## Does early intervention with inhaled corticosteroids alter the natural history of mild persistent asthma?

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Abstract: In most patients, both adults and children, who have a new diagnosis of asthma and whose symptoms are mild but persistent, treatment with inhaled corticosteroids (ICS) should be recommended as soon as the diagnosis is made. This is a cost-effective and safe treatment. Patients should be cautioned that their asthma will not be cured with short-term treatment and that their symptoms may recur and their lung function may decline again if treatment is discontinued. If patients are reluctant to use ICS daily for long periods of time, it would be reasonable to delay the onset of treatment with ICS. They could subsequently be managed with intermittent therapy with either ICS or in combination with other medications, such as long-acting  $\beta$ -agonists. Initial therapy with leukotriene receptor antagonist is not likely to be as effective as initial therapy with ICS. Since treatment adjustments based on eosinophil counts in sputum can reliably predict short-term responses to corticosteroids and help identify the appropriate add-on therapy, it may be useful to use this measurement, when available, to guide intermittent therapy.

**Key words:** asthma, early intervention, inhaled corticosteroids, intermittent therapy

## INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective anti--inflammatory drugs in the management of asthma [1]. They control airway inflammation, particularly eosinophilic inflammation [2], improve airway calibre and airway hyperresponsiveness [3], protect the airway against bronchoconstrictor stimuli such as exercise [4] and allergen [5] and prevent asthma exacerbations [6]. These effects improve symptoms and quality of life, and decrease morbidity and asthma related mortality [7]. Despite more than 25 years of experience with these drugs, there are lingering doubts whether they are necessary for patients with mild asthma as soon as they are diagnosed and whether they need to be taken continuously and whether they alter the natural history of asthma, particularly in children. This commentary examines the evidence provided for early intervention in The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study and discusses other recent publications that investigated whether regular therapy with ICS modifies the natural history of asthma.

### Early intervention (START study)

Most guidelines recommend a step-wise approach to asthma therapy, starting with short-acting  $\beta_2$ -agonists for symptomatic relief and using ICS when the asthma is mildly uncontrolled. However, since even the mildest form of asthma is associated with airway inflammatory changes, it seems reasonable to start treatment with ICS as soon as asthma is diagnosed. The most comprehensive study of early intervention with ICS is a 2-stage, multi-center study [8,9] of 103 patients

with asthma diagnosed less than 12 months previously. Patients treated with budesonide 600 µg bid showed a rapid and significant increase in peak expiratory flow (PEF), which was maintained throughout the 2-year study period compared to the terbutaline-treated patients. Their PEF was well maintained for a further year when they were switched to a lower dose of budesonide. However, patients who were switched from placebo to budesonide showed a significant improvement in lung function, but, at the end of the year, their lung function was still significantly lower than that in patients who had received budesonide from the start of the study. Further, the increase in PEF in patients in whom the introduction of budesonide was delayed for 2 years was consistently about half that seen in patients receiving budesonide from the start of the study.

This benefit was confirmed in the recently published START study [10]. This is one of the largest asthma studies ever conducted. 7241 patients aged 5 to 66 years with mild persistent asthma of less than 2 years duration were enrolled. Patients were randomized to low dose budesonide (400 µg once daily for adults and 200 µg once daily for children) or placebo in addition to their usual therapy for 3 years. At the end of this period, all patients received budesonide (open-label)

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### **REVIEW ARTICLES**

for 2 more years. This study differed from the previous studies in a number of respects. It was larger and examined effectiveness rather than efficacy. It included significantly milder patients and a significantly larger number of children. The dose of ICS used was lower. Most importantly, exacerbations rather than lung function were the primary outcome.

At the end of the 3 years of double-blind treatment, 198 of 3568 patients on placebo and 117 of 3597 on budesonide had at least one severe asthma exacerbation; hazard ratio 0.56 (95% CI 0.45–0.71, p <0.0001). Patients on budesonide had fewer courses of systemic corticosteroids and more symptom-free days than did those on placebo. Compared with placebo, budesonide increased post bronchodilator forced expiratory volume in the first second (FEV<sub>1</sub>) from baseline by 1.48% (p <0.0001) after 1 year and by 0.88% (p = 0.0005) after 3 years (expressed as percent of the predicted value). The effect of treatment was independent of the baseline lung function or baseline medication.

Similar overall benefit was also seen in the 1000 children who received budesonide compared to the 974 children who received placebo [11]. The relative risk of a severe asthma related event was reduced by 40% (p = 0.012). Children receiving budesonide also needed significantly less intervention with other ICS (12.3% vs. 22.5% over 3 years; p <0.01), with trends towards decreased usage of systemic corticosteroids and inhaled short-acting  $\beta_2$ -agonists.

