EFFICACY OF THE COMBINATION OF FLUTICASONE PROPIONATE AND SALMETEROL IN PATIENTS WITH MODERATE PERSISTENT ASTHMA WITHIN A „REAL-LIFE" SETTING*

M. Trautmann[1], N. Banik[1], J. T. Tews[1], R. A. Jörres[2], D. Nowak[2]

[1]GlaxoSmithKline, Munich, Germany
[2]Institute and Outpatient Clinic for Occupational and Environmental Medicine, Ludwig-Maximilians-University, Munich, Germany

Abstract

There are only few data on the effectiveness of recommended drug therapies in asthma under "real-life" conditions without targeted intervention. The study aimed at analyzing the efficacy of the fixed combination of the inhaled corticosteroid fluticasone propionate and the long-acting β_2-agonist salmeterol (FS) for maintenance treatment of moderate persistent asthma (GINA stage 3) within an observational design, mimicking "real-life" as closely as possible. The fixed combination was compared with other forms of treatment that were in accordance with treatment guidelines (pooled comparison (PC) group). Patients kept a diary during a 12-month observation period and routine visits were taken for surveillance. Among 596 patients, 371 patients belonged to the FS and 225 patients to the PC group. The proportion of symptom-free days (SFD) was higher in the FS than PC group (median, 76 vs 67%; p=0.002). Furthermore, the change in asthma control score (p<0.0001) and the percent increase in FEV_1 (p<0.05) after 12 months were greater. There was a lower percentage of patients with hospital stays (p<0.05). The proportions of episode-free or sick-leave days and the number of routine or emergency visits did not significantly differ between groups. Direct costs of treatment per SFD were lower in the FS than PC group (median, 3.78 vs 4.41€; p<0.05). We conclude that in a setup close to clinical practice treatment of patients with moderate persistent asthma with the fixed combination of fluticasone propionate and salmeterol has beneficial effects compared to other forms of therapy and can improve cost-efficiency.

Key words: Asthma control, combination therapy, hospital admission, inhaled corticosteroid, long-acting β_2-agonist, lung function, symptom-free day

INTRODUCTION

Asthma is an inflammatory airway disease characterized by airway hyperresponsiveness, eosinophilic inflammation and variable airway obstruction [1]. The current treatment strategy aims at reducing symptom rates and normalizing lung function as well as preventing exacerbations and disease progress. Depending on asthma severity, the recommended maintenance treatment [1] still offers room for different options that can be, and actually are, followed in clinical practice. In moderate asthma (stage 3) maintenance medication is based on long-acting β_2-agonists (LABA) and regular inhaled corticosteroids (ICS) [1, 2], with antileukotrienes and theophylline as potential add-on therapy.

A large number of clinical trials have compared different treatment modalities with each other. In most of these trials combinations of ICS and LABA were superior to ICS or LABA alone [4-13] or a leukotriene receptor antagonist, either alone [14] or in combination with ICS [15], especially in patients with moderate asthma. In the majority of studies, the ICS tested was fluticasone propionate or budesonide, and the LABA was salmeterol or formoterol. There are data indicating that the fixed combination of ICS and LABA, specifically fluticasone propionate and salmeterol, might be superior to their free combination [16-18]. Synergistic effects occurred in terms of lung function, symptom scores and quality of life. Some studies also indicated the cost-effectiveness of the fluticasone propionate-salmeterol combination relative to other combination or single therapies [19, 20], as well as of the budesonide-formoterol combination [21].

Whilst all of these data have been obtained in controlled trials, it is not clear whether their results also apply to the much less controlled conditions of everyday practice. In view of the well-known problem of patients' variable compliance [3] and restrictions given by budgets and physicians' personal preferences, it does not seem *a priori* guaranteed that benefits established in clinical trials translate into equivalent benefits in clinical practice. It is also obvious that realistic estimates of cost-benefit relationships can be obtained only under "real-life" conditions. Though such analyses are, by the very nature of their design, less standardized than clinical trials and potentially subject to biases generated by the healthcare system, they can provide insight into the efficacy of asthma treatment and give clues for bridging the gap between clinical studies and the implementation of their results into practice.

Based on these considerations we performed a prospective, observational study approximating as far as possible real-life conditions in patients with moderate persistent asthma. For this purpose, the outcome

of different asthma treatments chosen by GPs and pulmonologists in accordance with guidelines was recorded over one year, without targeted intervention, and compared between two major treatments represented by the fixed combination of LABA and ICS, specifically salmeterol and fluticasone propionate, versus other modes of treatment. Outcome variables of interest were treatment efficacy as quantified by the number of symptom-free days, quality of asthma control, lung function, as well as cost-effectiveness.

