Allergology International (2002) **51**: 75–83

Review Article

Early treatment in asthma: How early is early?

Tari Haahtela

Division of Allergy, Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland

Abstract

In the 1990s, the definition of asthma changed as we realized that asthma is fundamentally an inflammatory disorder. It was also shown in both adults and children that treatment should be initiated with anti-inflammatory medication (preferably inhaled steroids) and delayed treatment may worsen lung function outcome. There is increasing evidence that, in both children and adults, early and effective therapy with inhaled steroids results in long-term remission in the majority of patients. In future, even intermittent asthma symptoms will be treated with inhaled steroids. The first signs of asthma should be treated effectively, even in small babies. In children with atopic dermatitis, early pharmacotherapy may prevent asthma and in children with hay fever, specific immunotherapy may reduce the asthma risk. Airway eosinophilia predisposes a patient to asthma. The benefit of early intervention in patients who show eosinophilic airway inflammation but have normal or near normal lung function has been recently demonstrated. It seems that we should treat 'asthma even before asthma', if the disease is defined in terms of lung function. Persistent asthma is difficult to reverse, but early stages of asthma could be more responsive to novel therapies, such as drugs modifying the pro-inflammatory cytokines or monoclonal antibodies against IgE. The emerging new methods to assess airway inflammation will cast light on the origin of asthma, as well as on the determinants of disease persistence. Along with the development of practical inflammatory markers, the doctor gets a clearer picture of the disease. This means a better understanding for the doctor and better tailored treatment for the patient and this will further improve treatment results.

Correspondence: Professor Tari Haahtela, Division of Allergy, Skin and Allergy Hospital, Helsinki University Central Hospital, PO Box 160, 00029 HUS, Finland.
Email: tari.haahtela@hus.fi
Received 15 January 2002.

Key words: early asthma, eosinophilic inflammation, inhaled corticosteroids.

Introduction

Our thinking has changed along with the appraisal of bronchial asthma as an inflammatory disease. The mechanistic idea of asthma as an enhanced bronchospasm has been replaced by a more holistic view regarding asthma as a biologic continuum from mild episodes of 'asthmatic' inflammation to fatal attacks. Asthma is a man-made definition and quite arbitrary. Lung function tests (e.g. peak flow measurements) are useful in monitoring patients with moderate to severe persistent asthma, but they give only indirect evidence of the airway pathology and are insensitive to early signs of asthma.

Asthma, as defined by lung function terms, is a consequence of airway inflammation, in which eosinophils play a central role. Initiation of effective treatment and treatment guidance has relied mainly on repeated lung function measurements. We also need practical tools for detection of asthmatic inflammation and to monitor its course. This is especially important because there is growing evidence that early pharmacologic intervention can modify the course of asthma and even prevent the development of asthma in patients with early manifestations of atopic disease.

The key feature affecting disease persistence is airway remodeling (with changes in airway smooth muscle) as a result of poorly controlled inflammation.[1] Delay of anti-inflammatory treatment is associated with lung function loss over time,[2] even though in the majority of patients the risk for clinically significant lung function decline seems to be relatively small.

How early is early?

The benefits of acting early are well-illustrated by a comparison of the effect of nebulized budesonide versus symptomatic treatment with bronchodilators in infants

(mean age 2.3 months) hospitalized with severe respiratory syncytial virus (RSV) bronchiolitis.[3] By the time the infants were 2–3 years of age, the incidence of asthma among those babies who had received the inhaled corticosteroid was approximately 50% lower than those who received only conventional symptomatic treatment (Fig. 1). However, the study was an open one and the result should be confirmed in a carefully controlled trial.

Early intervention with antihistamines has also been shown to reduce the incidence of asthma in a selected group of children with atopic dermatitis syndrome. In the Early Treatment of Atopic Child (ETAC) study, the incidence of asthma in grass- and mite-sensitized 1–2-year-old children with atopic dermatitis was reduced by approximately half following 18 months treatment with cetirizine compared with placebo.[4] The study was continued with an 18 month follow up and the effect of cetirizine was sustained for the grass pollen-sensitized infants over the full 36 months.[5] The clinical relevance of this study can be questioned because only a few children of this age are grass pollen or mite sensitized. However, there are at least two earlier studies that indicate the same: antihistamine treatment may reduce asthma risk in atopic children. Iikura *et al.*[6] treated infants with atopic dermatitis with either the antihistamine ketotifen or placebo for 1 year. Asthma was observed in 13% of infants in the ketotifen group and in 42% of infants in the placebo group. In a study over 3 years with the antihistamine ketotifen in children with elevated total IgE and a family history of atopy, treatment reduced the incidence of asthma compared with placebo (35 *vs* 9%, respectively).[7]

As an alternative approach, the Preventive Allergy Treatment (PAT) study shows that it is possible to modulate the immune system if treatment is started early enough. In the PAT study of children aged 5–13 years with seasonal allergic rhinoconjunctivitis, the incidence of asthma after 5 years was reduced from 56% in control subjects receiving conventional drug therapy to 23% in children receiving specific immunotherapy.[8] The result should be appreciated even though the study was not placebo controlled. These kind of long-term interventions and follow ups are difficult to perform in a fully controlled manner.

