Eur Respir J 1997; 10: 2210–2215
DOI: 10.1183/09031936.97.10102210

European Respiratory Journal
ISSN 0903 - 1936

Effect of 1 year daily treatment with 400 µg budesonide (Pulmicort® Turbuhaler®) in newly diagnosed asthmatics

K. Osterman*, M. Carlholm§, J. Ekelund§, J. Kiviloog**, K. Nikander§, L. Nilholm**, P. Salomonsson+, V. Strand+, P. Venge++, O. Zetterström*

Effect of 1 year daily treatment with 400 µg budesonide (Pulmicort® Turbuhaler®) in newly diagnosed asthmatics. K. Osterman, M. Carlholm, J. Ekelund, J. Kiviloog, K. Nikander, L. Nilholm, P. Salomonsson, V. Strand, P. Venge, O. Zetterström. ©ERS Journals Ltd 1997.

ABSTRACT: The aim of this study was to investigate whether treatment with a low daily dose of 400 µg inhaled budesonide (Pulmicort® Turbuhaler®) in newly diagnosed asthmatics could influence the course of asthma.

Seventy five adult patients, mostly with mild asthma, diagnosed during the previous year and bronchial hyperresponsiveness, participated in a double-blind, randomized, parallel-group multicentre study. They were treated with budesonide 200 µg *b.i.d.* or placebo, delivered *via* Turbuhaler® for 12 months and followed-up for another 6 months without inhaled steroid treatment. Airway function, symptom scores, reactivity to histamine and inflammatory indices in blood were assessed.

The mean increase in morning peak expiratory flow (PEF) was 28 L·min^{-1} after budesonide treatment compared with no increase in the placebo group (p=0.011). The provocative dose of histamine causing a 20% fall in forced expiratory volume in one second (PD_{20}) (geometric mean) increased in the budesonide group by approximately two doubling dose steps, but not in the placebo group (p=0.0003). The difference between groups with regard to improvement in asthma symptom scores and inflammatory indices did not reach statistical significance. During the 6 month follow-up, the PEF values of the patients who had previously been treated with budesonide decreased by 18 L·min^{-1} while the PD_{20} decreased by approximately one doubling dose step.

In conclusion, early treatment with a low dose of budesonide improves airway function and decreases bronchial responsiveness, but the improvements are short-lasting without continued treatment.

Eur Respir J 1997; 10: 2210–2215.

*Dept of Allergology, Karolinska Hospital, Stockholm, Sweden. **Pulmonary Dept, Regional Hospital, Örebro, Sweden. +Dept of Allergology, Huddinge Hospital, Huddinge. ++Dept of Clinical Chemistry, University Hospital, Uppsala. §Medical Dept and Dept of Biostatistics and Data Processing, Astra Draco AB, Lund, Sweden.

Correspondence: K. Osterman
Asthma-Allergy Clinic
Åreklinikerna
S-830 13 Åre
Sweden

Keywords: Asthma
bronchial hyperresponsiveness
budesonide
eosinophil cationic protein
peak expiratory flow rate
Turbuhaler®

Received: July 9 1996
Accepted after revision July 27 1997

Asthma is generally recognized as an inflammatory disease [1]. Asthma management and treatment guidelines recommend early introduction of anti-inflammatory therapy [2]. There is also some evidence that early initiation of treatment with inhaled corticosteroids may result in a long-lasting stable phase even after asthma treatment has been discontinued after 1 [3] and 2–3 [4] yrs of treatment.

In the study by HAAHTELA and co-workers [4, 5], a significant increase in mean morning peak expiratory flow (PEF) of 34.6 L·min^{-1} and a mean improvement in the provocative concentration of histamine causing a fall of 15% in forced expiratory volume in one second (FEV_1) (PC_{15}) of 1.19 dose steps were seen after 6–12 weeks of treatment. The daily dose of budesonide *via* a pressurized metered-dose inhaler (pMDI) with a spacer (Nebuhaler®; Astra, Sweden) over 2 yrs was 1,200 µg, which could be considered a fairly high dose. The aim of the present study was to perform a long-term study with a lower daily dose of budesonide in a similar patient population.