METHODS

PATIENTS

The study was performed between January 2001 and November 2003 in an outpatient setting involving GPs and pulmonologists from all regions of Germany. Patients (age ≥18 years) were required to have a diagnosis of moderate persistent asthma (stage 3) as defined by FEV_1 or PEF <80 but >60 % predicted [1, 22], in the absence of other chronic lung diseases, such as COPD. The diagnosis had to be confirmed by a ≥12% response in FEV_1 or PEF after inhalation of 200-400 μg salbutamol, as documented within 24 months before inclusion.

In addition, patients were required to have experienced at least one asthma exacerbation in the preceding 12 months and at least one hospital stay due to asthma in the last 3 years. Patients also had to have received asthma treatment ≥6 months, without changes in medication within two months before inclusion. If daily steroid doses were >1200 μg beclomethasone dipropionate or flunisolide or budesonide, or >500 μg fluticasone propionate, patients were not included, as this was taken as evidence for more severe disease. Patients did not have a respiratory tract infection within 6 weeks before inclusion.

STUDY PROTOCOL

The study comprised at least three visits over a 12-month period. At the first visit, clinical history and lung function were assessed and patients completed the Asthma Control Questionnaire (ACQ). For patients meeting the inclusion criteria and agreeing to participate, a diary covering the first 6-month period was issued. Following usual clinical practice, routine visits were planned at least every 6 months. Therefore, at least one visit after approximately half of the 12-month observation period and a final visit after 12 months were available. All visits were either routine visits or unscheduled emergency visits due to asthma worsening. There were no mandatory visits which would have affected cost-efficiency estimates.

At the follow-up visits, the reasons for the visit, adverse events, changes in medication, as well as lung function were assessed. Furthermore, physicians checked the diaries and the adequacy of medication. At the appropriate time, a diary covering the second 6-month period was handed to the patient. At the final visit, 12 months after inclusion, the same measures were taken as in the follow-up visits. Additionally, the number of emergency calls and hospital admissions over the last 12 months as well as the answers to the ACQ were assessed.

TREATMENT AND ANALYSIS GROUPS

Treatment of individual patients was left to the physicians' decision. To describe treatments, four groups turned out to be sufficient. The first group comprised combinations of ICS and LABA via a single inhaler, the second group combinations of ICS and LABA, via a single inhaler, plus oral steroids over a period of ≤6 weeks, the third group combinations of ICS and LABA via separate inhalers, and the fourth group free combinations of ICS and LABA, via separate inhalers, plus possibly methylxanthine (but without other drugs such as cromones). Short-acting β_2-agonists for symptom relief were always allowed.

Since we were primarily interested in a specific fixed combination and groups were of largely different size, patients were re-categorized into two groups for analysis. The Fluticasone propionate-Salmeterol (FS) group comprised all patients treated with the fixed combination of salmeterol-fluticasone propionate (Viani®; 25/50, 25/125, 25/250 μg MDI, or 50/100, 50/250, 50/500 μg Diskus). It was additionally required that the duration of treatment was ≥4 months in case that 6 of 12 months were considered as sufficiently documented, and ≥8 months if the full 12-month period was documented (see below). The Pooled Comparison (PC) group comprised all other patients, including those with other fixed combinations than fluticasone propionate plus salmeterol, such as budesonide plus formoterol (n = 88).

ASSESSMENTS

Documentation by both patients and physicians was done on paper forms. Patients' diaries comprised three items per day and four items per month. The daily questions addressed symptoms of asthma during the last 24 hours, nighttime awakings because of asthma, or inhalation of short-acting β_2-agonists for relief. At the end of the month, the patient summed up the number of days with asthma symptoms or nighttime awakening due to asthma and reported the number of emergency calls and routine visits at the physician.

Quality of asthma control was assessed using the German translation of the Asthma Control Questionnaire (ACQ) [23] (Diary-ACQ-1, Diary-ACQ-2). The sum (best = 0, worst = 36) of 6 items was taken, each of which could take scores between 0 and 6, with lower values indicating better asthma control. Only complete questionnaires were considered for analysis. Lung function parameters were either forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEF), depending on the availability of equipment. Quality control of lung function data followed ERS guidelines as far as applicable [24].

OUTCOME MEASURES

Primary outcome measure was the number of symptom-free days (SFD) defined as 24-hour intervals in which there was no indication of asthma symptoms according to the diary. Assuming that the patient

would not miss indicating the occurrence of symptoms, missing values were taken as absence of symptoms. Episode-free days (EFD) were defined as 24-hour intervals without symptoms of asthma, nighttime awakenings due to asthma or use of short-acting β-agonists. In contrast to SFD, EFD required explicit denial of each of the respective questions. Owing to irregular lack of data this outcome measure tended to be conservative.