Eosinophilic inflammation: Unmasking an important target group

It seems that an important opportunity to prevent asthma is often overlooked in patients who show some of the signs of the disease (e.g. prolonged cough) but record

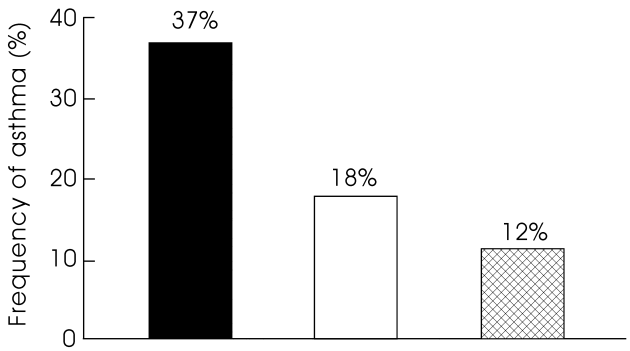

Fig. 1 Infants (mean age 2.6 months; range 0–9 months) receiving nebulized budesonide to treat obstruction associated with respiratory syncytial virus bronchiolitis had a lower risk of developing asthma at 2–3 years of age than infants who received conventional symptomatic treatment. (■), symptomatic treatment; (□), budesonide 500 μg × 3, 7 days; (▩), 500 μg × 2, 2 months. Redrawn from Kajosaari *et al.*[3]

normal or near normal lung function. As a result, they receive little, or inappropriate, treatment. We hypothesized that many of these patients would show eosinophilic inflammation, which is a characteristic marker of the airway pathology usually encountered in asthma. This could then be used to identify patients for appropriate treatment with anti-inflammatory medication (e.g. inhaled steroids or antileukotrienes).

To test the hypothesis, we investigated a population of 82 consecutive patients presenting to their general practitioners with prolonged cough (more than 2 months) but not other signs of asthma or any other pulmonary disease, gastroesophageal reflux or rhinosinusitis.[9] Approximately one-fifth of these patients showed sputum eosinophilia. When tested for lung function, 36% of patients with sputum eosinophilia were revealed as asthmatics, yet the majority (64%) did not fulfill the functional criteria for asthma. Further analysis of inflammatory markers in another similar study population showed that patients with eosinophilia, but relatively normal lung function, form an intermediate group between real asthmatics and healthy individuals.[10]

The literature suggests that patients with cough and eosinophilia, but normal lung function, are relatively rare.[11,12] However, our experience indicates that they are not rare and could be, in fact, more common than patients with asthma. There is evidence that the condition is an important and rather usual cause of prolonged cough.[13] It seems that both children and adults can have episodes of eosinophilic inflammation during respiratory infections or allergen exposure while having, most of the

time, normal or close to normal lung function. Because epidemiologic data on sputum eosinophilia in general populations has been lacking, we made a survey in Finland and Russia.

Eosinophilic inflammation: Common in the general population

We assessed the occurrence of sputum eosinophilia in two geographically adjacent areas: North Karelia, Finland, and in Pitkäranta, Russia. Seven hundred and ninety Finns and 387 Russians, aged 25–54 years, were randomly selected from the population registers. Patients with known asthma were excluded from the study. The prevalence of sputum eosinophilia was 22% among the Finns and 19% among the Russians (T Petäys, pers. comm.). Current smoking was significantly associated with sputum eosinophilia and atopy was another risk factor. The association of sputum eosinophilia and bronchial hyperreactivity was not straightforward. There were many individuals in the general population who showed eosinophilia but not bronchial hyperreactivity. The study indicated that sputum eosinophilia is common in general populations and is partly associated with cough and wheezing.

Intervene early in airway eosinophilia

Airway eosinophilia predisoposes a patient to asthma. For example, in a study of 147 patients with prolonged cough, the consequence of a delayed diagnosis of asthmatic inflammation was that, after 1 year, 46 (31%) had developed asthma.[14] Indeed, in that study the presence of eosinophilia in blood, sputum or nasal secretion in the first place represented a highly significant, approximately fourfold, increase in the risk of developing asthma. Similarly, of 33 children with symptoms suggesting asthma but normal lung function, one-third went on to develop the disease in 2 years.[15] The data are still scanty, but there seems to be an increased risk of asthma in patients who have symptoms of disease, especially prolonged cough and eosinophilia.

The benefit of early intervention in patients who show some signs of asthma but have relatively normal lung function was demonstrated in a study of adult patients with prolonged cough and, in many cases, also eosinophilic airway inflammation.[10] Patients were randomized to receive either inhaled beclomethasone dipropionate or placebo for 3 months and were followed up for 1 year.

