Thirteen-year follow-up of early intervention with an inhaled corticosteroid in patients with asthma

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Background: In a 3-year study, adult patients who recently developed asthma (symptoms for less than 1 year) were treated for 2 years with the inhaled corticosteroid (ICS) budesonide (early therapy) or terbutaline. During the third year of the study, terbutaline-treated patients received budesonide (delayed therapy). Differences in lung function and bronchial responsiveness to histamine were observed between the 2 groups.

Objective: We compared the effects of early versus delayed budesonide therapy after a 10-year follow-up period (13 years after the study began) and current real-life data.

Methods: Of the original 103 patients, 90 were re-examined 13 years after study initiation. After the third year of the study, all patients had their medications, including the dose of ICS, individually adjusted.

Results: After the follow-up period, lung function was within the normal range for the entire group (all patients); bronchial responsiveness significantly improved compared with baseline data. No statistically significant differences in clinical or functional variables were found between patients given early or delayed budesonide therapy. However, the delayed therapy group had a higher neutrophil count and higher concentrations of eosinophilic cationic protein and myeloperoxidase in induced sputum. This group had also used more asthma medication and hospital days.

Conclusions: Patients with relatively mild asthma who received ICS within 12 months of their first asthma symptoms or after a 2-year delay achieved equally good functional control of asthma after 10 years of individualized therapy. However, the delayed therapy group exhibited slightly less optimal disease control and more signs of airway inflammation. (J Allergy Clin Immunol 2009;124:1180-5.)

Key words: *Asthma, asthma control, budesonide, early intervention, inhaled corticosteroids, prebronchodilator FEV_1, terbutaline*

Since the early 1990s, there has been increasing emphasis on early diagnosis and treatment of asthma, but the long-term effects of this strategy for asthma control have been poorly evaluated. Adult patients with persistent asthma undergo a faster decline in lung function than individuals without asthma,[1,2] and severe asthma exacerbations are associated with a more rapid loss in lung function.[3] This may be the result of structural changes, "remodeling" of the airways, caused by persistent inflammatory processes.[4] The 3-year study of inhaled steroid treatment as regular therapy (Inhaled Steroid Treatment as Regular Therapy in Early Asthma [START]) in patients with early-stage asthma showed that administration of once-daily, low-dose budesonide to patients with recent-onset, mild asthma improved both prebronchodilator and postbronchodilator FEV_1 compared with placebo.[5] Furthermore, the loss of lung function was slightly reduced over time.[6] However, many patients with mild asthma never show a significant decline in FEV_1; it is now considered to be more important to maintain control of symptoms than to normalize lung function completely.[7]

Our previously reported 2-year study showed that regular therapy with the inhaled corticosteroid (ICS) budesonide was superior first-line treatment (in terms of improvements in lung function, tolerance to inhaled histamine, reduction of symptoms, and need for reliever medication) compared with the inhaled β_2-agonist terbutaline in patients with newly detected asthma.[8] When the trial was extended to a third year, the double-blind study showed that continuous treatment with a reduced dose of budesonide resulted in good control of the disease.[9] Discontinuation of treatment (patients given placebo) was accompanied by a mean increase of symptoms and bronchial responsiveness and a slight decline in prebronchodilator FEV_1 in some patients. Asthma remained well controlled among one third of the patients given placebo. Patients treated with terbutaline for 2 years received budesonide during the third year at doses identical to those of the group given budesonide from the outset; these patients improved, but not to the same degree as those treated with budesonide for all 3 years. Thus, a 2-year delay in initiating ICS therapy seemed to result in a less favorable clinical response in terms of asthma control, lung function, and bronchial reactivity.[9]

We report the results of the follow-up examination of these patients 13 years after the study was initiated (10 years after the 3-year intervention trial was completed). We asked the following questions:

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Abbreviations used
ECP: Eosinophilic cationic protein
FE_{NO}: Fractionated exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
PC_{15}: Provocative concentration of histamine diphosphate causing a decrease in FEV_1 of 15%
PEF: Peak expiratory flow
START: Inhaled Steroid Treatment as Regular Therapy in Early Asthma

1. How was the overall asthma control in the entire group10 years after completion of the initial study?
2. Did asthma control, cost of medication, and need for medical care during the 10-year follow-up period differ between the group given ICS therapy for all 3 years of the study (early) and the group given ICS for only the third year (delayed)?
3. Is there a difference between the 2 groups in inflammatory indices?

