

## SNIPPETS FROM OTHER ALLERGY JOURNALS

### Allan S Puterman

My intention is to primarily review two articles in the May 11 issue of the *New England Journal of Medicine* which have the potential of being misquoted and misunderstood.

### **Intermittent inhaled corticosteroids in infants with episodic wheezing**

Hans Bisgaard, *et al.* *N Engl J Med* 2006; **354**: 1998-2005

The authors hypothesised that asthma is preceded by a stage of recurrent episodes of wheezing during the first years of life. Inhaled corticosteroids (ICS) during *symptomatic episodes* may delay progression to persistent asthma!

Infants enrolled in this study were a cohort of infants whose mothers were physician-diagnosed asthmatics. The infants were enrolled at 1 month of age but were not randomised to treatment until they had a first episode of wheezing.

Treatment was either budesonide 400 µg per day via pressurised metered-dose inhaler (pMDI) and spacer or placebo. Of note, the treatment was for a 2-week period per wheezy episode. Open-label budesonide (400 µg) could be added to the study treatment for periods of 2 weeks for severe symptoms.

Of the 411 infants enrolled, 301 were randomised (110 had no episodes of wheeze) and 149 infants received budesonide while 145 received placebo for 2 weeks per episode of wheeze. The treatment commenced on the third day of each wheezy episode. This continued over a 3-year period. Children discontinued participation if they had persistent wheezing, defined as five episodes (each lasting at least 3 days) within 6 months or daily symptoms for 4 weeks or were hospitalised for severe asthma and received oral corticosteroids.

The characteristics of the children in the two groups were similar. The average age at first dose of study treatment was 10 months. Sixty children had pneumonia at randomisation and at least 149 children had pneumonia during the course of the study.

The outcomes in both groups were very similar with near equal symptom-free days and rescue medication-free days. The incident number of episodes of wheeze per child per year was three. Twenty four per cent of the children were withdrawn because of persistent wheezing. Open-label treatment was needed on 59 occasions in the budesonide group and 37 occasions in the placebo group. Lung functions were similar in both groups. Of interest, the pre-study statistical power calculations assumed that 36% of these high-risk children would develop persistent wheeze and that treatment would reduce this proportion to 22%.

The authors correctly concluded that episodic (intermittent), short-term treatment of ICS in infants with pre-asthma symptoms does not provide any benefits. In the discussion the authors suggest that regular therapy may be required. I for one am disappointed that this was not offered to a sub-group of these children as this forms the crux of the dilemma facing paediatricians in private practice in South Africa. Two weeks of ICS per wheezy episode is not a common practice here. Most children would have received 30 days of budesonide per year and therefore the above results are not unexpected.

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### **Long-term inhaled corticosteroids in preschool children at high risk for asthma**

Theresa W Guilbert, *et al.* *N Engl J Med* 2006; **354**: 1985-1997.

This article has a list of authors that represents the cream of American asthma and allergy specialists yet I find it to be one of the most disappointing articles of the year.

The authors query whether ICS can modify *the subsequent development* of asthma in preschool children at high risk for asthma. They assigned 2 or 3-year-olds with a positive asthma predictive index to 2 years of regular inhaled fluticasone or placebo. I will elaborate further on this study but at the outset must point out that the characteristics of the children enrolled indicate that their asthma was already established.

Of 456 children enrolled, 285 were randomised with 143 assigned to fluticasone 88 µg twice daily and the rest to placebo. The treatment phase extended for 2 years and was then stopped for a full year and the children were reassessed.

The listed characteristics of the children, in both groups, prior to treatment were informative:

- The average age at enrolment was 3 years (cf the previous article of 10 months).
- The listed average age of first asthma symptoms was 1 year.
- The listed average age of first diagnosis of asthma by a doctor was 15 months.
- During the enrolment month, and prior to ICS treatment, the children used albuterol an average of once per week and were symptomatic at least 25% of the time. Night awakening due to asthma occurred on average twice in the month.
- At least 66% of the children had one or more emergency room visits for asthma exacerbations in the year before enrolment, and 10% had been hospitalised.

The reviewer finds it hard to understand why these children were labelled as 'at risk for asthma' when they are clearly asthmatic.

The authors note that only children who received not more than 4 months of ICS before enrolment and whose asthma symptoms did not require ICS during the run-in month were eligible.

During the 2 years of treatment, the children receiving fluticasone were significantly less symptomatic than the placebo group and showed a trend towards improved lung functions.

After the 2-year treatment period, treatment was stopped for a year and the children were reassessed.

At the end of the 1-year observation period the children in both groups reverted to similar symptoms and lung functions.

The authors concluded that 2 years of treatment with ICS did not modify the natural course of asthma in young children at high risk for subsequent asthma. The reviewer contends that the subjects were not at risk for asthma, but were asthmatic. Further, the children on active treatment were significantly less symptomatic and tended toward improved lung function. Finally, it is hard to justify stopping treatment that is confirmed to be effective unless/until symptoms have resolved completely.