, the growth velocity was similar in both study groups, and during the observation year, the growth velocity in the inhaled-corticosteroid group was actually greater than in the placebo group ( $7.0\pm 0.8$  cm per year vs.  $6.4\pm 0.9$  cm per year, from months 24 to 32,  $p=0.001$ ).

The second study by Bisgaard et al.<sup>13</sup> also showed no significant differences in control of wheezing symptoms between the treatment and placebo groups. The proportions of symptom-free days and days free of the need for rescue medication were similar in the two groups ( $0.83\pm 0.24$  in the budesonide group vs.  $0.82\pm 0.27$  in the placebo group). The frequency of wheezing episodes after randomization was 3.1 per child per year in the budesonide group and 2.7 per child per year in the placebo group after randomization (estimated hazard ratio, 1.16; 95% confidence interval, 0.95 to 1.41). Two-week, open-label, add-on treatment was needed on 59 occasions in the budesonide group and 37 occasions in the placebo group (risk ratio, 1.66; 95% confidence interval, 0.96 to 2.87). The length of wheezing episodes was similar in the two groups and was unaffected by the presence or absence of viruses in nasal secretions.

The treatment with budesonide did not show long-term effects either. Twenty-four per cent of children in the budesonide group developed persistent wheezing, as compared

with twenty-one per cent in the placebo group (hazard ratio, 1.22; 95% confidence interval, 0.71 to 2.13). This development was unaffected by the presence or absence of atopic dermatitis. The height and bone mineral density of the participants were also not affected by treatment.

### Implications

These two studies addressed the hypothesis that the natural history of asthma may be altered by early modification of the inflammatory pathology underlying the disease. They attempted to do so by administering continuous or intermittent doses of ICS to young children at above-average risk for asthma, when symptoms suggestive of the disease first occur and the clinical diagnosis of asthma is still uncertain. Unfortunately, both studies conclude that ICS, as administered in the studies, do not alter the natural history of the disease and do not decrease the chance that wheezing will persist beyond the first years of life.

The study by Guilbert et al.<sup>11</sup> examined the effects of daily budesonide in children past the age of two who are at high risk for asthma, as assessed by a modified version of the "positive asthma predictive index."<sup>11</sup> These were children with an established history of four or more wheezing episodes in the first two to three years of life, in addition to other risk factors for asthma, such as wheezing without colds, a family history of asthma, atopic dermatitis or allergy (especially to aeroallergens), and eosinophilia. While this study confirms previous studies about the efficacy of ICS in the symptomatic control of asthma and its deleterious effects on the rate of growth, it fails to show any lasting benefit a year after the medication is discontinued.

This study was conducted on a selective subgroup that was at high risk of developing asthma and, presumably, more likely to benefit from treatment compared to other children with wheezing. As expected, the burden of disease among these children progressively increased with time, especially during periods when they were not on any active corticosteroid therapy. One could argue that the dose of medication might have been insufficient to alter the course of the disease. However, the dose was large enough to show significant effects (compared to placebo) on participants' asthma control for the duration of treatment, and was large enough to show negative effects on their growth.

The study by Bisgaard et al.<sup>13</sup> took a different approach to the issue. The group used intermittent instead of continuous corticosteroid therapy on children after three-day episodes of wheezing, but this treatment plan was initiated within the first year of the participants' life. This study also showed no effect of ICS treatment (compared to placebo) on the progression from episodic to persistent wheezing. This group was more heterogeneous than the group in the study by Guilbert et al.<sup>11</sup>, as it enrolled infants with a maternal history of asthma after only one episode of wheezing. This might have contributed to the lack of perceived effect, as this study sample constituted a very diverse group with various possible etiologies for the observed symptom of wheezing. There may have been a positive effect on a subgroup that had a pathophysiological tendency towards developing asthma that went undetected, due to the heterogeneity of the study sample.

In light of these two trials, one can argue that the early

administration of ICS has no effect on the progression of episodic wheezing to asthma. While this may be true, this conclusion cannot be drawn at this stage. It might be that the population needs to be better selected to optimize such an effect. Another possibility is that ICS therapy needs to be initiated at an earlier point in the development of the disease (i.e. wheezing children might already be too far along the course of the disease for it to be reversed). It would have been intriguing to see the effects of continuous ICS therapy as applied by Guilbert et al.<sup>11</sup> on the cohort of infants studied by Bisgaard et al.<sup>13</sup> However, it would be difficult to justify administering long-term ICS treatment to such a heterogeneous sample at such an early age. Consequently, a critical component of approaches to asthma prevention will be to develop better tools to identify at-risk children before their disease process has become irreversible. Such issues will have to be thoroughly addressed before any definite conclusions can be made about the utility of ICS or other treatments in the prevention of asthma in at-risk children.

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