The numbers of routine visits, emergency visits (EV) and hospital admissions (HA) as taken from diaries were checked against the physicians' documentation. In case of discrepant data, the higher values were used. If data on the duration of the HA were incomplete, the mean from patients with a specified number of days in the respective treatment group was taken. The information whether HA were related to acute events or rehabilitation was used in the cost estimates. Information on sick-leave days (SLD) as derived from the diary was evaluated only for patients being employed or working self-employed. Data quality control, cross-checks and selection were carried out independently from statistical analysis.

Resource utilization in terms of direct costs (per day or SFD or year) was computed from the costs of asthma drugs, routine and emergency visits and hospital stays (acute events only) based on German sources (routine consultation 28.00 €, emergency consultation 43.30 €, hospital day 325.20 €) [25]. Drug costs were calculated by merging German Pharmacists Association sales prices (ABDA, May 2003) with documented drug prescriptions. If this information was (partially) missing, a compliance of 80 % was assumed.

DEFINITION OF THE DATA SET

Patients were excluded if they did not meet the inclusion criteria, could not be allocated to a treatment group, no diary data from at least one of the two 6-month periods were available, baseline and/or final examination data were missing, or if there was not at least one item documented in the physician's forms. A diary was considered acceptable when ≥5 of 12

months were documented. Data were cross-checked as far as possible for final assessments.

If these criteria were met, the patient's data were included into the analysis. To get additional insight into the potential influence of incomplete documentation, we also analyzed some measures in a more stringently defined "per-protocol" population. This required complete (≥5 of 6 months) diary data in both consecutive 6-month observation periods, as well as a total duration of ≥8 months of combined fixed therapy in the FS group.

STATISTICAL ANALYSIS

For data description, median values and quartiles were computed for each of the outcome measures. Comparisons between the FS and PC group upon entry were performed using the Mann-Whitney U-test for quantitative measures, and χ^2-statistics or Fisher's exact test for qualitative measures. The same tests were utilized to compare the two groups regarding measures for which there was one value describing the effect of treatment over the 12-month observation period, such as the proportions of SFD or patients with ≥1 SFD.

ACQ and lung function were assessed upon entry into the study as well as after 12 months. Differences between groups regarding the 12-month value relative to the initial value were evaluated by analysis of covariance (ANCOVA), whereby the initial value was treated as covariate and the two groups as fixed factor. Statistical significance was assumed when p-values were <0.05. All tests were performed two-sided.

RESULTS

STUDY POPULATION

Overall, 1292 patients were enrolled by 284 physicians, whereby 407 patients were excluded due to insufficient data, 285 patients because of inappropriate asthma treatment [1, 2, 22], and 4 patients who could not be reasonably allocated to the treatment groups. As a re-

Table 1. Patients' characteristics upon entry.

		Total	FS group	PC group	P
n		596	371	225	-
Sex	% f/m	56/44	57/43	53/47	0.276
Age	y	51 (38; 63)	51 (38; 63)	51 (37; 63)	0.545
FEV_1 (n=423)	L	2.20 (1.70; 2.91)	2.18 (1.70; 2.84)	2.23 (1.72; 3.05)	0.488
PEF (n=173)*	L/s	4.84 (3.33; 6.58)	5.00 (3.40; 6.83)	4.70 (3.20; 6.20)	0.645
Duration of asthma	y	10 (5.5; 18)	10 (5; 17)	10 (6; 20)	0.396
Asthma Control Quest.	score	11 (5; 17)	11 (6; 17)	11 (5; 16)	0.708
Smoking	no/ex/current	352/147/93	231/83/57	121/64/36	0.149
Employment	yes/no	292/295	187/179	105/116	0.400

Median values and quartiles (in parentheses) are given. P-values refer to the comparison of the FS group and the PC group. Minor deviations in total sums were due to incompleteness of data which did not lead to exclusion from the study. * Given for patients in whom physicians measured PEF but not FEV_1

Table 2. Results obtained during the 12-month observation period.

		FS group	PC group	P
Observation period (diary)	months	368 (348; 387)	366 (341; 390)	0.540
Symptom-free days (SFD)				
Proportion of SFD per year	%	76.2 (52.6; 92.3)	67.1 (42.0; 89.3)	0.002
Proportion of weeks with ≥1 SFD [§]	%	90	83	0.004
Proportion of patients with ≥1 SFD	%	96.5	94.2	0.188
Patients with ≥1 SFD every week	%	60.4	56.4	0.347
Episode-free days (EFD)				
Proportion of EFD	%	0.6 (0.0; 73.5)	0.3 (0.0; 54.2)	0.138
Sick-leave days (SLD)				
Proportion of patients with ≥1 SLD	%	10.2	11.4	0.736
Number of SLD per patient[$]	n	15 (3; 23)	14 (12; 21)	0.702
Routine visits per year	n	6 (3; 9)	6 (3; 9)	0.893
Emergency visits (EV)				
Proportion of patients with ≥1 EV	%	22.1	28.9	0.077
Hospital admissions (HA)				
Proportion of patients with ≥1 HA	%	3.8	7.6	0.044