METHODS

Patients and study design

In the initial trial, 103 adult white patients with asthma symptoms present for less than 12 months received high-dose budesonide (600 μg twice daily; n = 50) or terbutaline (375 μg twice daily; n = 53) delivered via a pressurized metered-dose inhaler and large volume spacer (Nebuhaler; AstraZeneca, Södertälje, Sweden).[8] After 2 years, the study was divided into a double-blind arm and an open-label arm and continued for a third year.[9] The double-blind arm was composed of patients initially assigned to receive budesonide treatment and then randomly assigned to groups given either lower-dose budesonide or placebo.[9]

The open-label study arm was composed of patients initially given terbutaline; they received budesonide in an identical manner to those who received budesonide from the beginning of the study.

After the third year of the study, patients were seen by their own physicians and treated individually with ICS, rescue β_2-agonists, and other asthma drugs if required. Initially there was no plan to follow up on these patients further. However, because of the increase in knowledge about the benefits of early intervention with ICS in patients with asthma,[5,6,10-12] we performed follow-up examinations. Register data with information about patients' prescriptions, costs, and hospitalizations during the past years were also available.

Ten years after the 3-year study was completed, 97 of the patients were invited to a follow-up examination. In total, 90 patients (24 males, 66 females, mean age 50 years) were re-examined. The examiners (K.T., T.K.) were blind to the treatment arm to which the patients had been randomly assigned. A flow chart of the patients, from the initial randomization into 2 groups to the follow-up examination 13 years later, is shown in Fig 1.

Written consent was obtained from all patients. The Ethics Committee of the Department of Medicine, Helsinki University Central Hospital, approved the study protocol. The Social Insurance Institution in Finland gave the permission to obtain data on asthma medication used by the patients.

Register data

The Social Insurance Institution in Finland uses 2 registers: (1) a register of patients entitled to special drug cost reimbursement, and (2) the national prescription register, which includes data on all reimbursed purchases of medicines. From these 2 registers, patients can be identified, their medication recorded, and costs calculated. We determined the cost of asthma medication over the past 7 years for all patients in the follow-up study. Detailed information from earlier years was not available. Numbers of hospital days and emergency visits for the 10-year follow-up period were received from the National Research and Development Center for Welfare and Health.

Measurements

At the follow-up investigation, patients scored their asthma severity during the last year by using their status at the end of the initial double-blind study period as a reference (0 = asthma severity had not changed, up to maximum and minimum scores of +10 or −10 for subjective improvement or worsening, respectively). Patients also scored their own β_2-agonist use during the past year on a scale from 0 to 10.

Before the clinical re-examination, patients kept an asthma diary for 1 month that was identical to the one kept during the initial study.[8] In this they recorded morning and evening peak expiratory flow (PEF) before medication (Mini Wright Peak Flow Meter; Clement Clarke International, London, United Kingdom), asthma symptoms and use of rescue β_2-agonists. Clinical tests at the study center were performed in the following order: measurement of fractionated exhaled nitric oxide (FE_{NO}), spirometry, measurement of bronchial responsiveness, and induction of sputum. FE_{NO} was measured with a chemiluminescence analyzer (Exhaled Breath Analyzer; Aerocrine, Stockholm, Sweden) by using the online single exhalation technique recommended by the American Thoracic Society.[13] Forced vital capacity (FVC) and FEV_1 were measured with a dynamic wedge bellows spirometer (Vitalograph; Vitalograph Ltd, Buckingham, United Kingdom). Bronchial responsiveness was tested by using the same method as the initial study, namely by determining the provocative concentration of histamine diphosphate causing a decrease in FEV_1 of 15% (PC_{15}).[8] Salbutamol (0.4 mg) was given to all patients after the histamine challenge test and 15 minutes before sputum induction.