Treatment with low dose ICS for 3 years was not associated with any more adverse effects than observed with placebo [12]. Overall, 7221 patients were included in the safety analysis, and a total of 21,520 adverse events were reported (10,850 in the budesonide group and 10,670 in the placebo group). The number of deaths and serious adverse events were similar for children and adults in both groups. Longterm treatment with budesonide also appeared to be costeffective, especially in the younger patients [13].

However, at the end of the 5-year study period, post bronchodilator FEV, percent predicted decreased, irrespective of assigned treatment during the double-blind phase, by an average of 2.22% (SE 0.15%) [14]. There was no significant difference in lung function in either group compared to the start of the study. This is because, when they received budesonide, the placebo group quickly caught up to the treatment group. The number of exacerbations in this group was also no more frequent than in the patients who received budesonide throughout the study. Hence it would suggest from this study that there was no significant advantage from starting treatment with budesonide. However, there was greater use of concomitant additional medications in the control group. These included ICS other than budesonide, long--acting bronchodilators and cromones. It would therefore appear that the prescription of ICS can be delayed in some patients who may be reluctant to take them without significant deleterious effects as later introduction allows a catch-up of lung function. Asthma symptoms could be effectively controlled to the same degree as patients treated early with ICS

through additional treatment with long-acting bronchodilators (long-acting  $\beta_2$ -agonists). This may not be an option for young children in whom these drugs are not recommended for use. For adult subjects, the choice of initial therapy may depend on individual preferences and values. Thus some patients may prefer to use ICS intermittently.

## Regular vs. intermittent therapy (IMPACT study)

The efficacy of intermittent treatment with ICS was investigated in patients with mild persistent asthma over a one-year period in a clinical trial conducted by the Asthma Clinical Research Network supported by the US National Heart Lung and Blood Institute [15]. In a double-blind trial, 225 adults were randomized to daily budesonide (200 µg twice daily), oral zafirlukast, or placebo. All participants were provided with a symptom-based action plan of ICS therapy. The primary outcome was morning PEF averaged over 2 week periods of time. Secondary outcomes included FEV, before and after bronchodilator, frequency of exacerbations, degree of asthma control by questionnaire, the number of symptom-free days, and quality of life. Although the placebo group (intermittent ICS alone) took budesonide for an average of only 0.5 week total during the study, there was no difference in PEF between groups after one year. However, daily budesonide therapy produced improved pre-bronchodilator FEV,, reduced airway hyperresponsiveness, fewer sputum eosinophils, reduced exhaled nitric oxide, and improved symptoms compared to intermittent therapy with or without zafirlukast. There was no difference between groups in post-bronchodilator FEV,, but one year of follow up would be inadequate to detect airway remodelling using this measure. Quality of life did not differ between groups. The addition of daily zafirlukast did not differ significantly from intermittent ICS alone in any outcome measured. It may therefore be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen, but it should be noted that it is debatable whether the primary outcome variable of PEF was the most clinically relevant outcome variable in such a study.

# Natural history of asthma (Prevention of Early Asthma in Kids: PEAK study)

The recommendation to use ICS regularly would be strengthened if this altered the natural history of asthma, especially in children. This was examined in a clinical trial conducted by the Childhood Asthma Research and Education Network [16]. The asthma predictive index was used to select subjects at high risk of developing asthma. These 285 participants, two or three years of age were then randomized to treatment with fluticasone propionate (88  $\mu$ g twice daily) or placebo for 2 years. The primary outcome was the proportion of episode-free days during one year of observation without the study drug after the 2-year treatment period was complete. Secondary outcomes included exacerbations, lung function, supplementary use of controller medication, and the effect of treatment on growth in height. During the treatment phase, the ICS group had a greater proportion of episode-free days, fewer exacerbations, and less use of controller medications. During the observation phase, however, after treatment was complete, there was no significant difference between groups in those outcomes. Growth velocity was reduced in the ICS group during treatment. During the observation period, growth velocity in the group that had received ICS was greater than the placebo group, but a 0.7 cm difference in height change remained at the end of the study. Therefore two years of ICS therapy, while improving symptoms during treatment, does not change the incidence of asthma symptoms after the treatment is stopped.

### SUMMARY

Based on this evidence, it is reasonable to draw the following conclusions: In most patients, both adults and children who have a new diagnosis of asthma and whose symptoms are mild but persistent, treatment with ICS should be considered. Patients should be cautioned that with short-term treatment their symptoms may recur and lung function may decline again if treatment is discontinued. Even if treatment is continued regularly, it is unlikely to change the natural history of asthma. If patients are reluctant to use ICS daily for long periods of time, it would be reasonable to offer them intermittent therapy with ICS if they have mild persistent symptoms. Initial therapy with other anti-inflammatory therapies such as leukotriene receptor antagonists are not likely to be as effective as ICS. Since treatment adjustments based on eosinophil counts in sputum can reliably predict short-term responses to corticosteroids [17], it may be useful to use this measurement when available to guide intermittent therapy.

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