Median values and quartiles (in parentheses) are given. P-values refer to the comparison of the two groups. [§]Mean values and unpaired t-test results are given. [$]In patients with occupation showing at least 1 SLD

sult, 596 patients met the inclusion criteria and had complete data as defined above (Table 1). Of the 596 patients evaluated, 371 patients belonged to the FS group and 225 patients to the PC group. There were no statistically significant differences between groups regarding the distribution of age, sex, FEV_1 upon inclusion, duration of asthma, ACQ, smoking habits, or employment status (Table 1). Patients were recruited by 198 physicians, 75 of whom provided data from at least 4 patients each, and 99 from less than 3 patients. There was no difference in the distribution of recruited patients per physician between the FS and PC group.

The distributions of age, sex, FEV_1 or PEF upon inclusion, duration of asthma, ACQ, smoking habits, or employment status in the patients excluded (n=696) was not significantly different from the values of the final population (n = 596). There were also no significant differences between the final population and the per-protocol population (n = 465; n = 294 FS, n = 171 PC). According to the data obtained at the end of the observation period, the most frequently used daily dose of salmeterol/fluticasone propionate in the FS group was 100/500 μg (36 %).

The total number of Adverse Events was 36 (23 patients) in the FS group and 15 (12 patients) in the PC group, whereby 12 and 8 patients, respectively, experienced respiratory system-related Adverse Events. The respective proportions did not significantly differ between groups (p = 0.124 and 0.510). The number of

courses of systemic corticosteroids within the observation period was n = 6 in the FS and n = 0 in the PC group (p = 0.088).

CLINICAL EFFECTIVENESS

Frequency of asthma symptoms and asthma-related events
The percentage of SFD over the 12-month observation period was significantly different between the FS and PC group (p = 0.002; Table 2, Fig. 1). Furthermore, the proportion of weeks with ≥1 SFD differed between groups (p = 0.004, Table 2). In contrast, the proportion of patients reporting ≥1 SFD during the observation period or ≥1 SFD per week during this period did not differ. Regarding the proportion of EFD, there were no significant differences between groups (Table 2). The per-protocol population similarly showed a difference in the percentage of SFD (median value (quartiles): 81.6 (65.6; 94.6) vs 75.6 (49.1; 91.7) %; p=0.006), but not in the proportion of EFD.

The median number of routine visits or scheduled physician contacts per year was similar in the two groups. The proportion of patients reporting ≥1 emergency visit was slightly smaller in the FS than in the PC group (Table 2). However, in the FS group the proportion of patients with ≥1 hospital admission was only half that of the PC group (p=0.044). This was also observed in the per-protocol population (4.8 vs 9.9 %; p=0.031). The proportion of patients reporting ≥1 sick-leave day (SLD) and the number of SLD in
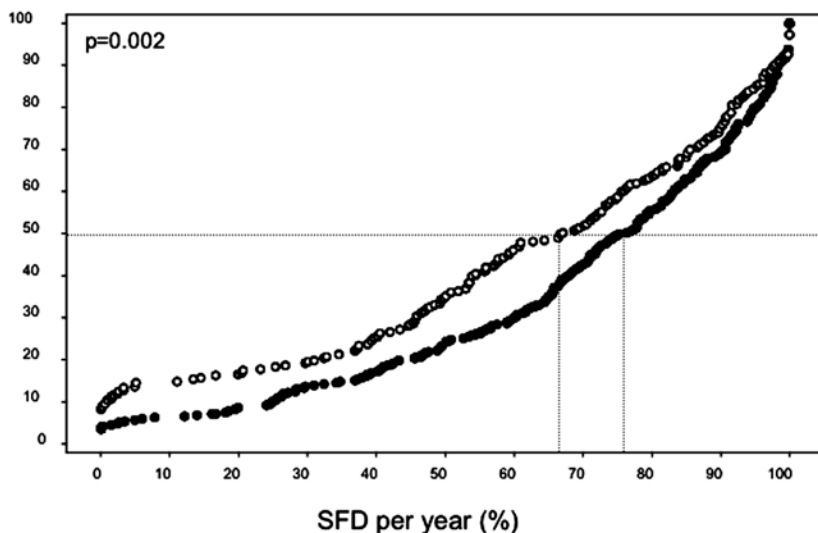
Fig. 1. Cumulative distribution of the percentage of symptom-free days (SFD). The horizontal axis indicates the proportion of SFD for individual patients within the observation period, ranging between 0 % (no SFD) and 100 % (all days SFD). The vertical axis indicates the cumulative percentages of patients who showed at most the proportion of SFD indicated on the horizontal axis. The filled circles represent the distribution of the FS group and the open circles that of the PC group. The horizontal line marks 50 %, the vertical lines indicate the median values of the two groups (see Table 2). The two distributions were significantly different from each other (p=0.002).