Sputum induction and processing methods have been described elsewhere.[14] Adequate sputum samples were obtained from 73 of the 84 patients (88%) who accepted the procedure. Coded cytospins were prepared to obtain cell differential counts. The results were expressed as a percentage based on the number of individual cells in relation to the total number of nonsquamous cells. Concentrations of eosinophilic cationic protein (ECP) and myeloperoxidase in thawed supernatants of the sputum samples were determined by using immunoassays (CAP System; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

Statistical methods

Results from all 90 patients are shown (intention-to-treat analysis). Results are presented descriptively as means ± SEMs. Data from treatment groups were compared by using *t* tests. PC_{15} values (mg/mL) are presented as geometric means, analyzed by using *t* tests after log transformation. Sputum data with skewed distributions were analyzed with Wilcoxon signed-rank tests.

A multifactorial regression analysis was performed for the entire study population to investigate whether any baseline factor could predict good asthma control after 13 years. Good asthma control was defined as symptom scores from 0 to 1 on the 0 to 10 scale (average over last 14 days) and FEV_1 percent predicted to be >90%. Included factors were age, sex, FEV_1 percent predicted, PEF percent predicted, PC_{15}, atopy, eosinophilia, asthma symptoms, and early or delayed budesonide therapy.

The study was not powered with respect to any specific outcome variable at the 13-year follow-up.

RESULTS

Thirteen-year, total follow-up data

Table I shows the lung function and diary card data for all 90 patients (irrespective of treatment group) at baseline and 13 years later. The mean prebronchodilator FEV_1 decreased from 3.14 L to 2.84 L, but the predicted value remained at exactly the same level of airway function (89% of predicted). The same was also true for FVC. Morning PEF, as a percentage of predicted normal value, decreased slightly (from a mean of 87% to 85%), but the difference was not significant. Bronchial responsiveness (PC_{15}

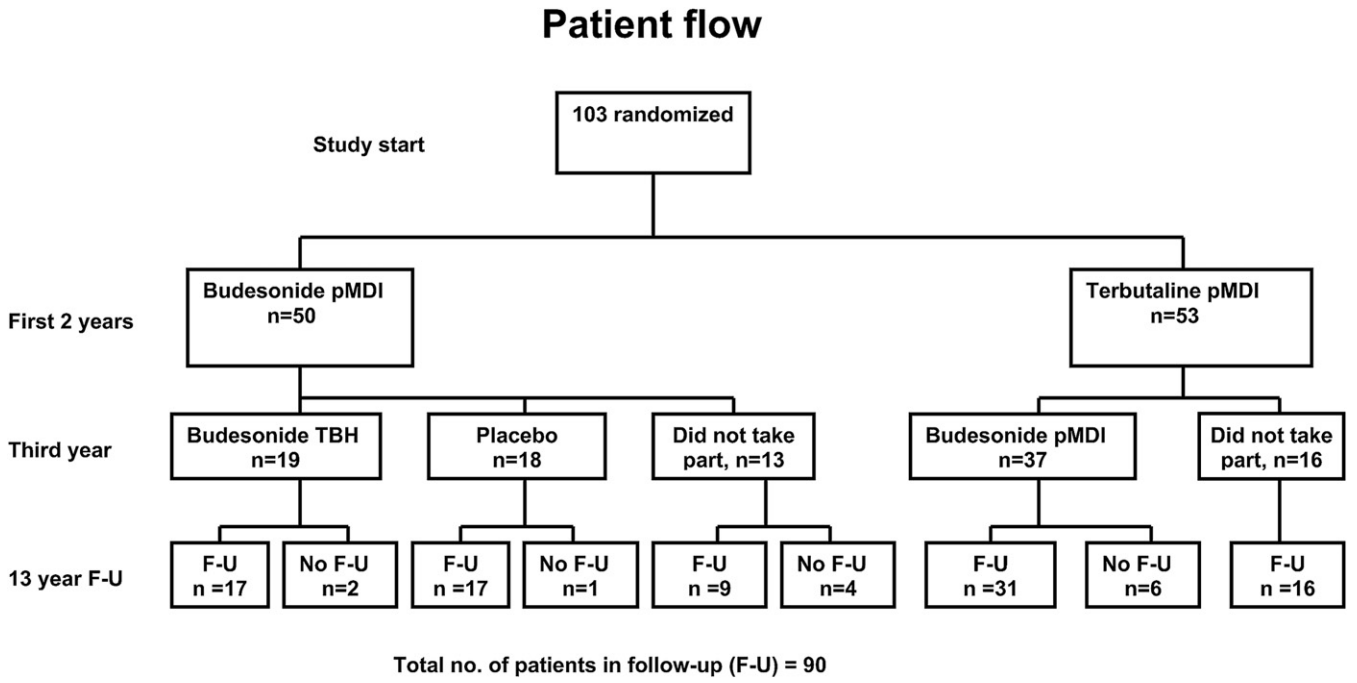

FIG 1. Flow chart of management of the patients from the initial random assignment to 2 groups to the 13-year follow-up examination. *pMDI,* Pressurized metered-dose inhaler; *TBH,* Turbuhaler.