The specific objectives of this study were to compare the effects of budesonide Turbuhaler® (200 µg *b.i.d.*) with placebo on airway function, subjective asthma symptoms, bronchial reactivity to inhaled histamine and inflammatory indices in blood. Patients with newly diagnosed, mild asthma were to be treated with budesonide for 1 yr and then followed for another 6 months without inhaled corticosteroid treatment, in order to determine the duration of the achieved effects.

Materials and methods

Patients

Patients who had asthma diagnosed not more than 1 yr before the start of the study were included. The patients had not been treated with anti-inflammatory drugs within 3 months prior to the study. The provocative dose of histamine causing a fall of 20% in FEV_1 (PD_{20}) was <660 µg at two visits before the start of the study.

Seventy five asthma patients (42 females, 33 males), all Caucasians, participated in the study. Their mean age

was 34 yrs (range 18–68 yrs). Sixteen patients were smokers. The initial mean FEV_1 was 91% of predicted normal (range 63–119%). The initial geometric mean value for PD_{20} histamine was 101 μg (range 4–616 μg). During the run-in period, all patients used inhaled β_2-agonists, five patients used oral β_2-agonists and 10 patients used theophylline. For comparison of histamine reactivity (PD_{20}) a group of 50 healthy subjects, 29 females and 21 males, mean age 40 yrs (range 18–63 yrs) was also studied [6].

Study design

The study was performed at three centres as a placebo-controlled, randomized, double-blind study with parallel groups. After a 2 week run-in period when patients used their ordinary inhaled or oral nonsteroidal medication, their baseline values were measured. The patients were then randomized to treatment for 12 months with either inhaled budesonide 200 μg *b.i.d.*, delivered *via* an inspiratory flow-driven, multidose, dry-powder inhaler (Pulmicort® Turbuhaler®, Astra, Sweden), or placebo *via* inhalers of identical appearance containing lactose. After treatment for 12 months the patients were followed for another 6 months.

During the entire study, including the follow-up period, the patients continued to take their ordinary inhaled or oral nonsteroidal symptomatic medication. Additional doses of inhaled β_2-agonists were used as needed. Acute exacerbations of asthma, as deemed by the investigator, were treated with courses of oral prednisolone for 6 days, beginning with 30 mg and decreasing to 25, 20, 15, 10 and 5 $mg \cdot day^{-1}$ in single daily doses. Patients could, at any time, stop the randomized treatment. At the discretion of the investigator, the patient could continue with budesonide in an open manner at an individually adjusted dose. The treatment code was not broken.

The clinic visits, tests performed and investigations are summarized in figure 1. Morning and evening PEF, asthma symptom scores and PD_{20} were the primary clinical efficacy variables.

The study was performed in accordance with the Declaration of Helsinki and according to Good Clinical Practice. The study protocol was approved by the Ethics Committee of the Karolinska Hospital, Stockholm and by the Swedish National Board of Health and Welfare. All patients received written information and gave their verbal informed consent to participate.

Compliance

No objective method for defining compliance was available. However, the inhalation technique was checked and the use of study medication was confirmed by questioning the patient at each visit.

Outcomes

Spirometry (forced vital capacity (FVC), FEV_1) was performed with a flow-volume spirometer (Vitalograph Compact, Vitalograph Ltd, Buckingham, UK) and all values were corrected for body temperature, standard barometric pressure and saturated with water vapour (BTPS).

Predicted values used were those of the European Coal and Steel Community (ECSC) [7]. Inhaled β_2-agonists were withheld for 5 h before the clinic visits.

The histamine challenge tests were performed according to NIEMINEN *et al.* [8] by using an automatic, inhalation-synchronized, dosimetric jet-nebulizer, Spira Elektro 2 (Respiratory Care Center, Hämeenlinna, Finland), with adjustable aerosol delivery time. The nebulization time was 0.5 $s \cdot breath^{-1}$ and the estimated output of solution about 7 $\mu L \cdot breath^{-1}$ during tidal breathing. Two concentrations (0.16 and 1.6%) of histamine diphosphate were used with one, three and six inhalations of the lower concentration and one, three, six and twelve inhalations of the higher concentration. Based on solution $output \cdot breath^{-1}$, one inhalation of the lower concentration was calculated to equal a dose of 11 μg histamine while one inhalation of the higher concentration was calculated to equal a dose of 110 μg histamine.