Table 3. Asthma control scores and lung function before start of treatment as well as changes after treatment.

		FS group	PC group	P
Asthma Control Questionnaire				
Valid upon entry	n	349	215	-
Baseline	Score	11 (6; 17)	11 (5; 16)	0.708
Valid difference at last assessment	n	270	162	-
Difference to baseline	Score	-3 (-10; 0)	-2 (-5; 1)	<0.0001
FEV$_1$				
Valid upon entry	n	268	155	-
Baseline	L	2.18 (1.70; 2.84)	2.23 (1.72; 3.05)	0.488
Valid difference at last assessment	n	202	115	-
Difference to baseline	L	0.30 (0.04; 0.60)	0.19 (0.01; 0.48)	0.107
Percent difference	%	15.5 (2.3; 33.1)	8.7 (0.6; 21.1)	0.036
PEF *				
Valid upon entry	n	113	61	-
Baseline	L/s	5.00 (3.40; 6.83)	4.70 (3.20; 6.20)	0.645
Valid difference at last assessment	n	103	52	-
Difference to baseline	L/s	0.04 (-0.10; 0.50)	0.01 (-0.08; 0.30)	0.795
Percent difference	%	1.1 (-1,7; 7.4)	0.9 (-1.5; 7.6)	0.874

Median values and quartiles (in parentheses) of the ITT-population are given. P-values refer to the comparison of the two treatment groups. Differences in sample size were due to incomplete data that did not lead to exclusion from the study. * Given for patients in whom physicians measured PEF but not FEV$_1$

patients having ≥1 SLD did not differ between groups (Table 2).

Comparison of changes occurring over the 12-month observation period
Upon inclusion, ACQ was not different between the FS and PC group (Table 3). After 12 months, however, the changes in ACQ were significantly different from each other   (p<0.0001, Table 3, Fig. 2), showing a

greater improvement after FS compared to PC therapy. A similar result was observed in the per-protocol population (p<0.0001).

Neither FEV$_1$ nor PEF showed significant differences between the FS and PC group upon inclusion (Table 3). There was a significant (p = 0.036) difference between groups with regard to the percent changes of FEV$_1$ occurring over 12 months (Table 3). Again, the improvement was greater in the FS than PC
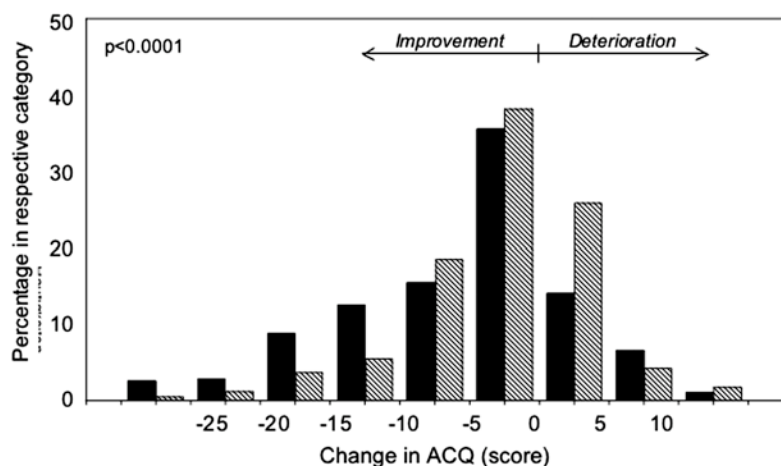
Fig. 2. Histogram of the changes in asthma control as given by the Asthma Control Questionnaire (ACQ). The horizontal axis represents the change in total ACQ score (range 0-36) between the last visit and the inclusion visit, the vertical axis the percentage of patients showing a change of the magnitude indicated on the horizontal axis (bins of width 5). Values less than zero represent improvements, values greater than zero deteriorations. The leftmost and rightmost bars of the histogram represent the tails of the distributions. The filled bars refer to the FS group, the hatched bars to the PC group, the two distributions of which did significantly differ (p<0.0001).

Table 4. Estimates of resource utilization.

		FS group	PC group	P
Total drug costs per year and patient	€	889 (487; 1045)	874 (487; 1125)	0.925
Total direct costs per year and patient[&]	€	1036 (688; 1383)	1085 (762; 1530)	0.291
Direct costs per SFD[&,§]	€/SFD	3.78 (2.75; 6.10)	4.41 (2.98; 9.37)	0.018

Median values and quartiles (in parentheses) are given. P-values refer to the comparison of the FS and PC group. [&] Computed from drug costs, routine and emergency visits, and asthma-related hospital admissions (acute events only). [§] Refers to patients with at least one symptom-free day (SFD).

group. No difference between groups was seen regarding PEF. The results of the per-protocol population were similar.