TABLE I. Lung function and diary card data from baseline and the 13-year follow-up examination in 90 patients, irrespective of whether initially given budesonide or terbutaline

Variable	Pretreatment	13 Years later	*P* value
FEV_1			
Actual, L (mean ± SEM)	3.14 ± 0.08	2.84 ± 0.09	
% Predicted (mean ± SEM)	88.8 ± 1.4	89.0 ± 1.8	.85
FVC			
Actual, L (mean ± SEM)	4.03 ± 0.10	3.72 ± 0.11	
% Predicted (mean ± SEM)	95.8 ± 1.4	95.4 ± 1.6	.80
Morning PEF			
Actual, L/min (mean ± SEM)*	440 ± 8	424 ± 11	.74
% Predicted (mean ± SEM)*	86.6 ± 1.2	85.0 ± 1.6	.80
PC_{15} histamine			
Actual, mg/mL (geometric mean)†	7.4	33.6	<.001
As dose steps (mean ± SEM)	2.89 ± 0.22	5.07 ± 0.16	<.001
Asthma symptom score, 0-10 (mean ± SEM)*	2.48 ± 0.18	1.59 ± 0.18	<.001
β_2-agonist dose, puffs/d (mean ± SEM)*	1.10 ± 0.16	0.47 ± 0.09	<.002

*Pretreatment average
†Patients without 15% fall in FEV_1 at the highest concentration, 32mg/mL, were considered to have PC_{15} = 64mg/mL.

histamine) significantly improved ($P < .001$), and asthma symptoms and use of rescue bronchodilators significantly decreased ($P < .001$ and $P < .002$, respectively). Thus, lung function did not change significantly over the 10-year period, but overall asthma control and bronchial responsiveness were clearly better at the follow-up visit compared with baseline.

During the 10-year period before the follow-up examination, the patients required, on average, less than 1 hospital day per patient per year for asthma exacerbations (Fig 2). However, at the 13-year follow-up, patients without hospitalizations during the preceding years had a mean morning PEF of 86.0% predicted normal, which was significantly higher ($P = .031$) than the 78.6% predicted normal among those who required hospitalization for asthma.

The multifactorial regression analysis did not identify factors that predicted good asthma control, with the exception that better lung function at baseline predicted a greater chance of good asthma control after 13 years ($P = .021$). If asthma symptom scores of 0 to 1 were used alone as definition of good asthma control, only a few symptoms at baseline predicted good asthma control ($P = .019$). Early or delayed budesonide therapy did not influence the odds of good asthma control.

Thirteen-year follow-up of patients on either budesonide or terbutaline for the first 2 years

Register data. Analysis of the register data showed fewer hospital days per patient per year (0.62 vs 1.09) in the early compared with the delayed group, respectively, although these differences were not significant (Fig 2).

Patient-reported outcomes. The subjective evaluation of asthma severity during the last year, as change from baseline (scale, –10 to +10), showed mean (±SEM) improvement values in the early and delayed groups of +6.3 (0.4) and +5.5 (0.4), respectively (Fig 2). During the last year, using a subjective scale (0 to 10), the mean need (SEM) for relief with β_2-agonists was 3.6 (0.5) vs 4.5 (0.4) in the early and delayed groups, respectively (Fig 2). Analyses of diary data showed that during the last month, β_2-agonists were used at mean values of 0.46 and 0.52 inhalations/d in the early and delayed groups, respectively ($P = .74$); mean (SEM) symptom scores were 1.50 (0.24) and 1.63 (0.23) in the early and delayed groups, respectively (Fig 2). A total of 51% of patients in the early group versus 41% in the delayed