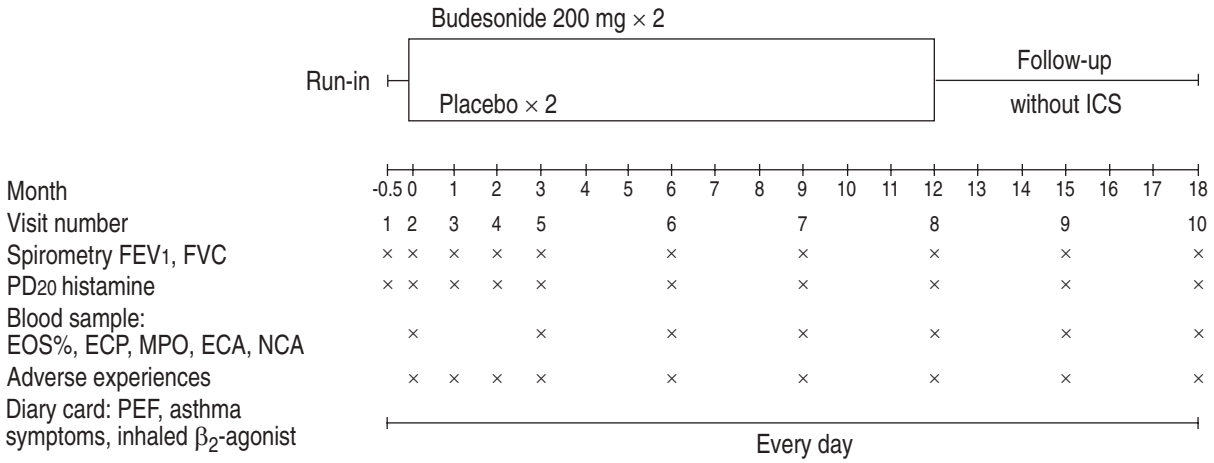

Fig. 1. – Study design with summary of assessments. ICS: inhaled corticosteroids; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PD20: provocative dose of histamine causing a 20% fall in FEV1; EOS%: blood eosinophils, differential count as a percentage of total leucocytes; ECP: eosinophil cationic protein; MPO: myeloperoxidase; ECA: eosinophil chemotactic activity; NCA: neutrophil chemotactic activity; PEF: peak expiratory flow.

Based on these single-breath doses, the doses of histamine were calculated to 11, 33, 66, 110, 330, 660 and 1,320 μg. The highest FEV_1 value of three was used as baseline. The provocation continued until at least a 20% fall in FEV_1 was noted. If FEV_1 fell more than 20% even with the lowest dose of histamine diphosphate, the PD_{20} was considered to be one third of the lowest dose. If FEV_1 dropped less than 20% even when the highest dose of histamine diphosphate was used, the PD_{20} was considered to be twice the highest dose. A similar method was used by HAAHTELA *et al*. [4, 5]. PD_{20} values were calculated by linear interpolation on a log dose scale with base e. Since the doses of histamine had not been doubled constantly, it was decided to use the natural logarithm instead of the logarithm with base 2.

Before the study and at 3 month intervals, blood samples were drawn for determination of serum eosinophil cationic protein (ECP), myeloperoxidase (MPO) and eosinophil and neutrophil chemotactic activities (ECA and NCA, respectively). The determinations of ECP and MPO in serum were performed by radioimmunoassay [9] (Pharmacia Diagnostics, Uppsala, Sweden), and ECA and NCA were determined by means of the leading-front method [10, 11], at the Dept of Clinical Chemistry, University Hospital, Uppsala, Sweden.

During the whole study, patients made daily recordings of morning and evening PEF values (best of three measurements), asthma symptoms (on a scale from 0–3, where 0 = none, 1 = mild, 2 = moderate and 3 = severe), and use of inhaled bronchodilators. The number of β_2-agonist puffs used has been recalculated from doses considered equipotent to terbutaline aerosol 0.25 mg·dose^{-1}, *e.g*. salbutamol aerosol 0.2 mg·dose^{-1} equals to two puffs.

Statistical analysis

For all variables analysed, a fixed-effects analysis of variance (ANOVA) model with the factors treatment, centre and treatment-by-centre interaction was used for comparison of the two treatments. The main comparison was applied to the change from baseline (Visit 2) to the last visit during the treatment period (Visit 8).