RESOURCE UTILIZATION

Total drug costs and total direct costs per patient were similar in the two groups and did not significantly differ from each other (Table 4). However, when direct costs were expressed as costs per SFD, there was a statistically significant difference, the FS group showing greater cost-effectiveness compared to the PC group (p = 0.018). A similar result applied in the per-protocol population (median (quartiles): 3.60 (2.61; 5.54) vs 4.30 (2.85; 9.99) €/SFD; p = 0.003).

DISCUSSION

The present data suggest that under „real-life" conditions treatment with the fixed combination of fluticasone propionate and salmeterol showed clinical benefits in patients with moderate persistent asthma, as compared to other modes of therapy. These benefits were reflected in a number of outcome measures, despite the natural limitations of an approach in which patients could not be as tightly controlled as in a conventional drug study. As a major result, the proportion of SFD per year was by about 10 % greater with the fixed FS combination and, correspondingly, the proportion of weeks with at least one SFD higher. Fig. 1 indicates that improvements occurred mainly in patients showing median or very low frequencies of SFD. This suggests that patients with not well-controlled asthma experienced a particular benefit.

Nevertheless, the average percentage of days at which asthma symptoms occurred was high, irrespective of the mode of therapy. This might raise questions about the adequacy of the therapy chosen by the physicians, despite being in accordance with guidelines. These questions cannot be answered from the present study. It might be noted, however, that lack of asthma control is not uncommon [3], though under the conditions of a controlled clinical trial the proportion of patients in whom asthma control is achievable can be substantially raised [26]. These considerations additionally suggest that the results of the present study mirror the real situation met in clinical practice under the conditions imposed by the health care system.

In contrast to SFD, the median number of EFD was very low (Table 2). This has to be attributed to their stringent definition requiring explicit documentation, as well as the fact that patients with moderate persistent asthma might not experience many of these episodes. Probably due to same factors the proportion of patients with at least one SFD per week over the whole observation period did not differ between groups. On the other hand, the percentage of patients with HA for asthma, though not the percentage of patients with EV, showed a reduction in the FS group. This finding appears to be consistent with the observation that especially patients with a high frequency of symptoms had a benefit from the FS therapy (Fig. 1), as one would expect these patients to be primary candidates for hospital admission.

It also seems noteworthy that the results regarding the proportion of SFD were corroborated by the highly significant difference of improvements in ACQ as reported after one year. The difference between groups was mainly reflected in the lower quartiles (Table 3), as an increase in the proportion of patients of the FS group showing a marked improvement, and a corresponding decrease in the proportion showing a slight deterioration (see Fig. 2).

As a functional correlate of these clinical measures, there was also a significant difference in the percent improvement in FEV_1 over time (Table 3). Again, the fact that the difference of relative changes was larger than that of absolute changes, is consistent with the suggestion that patients with low FEV_1 experienced a particular benefit from the FS therapy. The difference between groups was not observed in the patients who had PEF measurements only, probably because of the limited sensitivity of this measure compared to FEV_1. Lung function was evaluated upon inclusion and after the observation period. As in asthma variability of lung function over time is considered a characteristic feature of the disease [1], the observed difference in FEV_1 should not be overinterpreted. Irrespective of this, the observation matches the differences in ACQ and the proportion of SFD. This consistency is reassuring as it indicates that the present analysis did not extract random effects out of the number of measures assessed.

It is obvious that a real-life setting, which did not implement a planned, coordinated intervention, bears more chances for uncontrolled effects than a randomized controlled trial. The same is true regarding the quality of the data. This was reflected in the requirements for patients' inclusion and completeness of data which were weaker than in many conventional drug studies. Furthermore, the number of physicians participating in this study was quite large which inevitably raised the variability of the data. The results, however, suggest that the quality of assessments was high enough to reveal consistent differences between groups.

In this study, only regimens were compared that were in accordance with current recommendations for moderate persistent asthma. There was no sign of selective recruitment to one of the groups and baseline characteristics were similar (Table 1), as well as the number of routine visits, indicating a similar degree of care. Patients of the FS but not the PC group showed a few steroid courses, without statistically significant difference. There was no apparent link between these courses and other clinically relevant events. Thus we consider them as random effect not causally linked to therapy. Inevitably, inclusion into even a noninterventional study is likely to induce changes in the patient's and physician's attitude towards treatment compliance and control. Improvements over time regardless of medication were observed in both FEV_1 and ACQ (Table 3). Such improvements have been appreciated in many previous studies [e.g., 6, 27]. It is extremely difficult, if not impossible, to control for such involuntarily induced effects but the one year observation period was probably long enough to minimize the impact of transient effects resulting from inclusion into the study.