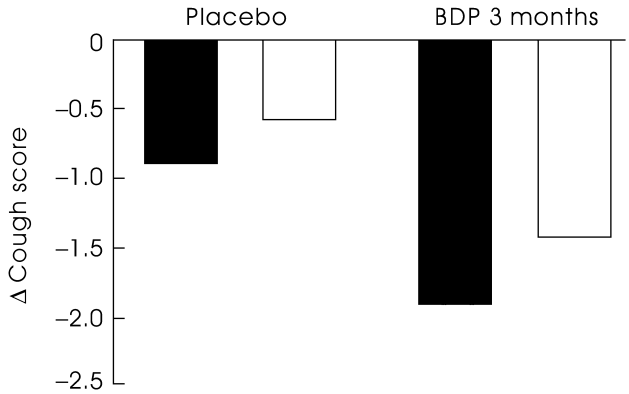

Fig. 2 Treatment with inhaled beclomethasone dipropionate (BDP) markedly reduced symptom score in patients with prolonged cough and eosinophilic inflammation, but not fulfilling the functional criteria for asthma, compared with placebo. (■), treatment for 3 months; (□), treatment for 1 year. Redrawn from Rytilä *et al*.[10]

Symptom score was markedly reduced at both 3 months and at 1 year compared with placebo (Fig. 2), as was the level of the inflammatory marker eosinophil peroxidase (EPO) in induced sputum.

The considerable delay in diagnosing asthma has been acknowledged.[16] In Helsinki, the mean delay from start of symptoms suggesting asthma to the actual diagnosis of asthma is 1 year 7 months in children and 5 years 4 months in adults.[17] This is mainly because the inflammatory component of asthma is not detected in symptomatic patients who still have, for most of the time, normal or near normal lung function.

Intervene early in asthma

Adults

The effects of early intervention have not been studied extensively. A directly relevant study compared prospectively two treatment strategies: (i) whether patients should be treated with inhaled steroid from the beginning; or (ii) whether treatment should be initiated with β_2-adrenergic receptor agonists alone.[18] Patients with asthmatic symptoms for less than 1 year and no previous anti-inflammatory therapy inhaled either budesonide 1200 μg or terbutaline 750 μg daily as the first and only regular medication. Two years treatment with inhaled budesonide resulted in almost complete clinical recovery and normalization of lung function and was superior compared with treatment with β_2-adrenergic receptor agonists. Bronchial biopsies were taken from a subgroup of

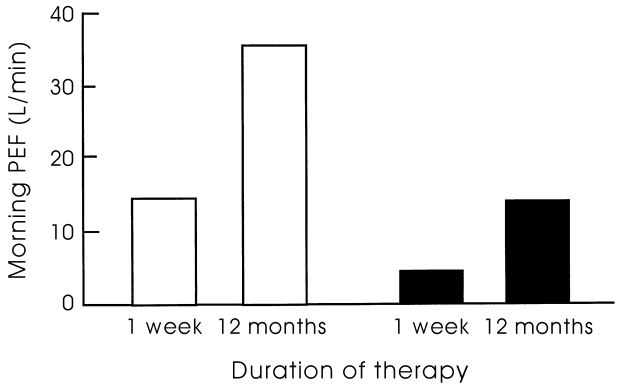

Fig. 3 Improvements in morning peak expiratory flow (PEF) values in patients with newly detected asthma who either received inhaled budesonide as first-line therapy immediately after the diagnosis (□) or who received budesonide 2 years after diagnosis (■). Redrawn from Haahtela *et al.*[2]

patients and, after 3 months, budesonide-treated subjects had a significantly greater fall in the number of inflammatory cells than terbutaline-treated patients.[19]

The study was continued for a 3rd year to investigate the effects of dose reduction or discontinuation of steroid treatment. A delayed introduction of inhaled steroid was also examined. The peak expiratory flow (PEF) level was well maintained for the 3rd year in patients in whom the daily budesonide dose was reduced from 1200 μg (by Nebuhaler; Astrazeneca, Sweden) to 400 μg (by Turbuhaler; Astrazeneca, Sweden). Most patients who switched from budesonide to placebo showed a gradual and slight decline in lung function, which became significant towards the end of the 3rd year, but some patients did not deteriorate at all.[2] The patients who were first treated with the β_2-adrenergic receptor agonist terbutaline for 2 years, and were only subsequently treated with budesonide, did not reach the same level of lung function within the 3rd year as those who were treated with budesonide from the beginning of the study (Fig. 3). Some functional reversibility was lost by delaying the start of steroid treatment.

