As-needed (intermittent) inhaled corticosteroid for mild asthma

Tari Haahtela, Professor
Skin and Allergy Hospital, Helsinki University Central Hospital, PO Box 160, 00029 HUS, Finland
e-mail: tari.haahtela@hus.fi
Asthma is a syndrome

Both in children and adults, asthma is a syndrome, an “umbrella” diagnosis. It is a variable (chronic), inflammatory condition of the lower airways characterized by largely reversible airflow obstruction, airway hyperresponsiveness, and episodic respiratory symptoms, including wheezing, productive cough, and sensations of breathlessness and chest tightness. Asthma covers several genotypes in terms of factors affecting disease severity or responses to treatments and drugs.

Most of asthma is mild

At the population level most of asthma is intermittent or mild (70-80%), and more often so in children compared to adults. These patients are probably not facing any significant lung function loss over time even regardless their treatment.

More attention should be paid on the mild end of the asthma spectrum, to the majority of patients to estimate better the treatment impact on different disease outcomes: symptom persistence, lung function loss over time, and need for regular medication. Under-treatment is still a major problem, but unnecessary or even harmful over-treatment is also becoming common. Strategies to treat mild asthma are not well based on evidence, neither in children nor adults. How intensive should the initial treatment be? For how long it should go on, in children and adults? When is intermittent treatment sufficient, and for how long should the treatment periods take? If treatment is altogether stopped by the patient, what is the risk for disease escalation?
Most asthma drug studies have been accomplished in patients with moderate persistent asthma (to have room for improvement and possibility to show treatment differences), and the results are often carelessly generalized to whole asthmatic population. Along with better options to measure not only lung function but the inflammatory component of asthma [1,2], the early and often milder stages of the disease, when lung function is still mostly preserved, can be better addressed. Asthma may commence already in infancy and continue to adult life, but the inflammation-structure-function relationships in infants have only recently been explored [3].

“Decliners” are minority

There are the lung function “decliners”, those patients (estimates in adults range from 20-30% of asthmatics) in whom significant irreversible airways obstruction develops over time. The possible “slowing down” effect of inhaled corticosteroids (ICS) may be seen more readily in them. Recent 10-year observational data from Denmark indicate that may be the case [4]. In a general population sample treatment of asthma with ICS was associated with a less steep decline in FEV1 of 18 ml/year compared with patients not receiving this treatment (p=0.01).

The clinical benefits of early treatment with anti-inflammatory therapy for persistent-type, but still mostly mild asthma were shown in the early 1990s [5]. The first results in the mid 1990s also indicated that delays in initiating ICS therapy may lead to an impaired functional response [6]. The non-randomized studies by Agertoft and Pedersen [7] and Selroos et al. [8] pointed to the same direction: delay was harmful. However, the prospective CAMP study questioned the benefit of inhaled corticosteroids on children lung function, but as no significant FEV1 decline was seen in the placebo group, treatment effect was difficult to demonstrate [9].
Whether ICS alter the long term functional (natural) course of asthma in children or adults is still debated, and may never be fully answered. Length of the follow-up required, ethical considerations and costs will prevent that. These doubts should not, however, hinder us to use the most effective treatment and use it early enough. At least in adults, the results of O’Byrne et al. [10] and Lange et al. [4] reassure our current practice of preventing all asthma events with regular use of ICS – the dose can vary – in patients who have symptoms on most days.

HEICA-study
The Helsinki Early Intervention Childhood Asthma Study (HEICA) is a landmark study to show that as-needed treatment may, in fact, be the strategy of choice for most children with mild asthma [11]. The study compared step-down inhaled budesonide given daily or as-needed (intermittently) in mild persistent childhood asthma.