The benefits of FS therapy were reflected in the derived measure of direct costs per SFD (Table 4) and the finding of reduced costs per SFD was obviously based on the reduction of the proportion of these days. The cost values used were taken from public sources for the time of the study. These values depend on the pricing by companies and health care institutions and thus may vary but the about 15 % difference between groups is likely to provide enough room for unpredictable changes in treatment costs without rendering the FS therapy at any time significantly more costly than the PC treatment. The present result renders it likely that the FS therapy is clinically more effective at lower or at most equivalent costs, which seems to be true also for other care systems that differ from that established in Germany [28].

As employment status was similar in the two groups and differences in the distribution of income are unlikely, the number of work days lost was taken as an estimate of indirect costs. Sick-leave frequencies might depend on workplace conditions, thus these numbers are likely to be of lower impact compared to symptoms, asthma control scores, or lung function.

The major results were virtually unaltered when patients treated with budesonide and formoterol in a single inhaler (n = 88) were omitted from the PC group. The median change (quartiles) of ACQ in the budesonide-formoterol subgroup was -1 (-5; 2) compared to -2 (-5; 1) in the total PC group. This was still different from the change by -3 (-10; 0) in the FS group (Table 3), noting that the lower quartile was the appropriate measure (Fig. 2). The proportion of SFD was 69.7 (35.6; 91.5) % in the budesonide-formoterol group compared to 67.1 (42.0; 89.3) % in the total PC group. Again this was clearly different from the 76.2 (52.6; 92.3) % in the FS group (Table 2). Based on this we considered it justified to leave patients with budesonide-formoterol treatment in the PC group, thereby increasing group size.

However, the fact that the budesonide-formoterol subgroup was not particularly large calls for caution in comparing the efficacy of the two ICS-LABA combinations within the present study. It is also not possible to deduce whether the fact that the combination was administered in one inhaler instead of two, has affected asthma control. Previous studies comparing the budesonide-formoterol combination of with that of fluticasone propionate-salmeterol led to different results [e.g., 29, 30]. Irrespective of this, we can safely conclude that under the assumption of similar efficacy inclusion of the budesonide-formoterol treatment into the PC group has not favoured the occurrence of the differences which we actually observed. There is also no evidence that differences in efficacy between metered dose and powder inhalers affected the result of the FS group, as both formulations have been shown to be clinically equivalent [31].

The findings of our study are in accordance with those of a number of controlled clinical trials. Synergistic effects of LABA and ICS have been advocated on the basis of pharmacological reasoning [32]. Indeed, in most of the studies, addition of a LABA such as salmeterol was superior to an increase in ICS dose

[27, 33, 34]. A recent comprehensive meta-analysis has shown additional benefits from the combined treatment over increasing ICS dose, in terms of lung function and symptoms [35], and other reviews have emphasized its therapeutic potential [36] or superiority [37,38]. Obviously, the majority of controlled studies achieved a higher degree of asthma control than that found under real-life conditions [3]. It seems noteworthy that our data are in accordance with the major results of the controlled trials, but also indicate the need for improving asthma therapy.

In summary, the present data provide evidence that under assessment conditions close to clinical practice patients with moderate persistent asthma experienced a higher benefit from treatment with the fixed combination of fluticasone propionate and salmeterol than from other forms of therapy. The benefit was reflected in the frequencies of symptom-free days and weeks, as well as asthma control scores and improvements in lung function. As a consequence, cost-efficiency per symptom-free day was also superior with this treatment. Irrespective of these results, the still considerable frequency of symptoms in patients treated according to current guidelines suggests room for improvement in general practice so that more patients may attain the levels of asthma control that have been shown to be achievable in controlled clinical trials.