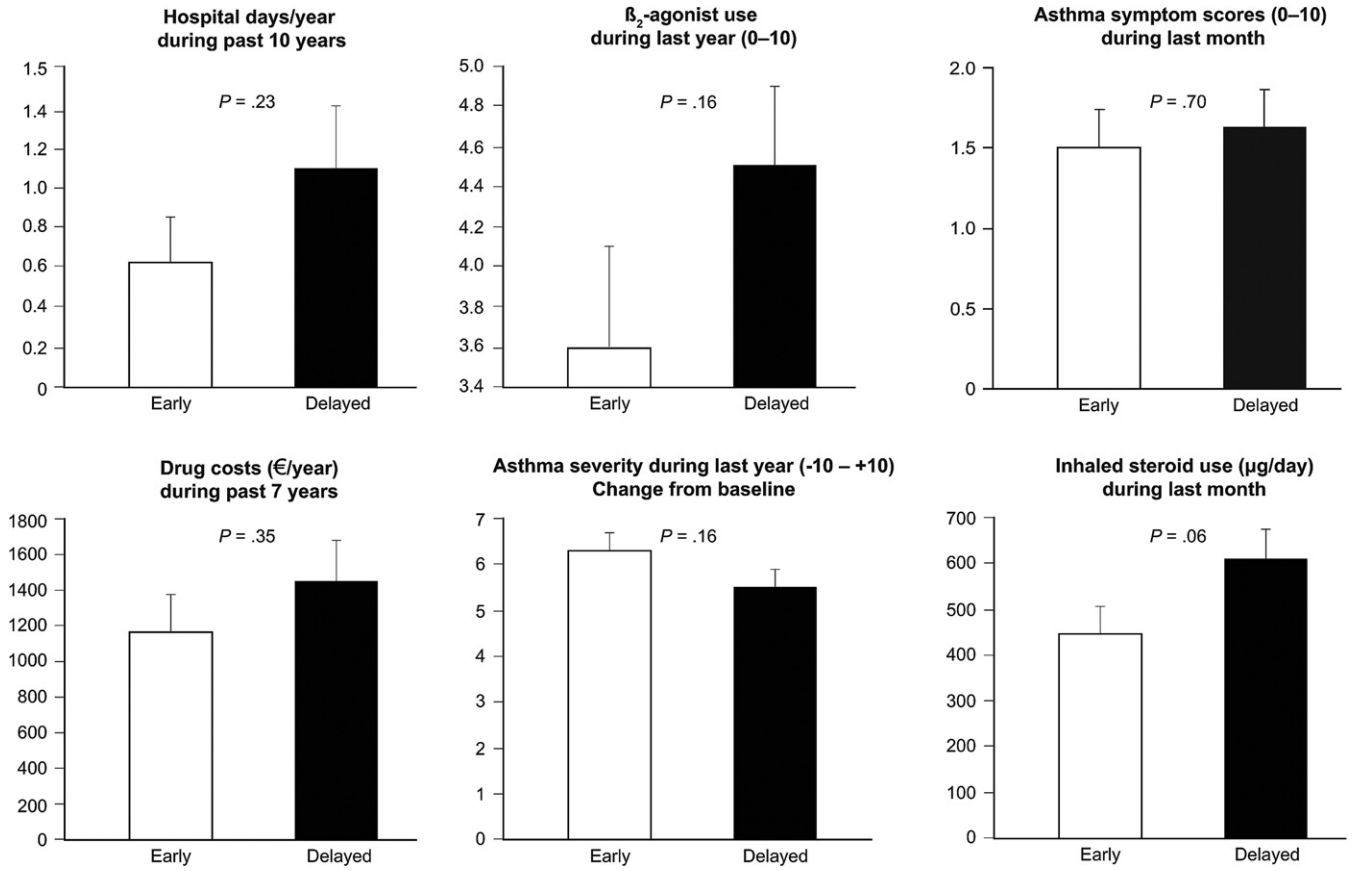

FIG 2. *Left,* Hospital days/year during the past 10 years and drug costs/year during the past 7 years. *Middle,* β_2-agonists and subjective change from baseline in asthma severity during the last year. *Right,* Asthma symptom scores during the last month and use of ICSs (μg/d) in patients treated early with inhaled budesonide or after a 2-year delay. Mean values and SEMs are shown.

group were virtually symptom-free (ie, symptom score of 0 or 1 on the 0-10 scale). During the last month, the mean (SEM) doses of ICS were 447 (55) μg/d in the early group compared with 609 (65) μg/d in the delayed group (Fig 2); this difference approached significance ($P = .06$).