Adult patients with persistent asthma or chronic obstructive pulmonary disease (COPD; baseline forced expiratory volume in 1 s (FEV_1) approximately 60% of predicted), half of them having already used inhaled steroids, had a 2.5 year intervention with bronchodilators alone or with a β_2-adrenergic receptor agonist (terbutaline) and steroid (beclomethasone).[20] The addition of inhaled steroid, but not an inhaled anticholinergic agent, to maintenance treatment with the β_2-adrenergic receptor agonist was very beneficial in terms of symptoms and bronchial responsiveness. The study was continued for 6 months after the first 2.5 years to investigate the effects of adding beclomethasone 800 μg daily to those patients who had not previously received it.[21] Airway hyperresponsiveness showed no significant change after 6 months during the new intervention, whereas it had shown a significant improvement at 3 months in patients who started beclomethasone in the first phase. It seemed that institution of inhaled steroid should not be postponed in asthmatics with documented airway obstruction. Although the investigation can hardly be considered an early intervention study (the patients had a disease of moderate severity and a long history of symptoms), it is important by showing the risks of delaying anti-inflammatory treatment.

Osterman *et al.*[22] studied adult asthmatics who had their asthma diagnosis established not more than 1 year before the study. However, most of them had a persistent, albeit a rather mild, disease with symptoms for years. The patients inhaled 400 μg budesonide daily (by Turbuhaler) for 1 year and showed marked improvement in lung function and bronchial responsiveness compared with placebo treatment.

Selroos *et al.*[23] examined retrospectively the influence of the duration of pretreatment symptoms on the response to inhaled steroid treatment in steroid-naïve adult patients with asthma. The duration of symptoms ranged from less than 6 months to more than 10 years. Most of the 105 patients were treated with budesonide 800 μg daily for 1 year. During the 2nd year, the dose was reduced when this was possible without a worsening of asthma control. The maximum effects were seen usually after 1 years treatment, with maintained control during the second year. A significant negative correlation was found between duration of symptoms and maximum increases in PEF and FEV_1 values. The results gave evidence that early treatment of asthma with inhaled steroid may prevent patients from developing chronic airway obstruction.

In a recent study, Selroos *et al.*[24] evaluated how goals had been achieved depending on when treatment with inhaled steroids in asthma had been started. In 1988–1991, treatment with budesonide was started in 462 patients (mean age 37 years) and they were followed for 3.5 years. Sixty-two percent of patients had had symptoms of asthma for less than 2 years and the remaining patients had had symptoms for 2–38 years. Early start of inhaled steroid resulted in better lung function (78 *vs* 41% of patients had $FEV_1 > 90\%$ predicted) and exercise tolerance compared with late start. Early treatment also decreased exacerbations and the need for rescue medication.

Children

The Dutch childhood study[25] included children with chronic obstruction and moderate to severe asthma. The aim was, in fact, not to investigate early intervention but whether long-term treatment with a regular β_2-adrenergic receptor agonist plus inhaled steroid was more effective than treatment with a β_2-adrenergic receptor agonist alone. The results were quite conclusive: the steroid-treated group managed better in every respect. However, full remission was achieved only by 60% of children, which indicated that, in many of these children, some of the functional reversibility was already lost when steroid treatment was initiated.

Agertoft and Pedersen[26] measured lung function and growth in 278 children with mild to moderate asthma during long-term treatment with inhaled budesonide and compared openly the findings with those obtained from children not treated with steroids. The children were 'old' asthmatics (mean duration of asthma $3^1/_2$ years) having used β_2-adrenergic receptor agonists and only occasionally steroids. The difference in FEV_1 and in many other outcome variables between the two groups was very significant in favor of the budesonide-treated children. Interestingly, the annual increase in FEV_1 was greatest in those children whose asthma was of shortest duration when inhaled budesonide was started. Early intervention with inhaled steroid seemed to prevent the development of irreversible airway obstruction and reduce the risk of undertreatment.

Konig and Shaffer[27] observed, during an 8.4 year follow up of children from the age of 6.5 years, that treatment with cromolyn sodium or inhaled steroid, but not as-needed bronchodilators alone, improved the long-term prognosis. However, the prognosis of mild childhood asthma is favorable even without any treatment.

Oswald *et al*.[28] followed 286 children for 28 years and concluded that airway obstruction in mid-adult life was present mainly in those with moderately severe asthma. Subjects with relatively mild asthma who had not taken inhaled steroids did not appear to be disadvantaged with respect to lung function.

In the real world, compliance with inhaled corticosteroids declines with time. Most patients tend to take their medication intermittently or periodically. The preliminary findings of the Helsinki Early Intervention Childhood Asthma (HEICA) study show that continuous and periodic treatment with inhaled budesonide reduced exacerbations in an almost similar manner following equivalent 6 month induction periods to remission.[29] The result shows that, provided we treat children early and effectively in the first place, a periodic approach (2 week courses of budesonide, as needed) may be just as effective as continuous therapy in the majority of children and is likely to be what happens in real life.