The main analysis was based on the All Patients Treated (APT) approach. Missing values were replaced using the Last Value Extended (LVE) principle. Values were extended within each of the following periods: run-in (Visit 1 to Visit 2), treatment (Visit 3 to Visit 8) and follow-up (Visit 9 to Visit 10). No values were extended between these three periods.

For diary variables, averages were calculated for periods of 4 weeks immediately before each clinic visit (Visits 3 to 10) and 2 weeks immediately before Visit 2. The period mean immediately before a visit was connected to that particular visit. Daily recordings not used for the above-mentioned averages were used for calculation of averages on a periodical basis for possible use with the LVE principle.

Once patients had started open budesonide treatment, they were no longer included in the efficacy analysis.

All tests were two-sided and a p-value of less than or equal to 0.05 was considered statistically significant.

Results

1 yr treatment

Patient allocations and withdrawals. Seventy six patients were randomized to receive treatment in the study. One patient was never treated. Patient characteristics are given in table 1.

Thirty eight of the 75 treated patients were randomized to budesonide treatment, and 35 completed the 12 month treatment period. Two patients discontinued, one because of a paranoid psychosis and one was lost to follow-up after 71 days in the study. One patient with treatment failure was given budesonide in an open manner after 112 days in the study. Thirty seven of the 75 treated patients were randomized to receive placebo treatment, and 27 completed the 12 month study. Four patients were given budesonide in an open manner because of treatment failures and six discontinued the treatment: one because of an adverse event (tremor), two because of pregnancy and three patients moved or were lost to follow-up.

Peak expiratory flow. The results of the morning PEF measurements are shown in figure 2. In the budesonide group, the baseline morning PEF was 473±84 L·min^{-1}; after the 1 yr treatment there was an increase of 28±45 L·min^{-1} (mean±SD). The corresponding change in the placebo group was -0.5±44 from a baseline of 456±93 L·min^{-1}. The difference between the changes in PEF was statistically significant (p=0.011). The baseline values for evening PEF were 496±93 for budesonide and 476±88 L·min^{-1} for placebo. The evening PEF showed an increase over baseline of 14±35 in the budesonide group and 3±40 L·min^{-1} in the placebo group (p=0.21).

Symptom scores. At baseline, the mean asthma symptom score (scale 0–3) during daytime was 0.60 in the budesonide group and 0.69 in the placebo group. The asthma symptom scores decreased by 0.23 with budesonide

Table 1. – Patient characteristics: demography and primary variables of the treatment groups at baseline

	Budesonide 400 μg		Placebo	
Male/Female	16/22		17/20	
Mean age yrs	33	(18–55)	35	(18–68)
Height cm	170.7	(8.2)	173.0	(9.3)
Time since diagnosis of asthma months	5.0	(3.2)	4.5	(3.5)
Allergy† n	25		17	
Smokers n	8		8	
PD_{20} μg‡	92	(182)	112	(151)
FEV_1/FVC %	80.2	(9.1)	78.0	(10.2)
Morning PEF L·min^{-1}	473	(84)	456	(93)
Evening PEF L·min^{-1}	496	(93)	476	(88)
PEF variation %§	7.2	(3.7)	7.4	(5.1)
Daytime symptom scores*	0.6	(0.5)	0.7	(0.6)
Night-time symptom scores*	0.4	(0.4)	0.4	(0.5)

Values are arithmetic mean (SD), unless otherwise indicated. †: clinically significant allergy based on clinical history and prestudy skin-prick testing. ‡: values are geometric mean (coefficient of variation %). §: PEF variation was calculated each day as (PEF_{HIGH} - PEF_{LOW})/(PEF_{HIGH}) ×100. *: symptoms score given as a scale of 0–3. For definitions, see legend to figure 1.