References

1. National Institute of Health. Global Initiative for Asthma – Global Strategy for Asthma Management and Prevention. 2002, update 2004. http://www.ginasthma.com/.
2. Bundesärztekammer (BÄK) Arbeitsgemeinschaft der Deutschen Ärztekammern, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Kassenärztliche Bundesvereinigung (KBV), and cooperating societies (eds). Nationale Versorgungsleitlinie Asthma. Version 1.1, Juni 2005 in der Fassung vom September 2005.
   http://www.asthma.versorgungsleitlinien.de/.
3. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 2004;114:40-47.
4. van Noord JA, Schreurs AJ, Mol SJ, Mulder PG. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. Thorax 1999;54:207-212.
5. Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, Baitinger L, House K, Prillaman B, Shah T. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. Am J Respir Crit Care Med 2000;161:527-534.
6. Jenkins C, Woolcock AJ, Saarelainen P, Lundback B, James MH. Salmeterol/fluticasone propionate combination therapy 50/250 microg twice daily is more effective than budesonide 800 microg twice daily in treating moderate to severe asthma. Respir Med 2000;94:715-723.
7. Juniper EF, Jenkins C, Price MJ, James MH. Impact of inhaled salmeterol/fluticasone propionate combination product versus budesonide on the health-related quality of life of patients with asthma. Am J Respir Med 2002;1:435-440.
8. Heyneman CA, Crafts R, Holland J, Arnold AD. Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. Ann Pharmacother 2002;36:1944-1949.
9. Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. Respir Med 2003;97:555-562.
10. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, Drazen JM, Ford JG, Israel E, Martin RJ, Mauger EA, Nachman SA, Spahn JD, Szefler SJ; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA 2001;285:2583-2593.
11. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337:1405-1411.
12. Juniper EF, Svensson K, O'Byrne PM, Barnes PJ, Bauer CA, Löfdahl CG, Postma DS, Pauwels RA, Tattersfield AE, Ullman A. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. Eur Respir J 1999;14:1038-1043.
13. Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, Ford JG, Israel E, Kraft M, Martin RJ, Nachman SA, Peters SP, Spahn JD, Szefler SJ; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA 2001; 285:2594-2603.
14. Calhoun WJ, Nelson HS, Nathan RA, Pepsin PJ, Kalberg C, Emmett A, Rickard KA, Dorinsky P. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta(2)-agonists alone. Am J Respir Crit Care Med 2001;164:759-763.
15. Ilowite J, Webb R, Friedman B, Kerwin E, Bird SR, Hustad CM, Edelman JM. Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. Ann Allergy Asthma Immunol 2004;92:641-648.
16. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ; EDICT Investigators. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respir Med 2002;96:851-861.
17. Martinat Y, Desfougeres JL. [Fixed-dose fluticasone-salmeterol combination: at least effective and better tolerated than open-dose combinations]. Rev Pneumol Clin 2003;59:139-148.
18. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol 2003;112: 29-36.
19. Lundbäck B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combi-

nation product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. International Study Group. Respir Med 2000;94:724-732.

20. Lyseng-Williamson KA, Plosker GL. Inhaled salmeterol/fluticasone propionate combination: a pharmacoeconomic review of its use in the management of asthma. Pharmacoeconomics 2003;21:951-989.

21. Andersson F, Stahl E, Barnes PJ, Löfdahl CG, O'Byrne PM, Pauwels RA, Postma DS, Tattersfield AE, Ullman A; Formoterol and Corticosteroid Establishing Therapy. International Study Group. Adding formoterol to budesonide in moderate asthma--health economic results from the FACET study. Respir Med 2001;95:505-512.

22. Wettengel R, Berdel D, Hofmann D, Krause J, Kroegel C, Kroidl RF, Leupold W, Lindemann H, Magnussen H, Meister R, Morr H, Nolte D, Rabe KF, Reinhardt D, Sauer R, Schultze-Werninghaus G, Ukena D, Worth H. [Asthma therapy in children and adults. Recommendations of the German Respiratory League of the German Society of Pneumology] Med Klin (Munich). 1998;93:639-650.

23. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-907.

24. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5-40.

25. Statistisches Jahrbuch 2003, Statistisches Bundesamt, Wiesbaden 2003, p. 448; Krankenhausreport 2003 (eds. Klauber J, Robra BP, Schellschmidt H), Schattauer Verlag, Stuttgart, 2004, p. 267-8; Einheitlicher Bewertungsmaßstab (EBM), Stand 1. Juli 1999, Deutscher Ärzteverlag, Köln, 2000, p. 114-116.

26. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004;170:836-844.

27. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996;153:1481-1488.

28. Detournay B, Pribil C, Jourdanne C, Price M. Budget impact model for determining the costs of introducing inhaled salmeterol/fluticasone propionate combination for the management of persistent asthma in France. Eur J Health Econ 2002;3:149-155.

29. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandström T, Jorup C, Welte T. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin 2004;20:225-240.

30. FitzGerald JM, Boulet LP, Follows RMA. The CONCEPT Trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clinical Therapeutics 2005;27:393-406.

31. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med 2001;95:136-146.

32. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. Eur Respir J 2002;19:182-191.

33. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 1994;344(8917):219-224.

34. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320(7246):1368-1373.

35. Greenstone I, Ni CM, Masse V, Danish A, Magdalinos H, Zhang X, Ducharme F. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev 2005;4:CD005533.

36. Jackson CM, Lipworth B. Benefit-risk assessment of long-acting beta2-agonists in asthma. Drug Saf 2004;27:243-270.

37. Reynolds NA, Lyseng-Williamson KA, Wiseman LR. Inhaled salmeterol/fluticasone propionate: a review of its use in asthma. Drugs 2005;65:1715-1734.

38. Garcia-Marcos L, Schuster A, Cobos Barroso N. Inhaled corticosteroids plus long-acting beta2-agonists as a combined therapy in asthma. Expert Opin Pharmacother 2003;4:23-39.

Address for correspondence
Prof. Dr. med. Dennis Nowak
Institute and Outpatient Clinic for Occupational and Environmental Medicine
Ludwig-Maximilians-University
Ziemssenstr. 1
80336 Munich