We need reassurement: The START study

The START (inhaled Steroid Treatment As Regular Therapy in early asthma) study was planned to evaluate the benefits of early intervention with inhaled steroids in patients with mild, persistent asthma in the 'real world'.[30] Patients were randomized to once-daily treatment with budesonide 200 μg (for patients < 11 years) or 400 μg (for patients > 11 years) or placebo for 3 years. The double-blind treatment was followed by a 2 year period of open budesonide treatment. The primary outcome measures were the time to the first severe exacerbation during the first 3 years and the change in post-bronchodilator FEV_1 during the entire 5 year study period. These measures were chosen to reflect the progression of mild asthma towards more severe disease and the extent of irreversible airflow limitation, which reflects airway remodeling. The first results will be ready this year and will certainly have an major impact in the treatment strategies.

Inhaled steroids: Do they modify the outcome?

Long-term influence

One possibility to explore the long-term influence is to study what happens when treatment is stopped. The studies of Haahtela *et al*.[2,18] answered only partly the questions how long should steroid treatment be continued after remission, can the dose be reduced and what kind of dosage schedules can be used? There are very few studies addressing these issues in adults or in children.

Short-term studies on the withdrawal of inhaled steroid therapy after treatment for periods of 4 weeks or less suggest that bronchial responsiveness increases within weeks of inhaled steroid reduction or withdrawal.[31,32] However, patients in these studies have had persistent asthma with a long symptom history. It has been shown that considerably longer periods of treatment than 4 weeks do not fully reverse the inflammatory changes in the airways, even in patients with relatively mild asthma.[33,34] Furthermore, van Den Toorn *et al*.[35] observed recently that atopic asthmatics in apparent clinical remission

showed clearly increased numbers of inflammatory cells in bronchial biopsies.

Juniper *et al*.[36] showed that the improvements in bronchial responsiveness induced by treatment with budesonide for 1 year were maintained for at least 3 months after cessation or reduction of treatment with an inhaled steroid. The result is remarkable, because the patients did not have early asthma but, rather, a persistent disease with at least moderate severity.

Van Schayck *et al*.[37] withdrew inhaled bechlomethasone from a group of patients after 4 years treatment. Before that, the patients were treated with bronchodilators for the first 2 years and with beclomethasone for the 3rd and 4th years. Some patients with poor lung function showed an accelerated rate of decline after withdrawal of the inhaled steroid, but those with good lung function showed no increase in the rate of decline of lung function. The investigators concluded that patients in the latter group could stop inhaled steroid after treatment for 2 years. Again, the patients had persistent asthma with a long history.

Osterman *et al*.[22] followed their patients after the treatment year for another 6 months without steroids. The budesonide-treated patients maintained approximately 50% of their achieved improvement in bronchial responsiveness during the follow-up period, but only patients with milder disease remained in the study, which somewhat invalidated the observations. Overall, the effects of low-dose budesonide treatment for 1 year were mainly temporary. Again, most of the patients did not have a 'new' disease.

Simons[38] treated children with mild or moderate persistent asthma with beclomethasone 400 μg daily for 1 year. The beneficial effect on increased bronchial responsiveness disappeared in 2 weeks after cessation of treatment.

We need more information of the possible disease-modifying effect. The problem is that the natural course of asthma is not well established and is very difficult to explore when all the patients are treated in one way or another. There is no doubt that inhaled steroids reduce mortality, hospital use, unscheduled visits to a physician and to the emergency room, days missed from work or school, use of rescue medication and the overall costs of medical care.[39,40] However, are inhaled steroids or any other medication only suppressing the disease or are they truly able to change the so-called natural course of the disease (e.g. to prevent the decline in lung function in the long term)? This is not known and it is going to be very difficult to get any scientifically satisfactory answers.

How to improve early diagnostics?

Eosinophils can be readily studied from induced sputum.[41,42] The presence of eosinophils in the sputum is a more sensitive marker of asthmatic airway inflammation than blood eosinophils or increased serum eosinophil cationic protein (ECP).[43,44] Soluble markers like ECP and myeloperoxidase have been measured from the sputum to assess the presence of eosinophils and neutrophils. Eosinophil cationic protein is often increased not only in asthma, but also in COPD and bronchiectasis and can be detected also in neutrophils.[45] This reduces the specificity of ECP to asthmatic inflammation. Myeloperoxidase is also detected in monocytes, which is a minor confounding factor.

In addition, more cell-specific markers have been introduced, such as eosinophil peroxidase (EPO)[46] and human neutrophilic lipocalin (HNL),[47] which appear clinically useful in the early detection of inflammatory processes.[10,48] Many other markers have been investigated, but mainly as research tools. Induced sputum is still not a method handy enough for quick diagnostics in clinical practice, even though it has been used in outpatient care[9] and sample processing has been simplified.[49]

Nitric oxide (NO) generation is increased in airway inflammation and can be measured in exhaled air. The measurement for the patient is simple and takes only approximately 20 min. With the new equipment available, the result is reliable but may be confounded by NO from the upper airways. Increased NO concentration is a sign of mucosal inflammation, but not specific to asthma. In clinical practice, however, it is not too difficult to rule out other possible causes of an abnormal result by taking a careful patient history. Thus, NO measurement seems to be a good tool to screen asthmatic inflammation and to monitor its course during treatment.[50] New applications for clinical practice and even for home monitoring are being developed. At the moment, the equipment is expensive and the method can be used in major hospitals only.