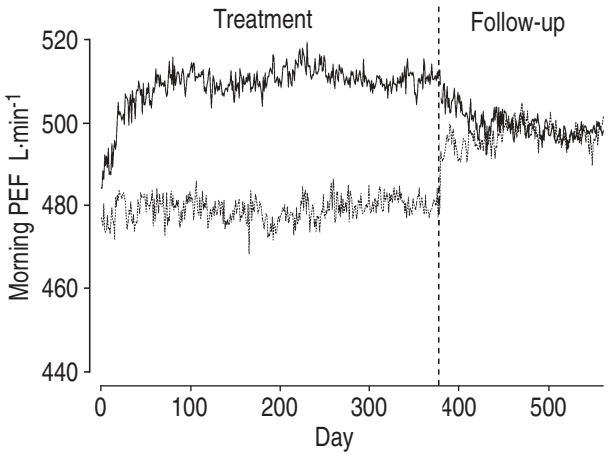

Fig. 2. – Mean morning peak expiratory flow (PEF) during the treatment and the follow-up period. The apparent increase in the placebo group at start of the follow-up is a result of the fact that the most severe patients dropped out during the treatment period (see Results). ——: budesonide 400 µg; ····· : placebo.

and 0.09 with placebo during the 12 month treatment period. For night-time symptoms, the baseline scores were 0.36 in the budesonide group and 0.39 in the placebo group and the decreases during treatment were 0.19 with budesonide and 0.05 with placebo. The differences in changes in symptom scores between the groups were not statistically significant (p-values 0.26 and 0.21 day and night, respectively).

PD20. The PD20 values are shown in figure 3. The geometric mean values at Visit 2 and coefficients of variation (CV) were 92 µg (CV=182%) in the budesonide group and 112 µg (CV=151%) in the placebo group. After the 1 yr treatment period, the PD20 value had increased by a factor of 3.78 (CV=177%) to 347 µg (CV=224%) in the budesonide group and by a factor of 1.19 (CV=228%) to 135 µg (CV=364%) in the placebo group. The difference between treatment effects was statistically significant (p=0.0003). In the budesonide group, the improvement in PD20 was almost one doubling dose after 1 month of treatment and approximately two doubling doses after 3 months.

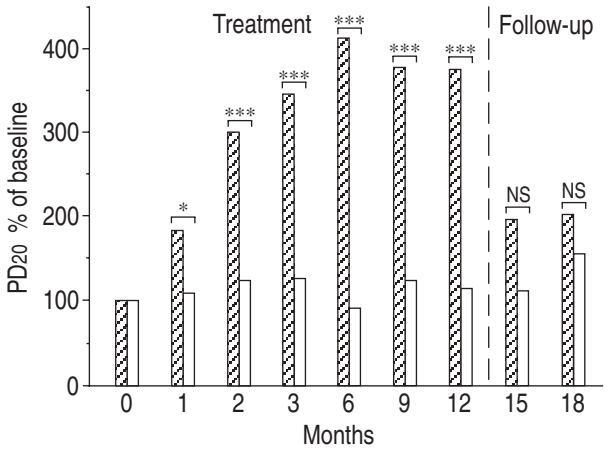

Fig. 3. – Provocative dose of histamine causing a 20% fall in forced expiratory volume in one second (PD20) (geometric mean, % of baseline) during the treatment and the follow-up period, in patients treated with budesonide 400 µg (▨) or placebo (□). *: p<0.05; ***: p<0.001; NS: nonsignificant.

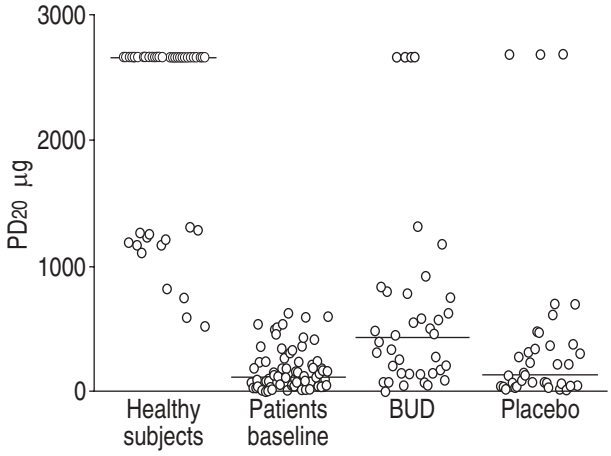

Fig. 4. – Distribution of PD20 in healthy subjects (n=49) and in patients at baseline (n=75), after 12 months of treatment with budesonide (BUD) 400 µg, and after 12 months of treatment with placebo (n=36). Points represent individual subjects and lines represent median values. PD20: provocative dose of histamine causing a 20% fall in forced expiratory volume in one second.