Lung function. Analysis of data from the 13-year follow-up examination revealed that differences in the changes from baseline in prebronchodilator FEV_1, morning PEF, and bronchial hyperresponsiveness between the early and delayed budesonide groups were small and nonsignificant (Table II). In calculating changes as percentage of predicted normal values, no differences were observed between groups.

Airway inflammation. The results of induced sputum examinations and FE_{NO} analysis are shown in Table III. These measurements were not performed in the initial study. Patients in the early group had fewer eosinophils and significantly fewer neutrophils in their sputum samples ($P = .0009$); the concentrations of ECP and myeloperoxidase were also significantly lower in the early compared with the delayed group ($P = .001$ and $P = .0026$, respectively). FE_{NO} was slightly lower in the early group, but the difference was not significant.

DISCUSSION

The essential goal for successful asthma management is to achieve and maintain control of symptoms.[7,15] Other goals are to achieve good activity levels, avoid exacerbations, and maintain good lung function.[7] These goals are in line with recent recommendations for asthma and allergies in general, such as the Global Alliance against Chronic Respiratory Diseases, issued by the World Health Organizatinon,[16] and the Finnish Allergy Program 2008-2018.[17]

Treatment with ICS reduces mortality, hospital use, unscheduled physician and emergency department visits, days missed from work or school, use of rescue medication, and the overall costs of medical care.[18,19] In Finland, a 10-year asthma program focused on early detection and treatment of inflammation considerably decreased the burden of asthma.[20]

In this follow-up study, we found that 13 years after initiation of anti-inflammatory therapy in patients who had had asthma symptoms for less than 1 or 3 years, the overall outcome of the entire patient group was good. About half of the patients had good asthma control, defined as normal lung function and very mild asthma symptoms (0-1 on the 0-10 scale). Subjectively, the patients reported significant improvement during the last 10 years (+5 to +6 on a scale from –10 to +10). It is important to remember that irrespective of the groups to which patients were randomly assigned, they all received ICS within 3 years from the onset of asthma symptoms (early treatment). After the 3-year controlled study period, the patients received ICS in individually adjusted doses. Nevertheless, although the differences were not statistically significant, patients treated with budesonide for the

TABLE II. Changes from baseline to the 13-year follow-up examination in airway function and bronchial reactivity in patients given early versus delayed therapy

Variable	Early therapy (n = 47)	Delayed therapy (n = 43)	*P* value
FEV_1 (L)	−0.33 ± 0.06	−0.28 ± 0.08	.64
% Predicted	−0.1 ± 2.0	0.6 ± 2.3	.84
Morning PEF (L/min)	−16.2 ± 9.6	−20.6 ± 8.9	.74
% Predicted	−1.8 ± 1.9	−2.5 ± 1.8	.80
Evening PEF (L/min)	−23.8 ± 8.8	−26.8 ± 8.4	.80
% Predicted	−3.3 ± 1.8	−3.7 ± 1.6	.86
PC_{15} histamine (dose steps)	2.39 ± 0.29	2.08 ± 0.38	.54

Early therapy patients were given budesonide within 1 year of first asthma symptoms; delayed therapy patients were given budesonide after 2 year. Values are expressed as mean change ± SEM from pretreatment period.

TABLE III. Comparison of induced sputum indices and fractionated exhaled nitric oxide concentrations at the 13-year follow-up examination in patients with early and delayed budesonide therapy

Variable	Early therapy	Delayed therapy	*P* value
Sputum samples			
Eosinophils (%)	3.2 ± 0.9	5.8 ± 1.4	.23
ECP ($\mu g \times L^{-1}$)	1,231 ± 369	2,481 ± 537	.001
Neutrophils (%)	33.0 ± 3.6	49.5 ± 3.8	.0009
MPO ($\mu g \times L^{-1}$)	6,487 ± 1,712	10,325 ± 1,670	.0026
FE_{NO} (ppb)	16.9 ± 2.5	18.7 ± 2.1	.25

MPO, Myeloperoxidase.
Results are presented as means ± SEMs.