Recent application of using exhaled air for clinical purposes has been studied with breath condensates. For example, nitrosothiols (RS-NOs), which may limit the detrimental effect of NO in the airways, are detectable in breath condensate of healthy subjects and are increased in patients with inflammatory airway diseases.[51]

In clinical work, the inflammatory component is increasingly assessed to make the correct diagnosis and to adjust the need of anti-inflammatory treatment, especially

inhaled steroids. Is it helpful to grade the severity of airway inflammation to identify those patients who are at risk of marked lung function decline? From clinical experience we know that inflammation may be severe, but lung function is not affected, or signs of inflammation are lacking, but the patient's bronchi are severely hyperreactive. Furthermore, patients in apparent clinical remission may show increased numbers of inflammatory cells in their bronchial mucosa.[35]

The emerging new methods will cast light on the origin of asthmatic inflammation as well as on the determinants of disease persistence. Along with the development of simple methods to assess airway inflammation, the doctor gets a clearer picture of the disease. This means a better understanding for the doctor and better tailored treatment for the patient, which will further improve treatment results.

Clinical reality and future options

When developing all the new methods, let us trust the experienced adult clinician who states:

> 'If asthma starts after a severe respiratory infection, is nonatopic (intrinsic), is associated with severe eosinophilic inflammation and marked bronchial hyperreactivity, the prognosis is poor. The patient usually obtains a remission but needs regular treatment.'

However, there is increasing evidence that, in both children and adults, early and effective therapy with inhaled steroids results in long-term remission in the majority of patients.[2,26,29]

The Finnish Asthma Programme[39] recommends, in line with many other guidelines, anti-inflammatory medication, preferably with inhaled steroids, as first-line treatment to gain control of the disease as fast as possible. Figure 4 illustrates the development of the use of inhaled steroids (preventers) and short-acting β_2-adrenergic receptor agonists (relievers) in Finland. In 1994, the ratio of preventers to those of relievers exceeded 1.0, indicating a profound change in treatment practices.

When treatment is started, the concept of induction treatment can be used. Induction is followed by maintenance treatment and treatment of relapses. Induction with a high dose of inhaled steroid is justified according to studies where markers of asthmatic inflammation have been used as outcome measures.[52,53] Tukiainen *et al.* observed, in newly detected asthmatics, that decreases in bronchial hyperreactivity and serum inflammation markers were larger with 800 μg budesonide daily compared with 200 μg, even though the lung function outcome measurements did not differ.[53]

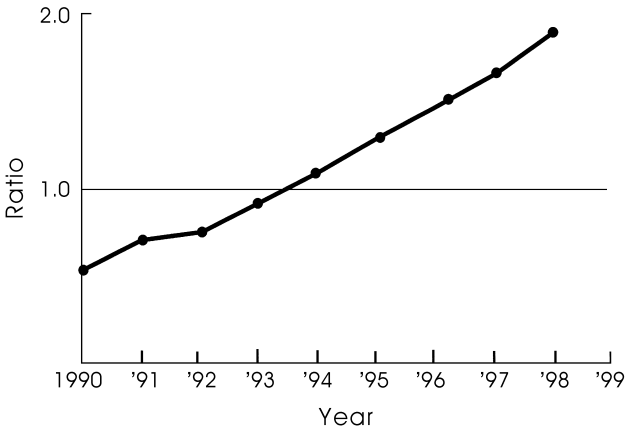

Fig. 4 Ratio of the use of inhaled corticosteroids to short-acting β_2-adrenergic receptor agonists in Finland from 1990 to 1999. From Haahtela *et al.*[39]

The future also holds other promises. Exploration of the role of various cytokines in the pathophysiology of asthma has provided ideas for novel therapies. There are several ways to inhibit the function of cytokines.[54] The proinflammatory cytokines interleukin (IL)-4, IL-5, IL-13 and tumor necrosis factor-α have been the first targets. The results of preliminary clinical trials have been variable and partly disappointing, which may also depend on the patients included. Persistent asthma is difficult to reverse, but early stages of asthma could be more responsive to these kind of approaches. The new monoclonal anti-IgE is helping even severe allergic asthmatics,[55,56] but could help best patients with newly detected asthma associated with other atopic manifestations, such as rhinitis and dermatitis.

References

1 Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola M. From bronchoconstriction to airways inflammation and remodeling. *Am. J. Respir. Crit. Care Med.* 2000; **161**: 1720–45.

2 Haahtela T, Järvinen M, Kava T *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N. Engl. J. Med.* 1994; **331**: 700–5.