176 children aged 5–10 years with newly detected asthma were randomized into three treatment groups: Group 1: continuous budesonide (400 µg twice daily for 1 month, 200 µg twice daily for months 2–6, 100 µg twice daily for months 7–18); Group 2: budesonide/placebo (identical treatment to Group 1 during Months 1–6, then budesonide for exacerbations as-needed for months 7–18); and Group 3: disodium cromoglycate (DSCG) 10 mg three-times daily for months 1–18. Exacerbations were treated with budesonide 400 µg twice daily for 2 weeks.

Compared with DSCG the initial regular budesonide treatment resulted in a significantly better improvement of lung function, fewer exacerbations and a small but significant decline in growth velocity. After 18 months, however, the lung function improvements did not differ between the
groups. During months 7-18, children receiving continuous low-dose budesonide treatment (100 µg twice daily) had significantly fewer exacerbations (mean 0.97), compared with 1.69 in Group 2 (budesonide only as needed) and 1.58 in Group 3 (most drop outs from this group, towards the end of the 1 ½ year trial treatment became mixed DSCG and budesonide because exacerbations were treated with budesonide). The number of asthma free days did not differ between regular and intermittent budesonide treatment. Growth velocity was normalized during continuous low-dose budesonide and budesonide therapy given as needed, but the latter was associated with catch-up growth.

It was concluded, that regular use of budesonide afforded somewhat better asthma control but more systemic effects than use of budesonide as needed only. The dose of ICS could be reduced as soon as asthma is controlled. The most important observation was, however, that a significant proportion of children with mild asthma (even majority!) does not seem to need continuous ICS treatment.

Real-life experience from Finland

In 1994, the Finnish asthma program was established to reduce morbidity of asthma in Finland with a focus on early detection and treatment of inflammation, as implemented by a network of asthma-responsible doctors, nurses, and pharmacists. While this program has not halted the increase of asthma in Finland, the burden of asthma has been greatly decreased over 10 years [12]. This outcome can be attributed mainly to early and more effective use of anti-inflammatory medication. Although there is no exact data, it seems that in real life most asthma patients in Fin-
land, both children and adults do use ICS as needed (intermittently), and this has been partly promoted by the guided self-management strategies in Finland, where increasing and decreasing of the ICS dose, according to symptoms and need for rapid-acting beta2-agonists, has been taught to the patients.

The problem is, of course, that patients (parents) tend to underestimate the severity of the condition (airway inflammation) and the anti-inflammatory treatment is far from optimal. Too liberal attitude to as-needed use of ICS may deteriorate overall asthma control in the population. Nevertheless, well educated and adherent patients (parents) may be able to use as-needed strategy, if they start treatment proactively (early enough) and keep it long enough (4 weeks). This is especially true in many of the children, who tend to become free of symptoms when approaching adolescency.

Our recommendation in Finland is at the moment the following. Children with newly diagnosed asthma should be on regular ICS for 6 months, and adults for 12 months. If patients are free of symptoms and with normal lung function (also eNO is considered), they may try as-needed approach. If too many exacerbations occur (more than 2 per year) they are put on regular ICS, the dose of which may vary.

Conclusions

In asthma the relationships of airway inflammation, remodeling and lung function are becoming better understood; they are consecutive but also parallel phenomenons, which vary largely both in severity and timing between individuals. Anti-inflammatory therapy with ICS still remains the
best option for the vast majority of patients to improve asthma control. The inflammatory element of asthma can be detected more readily than before by measuring exhaled NO, or examining cells and soluble markers in induced sputum. Increased airway responsiveness is a surrogate marker of inflammation and seems to reflect development of structural changes in the airways. Exacerbation rate is reduced, if inflammatory markers - exhaled NO [13], sputum eosinophils or hyperresponsiveness - guide the treatment. New modes of ICS therapy, especially as-needed therapy, have emerged, but are still not well established through clinical trials. Given the similarity that exists between the patterns of inflammation in asthma and allergic rhinitis, treatment should always focus the entire airway rather than only a part, as well as the skin (inflammation in atopic eczema) as necessary.
References