entire study reported fewer symptoms, reduced their use of β_2-agonists, and used lower doses of ICS compared with patients who received terbutaline for the first 2 years of the study. Moreover, the number of hospital days per year and the mean annual asthma drug costs were lower in the group given budesonide from the outset. These figures are in line with results from the START study, in which patients treated early with budesonide had a lower risk of a severe asthma-related event than those in the reference group, had improved asthma control, and used additional asthma medications less frequently.[21] In our study, patients treated early with budesonide had fewer hospitalizations than those treated early with terbutaline. The hospitalized patients had significantly lower lung function at the follow-up examination than those without hospitalizations, indicating the value of early treatment with ICS. This is in agreement with the results of the START study, in which severe exacerbations resulted in a more rapid decline in lung function.[3]

In this study, patients in the early group (3 years of budesonide) had significantly lower neutrophil counts and lower ECP and myeloperoxidase values in induced sputum samples than those in the delayed group (treated with terbutaline for the first 2 years of the study). The clinical importance of these differences is not clear but could indicate the value of early intervention with ICS.

After the initial 3-year study period, there was a slight decline in prebronchodilator FEV_1 and PEF values, but they remained within the normal predicted range. The differences in FEV_1 and PEF observed after 3 years between the groups initially given budesonide versus terbutaline had disappeared by the follow-up examination, possibly because the patients initially treated with terbutaline had used higher doses of ICS and other asthma medications when treated on an individual basis. Our results are in line with the 3-year results of the START study, in which once-daily, low-dose budesonide initially improved both prebronchodilator and postbronchodilator FEV_1 compared with the control group[6]; thereafter, an almost parallel, slight decline in lung function occurred in both groups. When patients in the START study who were given placebo for the first 3 years received budesonide for the next 2 years, an improvement in lung function was observed, and the difference between the groups became nonsignificant.[21]

The results of both studies raise important clinical questions such as when regular treatment with ICS should be started and what the significance is of airway remodeling in mild asthma. The results from the studies support the idea of giving patients the most effective treatment first, to achieve the best possible asthma control, although the long-term lung function outcome may not be greatly affected. In studies of nonrandomized subjects, both the symptom and lung function responses to treatment were reported to be better in patients treated early than those treated late.[10-12] Patients in this study received either relatively high doses of budesonide (1200 μg/d) for 2 years and a lower dose of 400 μg/d or 1200 μg/d only for the third year (after 2 years of terbutaline). Low doses of ICS reduce symptoms rapidly, improve lung function, and prevent exacerbations in mild asthma.[7,22] Induction with a high dose may affect the underlying airway pathology, such as bronchial responsiveness and structural changes, more effectively than low doses.[23,24] In this study, 3 months of treatment with budesonide (1200 μg/d) suppressed inflammation and repaired the bronchial epithelium in a subgroup of patients.[25]

A correct diagnosis is a prerequisite for early therapy. However, a 7-year delay in diagnosing asthma by functional criteria has been reported.[26] If the inflammatory component is not detected, patients with preserved lung function can continue for years without adequate treatment.

The current long-term results show that initiating ICS therapy within 3 years from the start of asthma symptoms results generally in good asthma control. No side effects were reported to cause withdrawal from ICS therapy. However, it is important to adjust the maintenance doses to the lowest effective level. As shown in other studies, the patients who had received early ICS therapy seemed to need lower ICS doses over time to control their disease than patients with delayed therapy, although the differences observed in this study were not statistically significant. Early budesonide therapy resulted in fewer signs of airway inflammation in induced sputum compared with delayed budesonide treatment. However, because no power calculation was possible for this follow-up with a limited number of patients, we cannot exclude the possibility that important clinical differences between early and delayed budesonide therapy have been missed.

We conclude that 13 years after the study began, patients with mostly mild asthma obtained good asthma control, irrespective whether budesonide therapy had been introduced within 1 year or with a 2-year delay after the first symptoms were reported. After the initial 3-year study, there were differences between the early and delayed groups in the clinical and functional variables; these had mostly disappeared by the follow-up examination 10 years later, but the delayed group exhibited more signs of airway inflammation than the early group. At the follow-up examination, patients in the delayed group had used more asthma medications and had more hospital days, increasing their medical costs.

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Clinical implications: Early treatment with ICS of patients with mild asthma results in good long-term asthma control. A 2-year delay with starting ICS therapy does not significantly affect lung function outcome but may result in less optimal disease control.

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