3 Kajosaari M, Syvänen P, Förars M *et al.* Inhaled corticosteroids decrease asthma after respiratory syncytial virus bronchiolitis. *Pediatr. Allergy Immunol.* 2000; **11**: 1076–9.

4 ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: First results of ETAC. *Pediatr. Allergy Immunol.* 1998; **9**: 116–24.

5 Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J. Allergy Clin. Immunol.* 2001; **108**: 929–37.

6 Iikura Y, Naspitz CK, Mikawa H *et al*. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann. Allergy* 1992; **68**: 233–6.

7 Bustos GJ, Bustos D, Romero D. Prevention of asthma with ketotifen in pre-asthmatic children: A three-year follow-up study. *Clin. Exp. Allergy* 1995; **25**: 568–73.

8 Möller C, Dreborg S, Ferdousi HA *et al*. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J. Allergy Clin. Immunol*. 2002; **169**: 251–6.

9 Rytilä P, Metso T, Petäys T *et al*. Eosinophilic inflammation as an underlying mechanism of undiagnosed prolonged cough in primary healthcare patients. *Respir. Med*. 2002; **96**: 52–8.

10 Rytilä P, Metso T, Heikkinen K, Saarelainen P, Helenius I, Haahtela T. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. *Eur. Respir. J.* 2000; **16**: 824–30.

11 Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: Eosinophilic bronchitis without asthma. *Lancet* 1989; **i**: 1346–8.

12 Gibson PG, Hargreave FE, Girgis-Gabardo A, Morris M, Denburg JA, Dolovich J. Chronic cough with eosinophilic bronchitis: Examination for variable airflow obstruction and response to corticosteroid. *Clin. Exp Allergy* 1995; **25**: 127–32.

13 Brightling CE, Pavord ID. Eosinophilic bronchitis: An important cause of prolonged cough. *Ann. Med.* 2000; **32**: 446–51.

14 Puolijoki H, Lahdensuo A. Chronic cough as a risk indicator of broncho-pulmonary disease. *Eur. J. Respir. Dis.* 1987; **71**: 77–85.

15 Remes ST, Korppi M, Remes K. Outcome of children with respiratory symptoms without objective evidence of asthma: A two-year, prospective, follow-up study. *Acta Paediatr.* 1998; **87**: 165–8.

16 Panhuysen CI, Vonk JM, Koeter GH *et al*. Adult patients may outgrow their asthma: A 25-year follow-up study. *Am. J. Respir. Crit. Care Med*. 1997; **155**: 1267–72.

17 Haahtela T. Early treatment of asthma. *Allergy* 1999; **54**: 74–81.

18 Haahtela T, Järvinen M, Kava T *et al*. Comparison of a β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N. Engl. J. Med.* 1991; **325**: 388–92.

19 Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β_2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: A randomized, double-blind, parallel-group controlled trial. *J. Allergy Clin. Immunol.* 1992; **90**: 32–42.

20 Kerstjens HAM, Brand PLP, Hughes MD *et al*. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N. Engl. J. Med.* 1992; **327**: 1413–19.

21 Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder PGH, Postma DS. Is delayed introduction of inhaled corticosteroid harmful in patients with obstructive airway disease? *Chest* 1996; **110**: 35–41.

22 Osterman K, Carlholm M, Ekelund J *et al*. Effect of 1 year daily treatment with 100 μg budesonide (Pulmicort Turbuhaler) in newly diagnosed asthmatics. *Eur. Respir. J.* 1997; **10**: 2210–15.

23 Selroos O, Pietinalho A, Löfroos A-B, Riska H. Effect of early vs. late intervention with inhaled corticosteroids in asthma. *Chest* 1995; **108**: 1228–34.

24 Selroos O, Löfroos A-B, Niemisto M, Pietinalho A, Backman R, Riska H. Early introduction with inhaled steroids in asthma results in achievement of treatment goals. *Am. J. Respir. Crit. Care Med.* 1999; **159**: A627 (Abstract).

25 van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Kerrebijn KF. Remission of childhood asthma after long-term treatment with an inhaled corticosteroid (budesonide): Can it be achieved? *Eur. Respir. J.* 1994; **7**: 63–8.

26 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir. Med.* 1994; **88**: 373–81.

27 Konig P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: A possible preview of the international guidelines. *J. Allergy Clin. Immunol.* 1996; **98**: 1103–11.

28 Oswald H, Phelan PD, Lanigan A *et al*. Childhood asthma and lung function in mid-adult life. *Pediatr. Pulmonol.* 1997; **23**: 14–20.

29 Turpeinen M for the HEICA Study Group. Helsinki Early Intervention Childhood Asthma (HEICA) Study: Inhaled budesonide halved the number of asthma exacerbations compared with disodium cromoglycate during 18 months of treatment. *Eur. Respir. J.* 2000; **16**: 824–30.

30 Pauwels RA, Busse WW, O'Byrne PM *et al*. The inhaled steroid treatment as regular therapy in early asthma (START) study: Rationale and design. *Control. Clin. Trials.* 2001; **22**: 405–19.