The PD20 values in patients before and after treatment and in healthy subjects are shown in figure 4. Although a statistically significant improvement was noted in the budesonide group, many patients still remained hyperresponsive and there was a marked difference between the budesonide-treated group and the healthy subjects.

Secondary variables. The secondary variables (FEV1, FEV1% pred, FVC, FVC% pred, use of β_2-agonists day and night, percentage eosinophils, ECP, MPO, ECA and NCA) before and after the 12 month treatment period are shown in table 2. There were no statistically significant differences between treatments with respect to change in any of these variables, but there was a trend towards a positive effect with budesonide.

Adverse events. Seven serious adverse events were reported, of which two occurred in the budesonide group. One was a patient who developed paranoid psychosis and one patient was hospitalized because of cholecystitis. A causal relationship to the study medication was deemed unlikely in both cases. In the placebo group, two patients had severe asthma exacerbations and three developed other diseases without possible connection to the study drug (appendicitis, salpingitis and plantar pustulosis).

Two patients discontinued the study because of adverse events: the patient with paranoid psychosis mentioned above, and one patient treated with placebo who experienced tremor after using terbutaline inhalations in association with a histamine challenge test and was not willing to continue in the study.

Follow-up

Of the 35 patients in the budesonide group who completed the 12 month study, 25 completed the 6 month follow-up. Ten patients discontinued the study because of asthma deterioration. In one patient, asthma deteriorated after 5 days, but in the others it took considerably longer (1–5 months). Six patients were given budesonide

Table 2. – Secondary variables before and after the 1 yr treatment period

	Budesonide 400 μg						Placebo					
	Baseline			Change after treatment			Baseline			Change after treatment		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
FEV1 L	38	3.31	0.66	38	0.11	0.35	37	3.23	0.77	36	-0.03	0.37
FEV1 % pred	38	93.1	10.8	38	3.7	9.5	37	88.7	12.2	36	-0.6	10.4
FVC L	38	4.17	0.88	38	0.05	0.35	37	4.19	1.13	36	-0.04	0.48
FVC % pred	38	99.8	12.8	38	1.8	8.2	37	97.2	14.4	36	-0.5	11.7
Use of β_2-agonist puffs·day^{-1}*	38	2.6	2.7	38	-1.1	2.8	36	3.0	3.2	36	-0.4	2.4
Use of β_2-agonist puffs·night^{-1}*	38	0.8	1.4	38	-0.2	2.1	33	0.8	1.4	33	0.1	1.4
Blood eosinophils %‡	38	5.4	3.1	36	-0.8	3.5	36	5.1	3.7	33	-0.5	3.7
ECP μg·L^{-1}§	38	17.1	12.5	36	-4.4	13.0	37	15.9	9.3	33	-2.6	10.3
MPO μg·L^{-1}¶	38	343	192	36	-9	190	37	338	172	33	-13	185
ECA % of control	26**	111.8	16.0	24**	-3.0	16.9	24**	103.3	11.9	22**	2.3	11.3
NCA % of control	26**	112.5	16.6	24**	-4.3	17.0	24**	104.8	12.4	22**	3.6	15.4

There were no significant differences between treatments with respect to change in any of these variables. *: recalculated to equipotent doses (see Materials and methods); §: normal ranges (95%) in a healthy nonallergic population (n=101) 2.3–15.9 μg·L^{-1}. ¶: normal ranges (95%) in a healthy nonallergic population (n=102) 107–478 μg·L^{-1}. **: samples from two centres (samples from one centre were defrosted during transport). ‡: reference range 1–6% centres 1 and 2, 1–5% centre 3. % pred: percentage of predicted values. For further definitions, see legend to figure 1.

in an open fashion. The mean morning PEF decreased from 501 to 483 L·min^{-1} (n=35), and the geometric mean PD20 in the budesonide group decreased from 351 to 183 μg (n=31) when the LVE principle was used for the 10 budesonide patients who had withdrawn from the follow-up.

Of the 37 patients randomized to the placebo group at the start of the study, 27 completed the treatment year and 23 completed the follow-up period. One patient discontinued the follow-up because of asthma deterioration and two patients started on budesonide in an open fashion (treatment failures). One patient withdrew due to pregnancy. The 10 patients that withdrew during the treatment period had on average lower PEF values than the ones that continued in the follow-up. The comparison between the groups at the end of the follow-up is conditional on the fact that patients have completed the treatment year. As the most severe patients dropped out during the first year of the study, this will introduce a selection bias into the follow-up period. The mean morning PEF in the placebo group decreased from 484 to 483 L·min^{-1} (n=26) and the geometric mean PD20 decreased from 219 to 204 μg (n=25) during the follow-up.