31 Kraan J, Koeter GH, van der Mark ThW *et al*. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: A comparison between budesonide and terbutaline. *J. Allergy Clin. Immunol.* 1985; **76**: 628–36.

32 Jenkins CR, Woolcock AJ. Effect of prednisone and bechlomethasone dipropionate on airway responsiveness in asthma: A comparative study. *Thorax* 1988; **43**: 378–84.

33 Laitinen LA, Laitinen A, Heino M, Haahtela T. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroid. *Am. Rev. Respir. Dis.* 1992; **143**: 423–7.

34 Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am. Rev. Respir. Dis.* 1993; **147**: 697–704.
35 van Den Toorn LM, Overbeek SE, De Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am. J. Respir. Crit. Care Med.* 2001; **164**: 2107–13.
36 Juniper EF, Kline PA, Vanzieleghem MA, O'Byrne PM, Hargreave FE. Reduction of budesonide after a year of increased use: A randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J. Allergy Clin. Immunol.* 1991; **87**: 483–9.
37 van Schayck CP, van den Broek PJ, den Otter JJ, van Herwaarden CL, Molema J, van Weel C. Periodic treatment regimens with inhaled steroids in asthma or chronic obstructive pulmonary disease. Is it possible? *JAMA* 1995; **274**: 161–4.
38 Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N. Engl. J. Med.* 1997; **337**: 1659–65.
39 Haahtela T, Klaukka T, Koskela K, Erhola M, Laitinen LA. Asthma programme in Finland: A community problem needs community solutions. *Thorax* 2001; **56**: 806–14.
40 Adams RJ, Fuhlbrigge A, Finkelstein JA *et al.* Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. *Pediatrics* 2001; **107**: 706–11.
41 Hargreave FE, Leigh R. Induced sputum, eosinophilic bronchitis, and chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 1999; **160**: S53–7.
42 Pin I, Gibson PG, Kolendowicz R *et al.* Use of induced sputum cell counts to investigate airway inflammation in asthma. *Thorax* 1992; **47**: 697–704.
43 Pizzichini E, Pizzichini MMM, Efthimiadis A, Dolovich J, Hargreave FE. Measuring airway inflammation in asthma: Eosinophils and eosinophilic cationic protein in induced sputum compared with peripheral blood. *J. Allergy Clin. Immunol.* 1997; **99**: 539–44.
44 Sorva R, Metso T, Turpeinen M, Juntunen-Backman K, Björksten F, Haahtela T. Eosinophil cationic protein in induced sputum as a marker of inflammation in asthmatic children. *Pediatr. Allergy Immunol.* 1997; **8**: 45–50.
45 Metso T, Venge P, Peterson C, Haahtela T, Seveus L. Cell-specific markers for eosinophils and neutrophils in sputum and bronchoalveolar lavage of patients with respiratory conditions and healtht persons. *Thorax* 2002 (in press).
46 Carlson MG, Peterson CG, Venge P. Human eosinophil peroxidase: Purification and characterization. *J. Immunol.* 1985; **134**: 1875–9.
47 Xu SY, Petersson CG, Carlson M, Venge P. The development of an assay for human neutrophil lipocalin (HNL) to be used as a specific marker of neutrophil activity *in vivo* and *in vitro*. *J. Immunol. Methods* 1994; **171**: 245–52.
48 Helenius IJ, Rytila P, Metso T, Haahtela T, Venge P, Tikkanen HO. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy* 1998; **53**: 346–52.
49 Metso T, Rytilä P, Peterson C, Haahtela T. Granulocyte markers in induced sputum in patients with respiratory disorders and healthy persons obtained by two sputum processing methods. *Respir. Med.* 2001; **95**: 48–55.
50 Kharitonov SA, Barnes PJ. Does exhaled nitric oxide reflect asthma control? Yes, it does! *Am. J. Respir. Crit. Care Med.* 2001; **164**: 727–8.
51 Corradi M, Montuschi P, Donnelly LE, Pesci A, Kharitonov SA, Barnes PJ. Increased nitrosothiols in exhaled breath condensate in inflammatory airway diseases. *Am. J. Respir. Crit. Care Med.* 2001; **163**: 854–8.
52 Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am. J. Respir. Crit. Care Med.* 1999; **159**: 1043–51.
53 Tukiainen H, Taivainen A, Majander R *et al.* Comparison of high and low dose of the inhaled steroid, budesonide, as an initial treatment in newly detected asthma. *Respir. Med.* 2000; **94**: 678–83.
54 Barnes J. Cytokine-directed therapies for asthma. *J. Allergy Clin. Immunol.* 2001; **108**: S72–6.
55 Milgrom H, Fick Jr RB , Su JQ *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N. Engl. J. Med.* 1999; **341**: 1966–73.
56 Milgrom H, Berger W, Nayak A *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; **108**: E36.