Discussion

The patients included in the study were newly diagnosed asthmatics, defined here as having been diagnosed 1 yr or less before inclusion. Baseline lung function was within normal range but the PD20 values showed a group of highly reactive patients, as compared with the healthy controls. Clinically, most had a mild-to-moderate asthma that had not been treated with steroids for at least 3 months before entering the study.

Treatment with a low daily dose of 400 μg budesonide resulted in a greater improvement in objective and subjective variables than did treatment with placebo. Significant differences between the two treatment groups were observed in morning PEF values and in PD20, but the decrease in symptoms and use of β_2-agonist did not reach statistical significance. In the budesonide-treated group, the average increase in the morning PEF values was 28 L·min^{-1} during the study year; most of the improvement took place in the first month. When mild-to-moderate asthmatics had been treated during 6–12 weeks with budesonide in daily doses ranging 400–1,600 μg, improvements in PEF values from 33–84 L·min^{-1} were observed [5, 12–14]. In these studies, the improvement was related to the given dose; a higher dose resulted in a greater increase in morning PEF values. However, a clear picture of the dose-response effect of budesonide on lung function is difficult to obtain from studies with different baseline values. The closer to normal the baseline values are, the less marked the change will be.

Most of the improvement in PD20 occurred in the first 2 months, which is in accordance with the study by HAAHTELA *et al*. [5], where the improvement with a higher dose of budesonide was apparent after the first 6 weeks of treatment. The patients in the present study were hyperreactive in the first place and showed a marked decrease in reactivity of two doubling dose steps in the histamine challenge test. However, after 12 months of treatment, they were still, with a few exceptions, much more reactive than the healthy subjects in the control group. The low daily dose of budesonide obviously has a significant effect on airway reactivity and higher doses have even more effect [15, 16], but permanent change is difficult to achieve especially if the disease has developed over a period of years [4, 14]. This was clearly shown by the high withdrawal rate during the 6 month follow-up period, when the patients did not receive inhaled steroid treatment. Compared with the patients in this study, those in the study of HAAHTELA *et al*. [5] had a similar lung function measured as a percentage of predicted at baseline, while their hyperresponsiveness was less severe.

The daily use of β_2-agonists differed markedly between the patients in the two studies; the patients in this study used about four times more of their rescue medication, indicating a more severe disease [17]. The patients in the study of HAAHTELA *et al*. [5] were treated with a higher daily dose of budesonide for a longer treatment period with better overall results.

Treatment with a daily dose of 400 μg budesonide over a year did not have a statistically significant effect

on blood eosinophils or serum ECP. In other studies, treatment with daily doses of 400 μg budesonide has been shown to reduce the concentration of ECP in induced sputum in children [18], and in bronchoalveolar lavage fluid, but not serum, in adults [19]. Higher daily doses of 1,600 μg budesonide have been shown to reduce serum ECP levels [20]. It seems that treatment with a daily dose of 400 μg budesonide mainly had a topical effect on the bronchial mucosa, which was enough to improve morning PEF values and airway reactivity, but the decrease in asthma symptoms and use of β_2-agonist did not reach statistical significance. A higher dose might be needed to achieve a more complete response. With low daily doses, the potential systemic effects are less, with a lower risk of long-term side-effects. However, a more pronounced and sustained effect may be especially important in the early phases of the disease. This might require some systemic activity of the inhaled corticosteroid, over and above the local effects, to influence the immunocompetent cells of the circulation and the bone marrow and modify the production of cytokines. Another possible explanation for the incomplete response in symptom scores and ECP is that the symptom scores were generally low and some patients did not have any symptoms at all during the run-in. The ECP values were relatively low and close to the normal values at the start of the study and there was also quite high variation in the assayed ECP values. These factors may also explain the lack of significant effect on ECP and symptom scores as they make it difficult to detect statistically significant treatment effects.

During the 6 month follow-up period without treatment with inhaled corticosteroids, a slight deterioration of the disease occurred in most of the patients and 10 out of 35 patients discontinued due to exacerbations. The result indicates that the improvements achieved during the 1 yr treatment with a low daily dose of budesonide were mainly temporary. However, part of the achieved improvement in bronchial responsiveness was maintained, suggesting that low daily doses of budesonide may have a disease-modifying effect in at least some patients. During the 6 month follow-up period, a selection bias was introduced into this part of the study as probably only the patients with the mildest disease remained in the study. The great number of drop-outs in the placebo group during the treatment period makes this group difficult to evaluate during the follow-up, due to the bias thereby introduced.

We have demonstrated the efficacy of a low daily dose of budesonide treatment in patients with newly diagnosed mild-to-moderate asthma. The degree of improvement was less than that seen in some other studies using higher daily doses of budesonide.

References

1. Barnes PJ. The changing face of asthma. *Q J Med* 1987; 63: 359–365.
2. British Thoracic Society/Royal College of Physicians. Guidelines for management of asthma in adults: I. chronic persistent asthma. *BMJ* 1990; 301: 651–653.
3. Juniper EF, Kline PA, Vanzeileghem M, 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: 483–489.
4. 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: 700–705.
5. 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: 388–392.
6. Zetterström O, Carlholm M, Ekelund J, Nikander K. Bronchial provocation with histamine in healthy subjects and asthmatics using dosimeter nebulization with controlled tidal breathing. *Eur Respir J* 1993; 6: Suppl. 17, 598s.
7. Quanjer Ph, ed. Standardized lung function testing. *Clin Resp Phys* 1983; 19 (Suppl. 5): 45–51.
8. Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A. Methacholine bronchial challenge using a dosimeter with controlled tidal breathing. *Thorax* 1988; 43: 896–900.
9. Peterson CGB, Enander I, Nystrand J, Anderson AS, Nilsson L, Venge P. Radioimmunoassay of human eosinophil cationic protein (ECP) by an improved method: establishment of normal levels in serum and turnover *in vivo*. *Clin Exp Allergy* 1991; 21: 561–567.
10. Håkansson L, Westerlund D, Venge P. New method for the measurement of eosinophil migration. *J Leukocyte Biol* 1987; 42: 689–696.
11. Venge P, Dahl R, Håkansson L, Pettersson C. Generation of heat-labile chemotactic activity in blood after inhalation challenge and its relationship to neutrophil and monocyte/macrophage turnover and activity. *Allergy* 1982; 37: 55–62.
12. Lorentzon S, Boe J, Eriksson G, Persson G. Use of inhaled corticosteroids in patients with mild asthma. *Thorax* 1990; 45: 733–735.
13. Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991; 143: 1317–1321.
14. Selroos O, Pietinalho A, Löfroos AB, Riska H. The effect of early *versus* late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108: 1228–1234.
15. Woolcock AJ, Jenkins C. Corticosteroids in the modulation of bronchial hyperresponsiveness. *Immunol Allergy Clin North Am* 1990; 10(3): 543–557.
16. Postma DS, Kerstjens HAM, Koëter GH. Long-term intervention in disease outcome. *In*: Postma DS, Gerritsen J, eds. Bronchitis V: Proceedings of the Fifth International Symposium on Advances in Understanding of Asthma and COPD. Groningen, The Netherlands, June 9-11, 1993. Van Gorcum, Assen 1994; pp. 253–256.
17. International Consensus Report on Diagnosis and Treatment of Asthma. National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, Publication No. 92-3091, March 1992. *Eur Respir J* 1992; 5: 601–641.
18. Sorva R, Metso T, Björksten F, Juntunen-Backman K, Haahtela T. Sputum ECP is a sensitive asthma marker in children. *Allergy Clin Immunol News* 1994; 6 (Suppl. 2): 143.
19. Ädelroth E, Rosenhall L, Johansson SA, Linden M, Venge P. Inflammatory cells and eosinophilic activity in asthmatics investigated by bronchoalveolar lavage: the effects of antiasthmatic treatment with budesonide or terbutaline. *Am Rev Respir Dis* 1990; 142: 91–99.
20. Venge P, Dahl R, Karlström R, Pedersen B, Peterson CG. Eosinophil and neutrophil activity in asthma in a one year double-blind trial with theophylline and two doses of inhaled budesonide. *J Allergy Clin Immunol* 1992; 89: 190.