An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing

Jörg D. Leuppi, Marc Salzberg, L. Meyer, S. E. Bucher, M. Nief, Martin H. Brutsch, Michael Tamm

Respiratory Medicine, Department of Internal Medicine, University Hospital, Basel, Switzerland
Pharma Brains Ltd, Basel, Switzerland
AstraZeneca AG, Zug, Switzerland

Summary

Principles: Current asthma management employing inhaled corticosteroids (ICS) and long-acting β₂-agonists (LABA) aims to rapidly achieve and maintain overall asthma control including symptoms with minimal medication. This study compared self-guided adjustable maintenance dosing with budesonide/formoterol in a single inhaler with fixed dosing.

Methods: In an open-label, parallel-group, multicentre study, 127 asthmatic patients, well controlled on ICS and LABA, were treated with budesonide/formoterol (Symbicort® Turbuhaler®) 200/6 μg (equivalent to 160/4.5 μg delivered dose) 2 inhalations bid for 4 weeks, and were then randomised to budesonide/formoterol adjustable dosing (n = 69) (guided self-adjustment of dose: 1 inhalation bid or 2 inhalations at night with interim step ups to 2 inhalations bid and if not sufficient up to 4 inhalations bid for 14 days) or fixed dosing (2 inhalations bid) (n = 58) for 12 weeks.

Results: Patients used adjustable dosing effectively; >50% used a decreased maintenance dose on >50% of the days. Seventy-two percent (50/69) from the adjustable-dosing group reduced their maintenance dose within the first 2 treatment weeks. Thirteen adjustable-dose patients (18.8%) never reduced their dose and 4 (5.8%) stepped up their dose. Symptom severity (NHLBI severity grade) decreased in both groups; however, the decrease was only statistically significant (p = 0.004) in the adjustable-dosing group. Treatment failures occurred in 17% and 24% of patients (adjustable and fixed dosing, respectively p = 0.35). Nocturnal awakenings (0.057 vs. 0.067/night, p = 0.006) and rescue medication use (0.15 vs. 0.23 inhalations/day, p <0.0001) were significantly less frequent with adjustable dosing, and the average daily medication dose was significantly reduced (3.0 vs. 3.9, p <0.0001) compared with fixed dosing. Lung function measurements (FEV₁ and PEF) were not significantly different between groups during the study. There were no asthma-related hospital admissions.

Conclusion: Asthma patients on adjustable maintenance dosing with budesonide/formoterol maintained control of symptoms using significantly less medication overall than fixed dosing. Thus, adjustable maintenance dosing achieved guideline goals of effective asthma control at an appropriately low maintenance dose. However, larger studies on adjustable maintenance dosing are needed.

Key words: asthma; inhaled corticosteroid; budesonide; long-acting β₂-agonist; formoterol; adjustable dosing; single inhaler

Introduction

Effective control of asthma inflammation and symptoms is critical for the long-term management of patients with persistent asthma. Current guidelines recommend a stepwise approach to asthma therapy based on disease severity [1]. When bronchodilators are needed more than occasionally, low-dose inhaled corticosteroids (ICS) are recommended for first-line maintenance therapy. For patients with more frequent symptoms, addition of long-acting β₂-agonists (LABA) is recommended in preference to increasing the dose of ICS. In many cases, episodes of asthma exacerbation can be effectively controlled at onset by temporarily increasing the ICS dose [2, 3]. Furthermore, studies have shown that exacerbation rates are reduced when a LABA is added to an ICS [4–7].
The synergistic effect of using budesonide and formoterol together has recently been explained on a molecular basis; β₂-agonists are capable of activating the glucocorticoid receptor, and combined low doses of formoterol and budesonide show anti-proliferative effects on bronchial smooth muscle cells by synchronizing cell-cycle control [7].

The aim of current asthma management is to achieve early control of asthma and then maintain control at the minimum effective medication dose [8, 9]. Successful long-term control of asthma requires patient involvement which includes status monitoring and adherence to a treatment regimen [1]. With a fixed-dosing regimen of a combination ICS and LABA product, more ICS than necessary may be given during periods when symptoms are well controlled. Low doses of both ICS and LABA have been shown to be effective for maintaining asthma control [10–13]. Their use together in a single inhaler product such as Symbicort® Turbuhaler® provides the opportunity, by simple adjustment of the number of inhalations, for low-level maintenance therapy during periods of good asthma control, and when asthma worsens, as a strategy to prevent exacerbations by temporarily increasing the dose. This latter approach is consistent with asthma treatment guidelines [1] and is supported by studies showing positive outcomes for a low-dose corticosteroid maintenance strategy involving short periods of higher doses to treat exacerbations [13, 14]. The aim of the present study was to investigate whether asthma control can be maintained when the patient uses individually tailored adjustable maintenance doses of budesonide/formoterol in a single inhaler in comparison with a fixed-dosing regimen.

Methods

Patients

One hundred and forty-two patients, aged ≥12 years, with a documented history of asthma for at least 6 months [1], were recruited at 32 investigational sites in Switzerland (7 outpatient clinics and 25 respiratory practitioners). The criteria for the diagnosis of asthma was a record of reversibility to short-acting bronchodilator of ≥12% and/or a history of short-term variation in airway function, and asthma symptoms responding promptly to conventional asthma therapy, as documented in patient files. No records of smoking habits were taken. Patients were included if, in the opinion of their investigator, their asthma was currently well controlled on ICS and LABA or they were symptomatic whilst receiving ICS and short-acting β₂-agonists (SABA). Asthma control was defined as having symptoms on no more than 2 days per week, using no more than 4 rescue inhalations of SABA per week, having had no more than 2 nights with nocturnal awakening due to asthma in the previous month, and exhibiting a peak expiratory flow (PEF) ≥80% predicted normal. Patients were required to be receiving at least 600 μg of budesonide daily (or the equivalent nominal dose of another ICS). Patients were excluded if, during the previous 4 weeks, they had suffered an asthma exacerbation requiring an oral corticosteroid treatment or an upper respiratory tract infection, or if they had a severe cardiovascular or other significant concomitant disease. Women were excluded if pregnant or planning pregnancy, or not taking adequate contraceptive measures.

All patients provided written informed consent prior to study commencement. For patients under the age of 18 years, both the patient and the parents/legal guardian had to sign the informed consent form. The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committees in Switzerland responsible for the regions involved approved the study, and the Swiss Regulatory Authorities were notified of the study.

Study design

This study was an open-label, randomised, multicentre study. There was a 4-week run-in period followed by a 12-week randomised parallel-treatment period. Patients visited the clinic on 3 occasions: at enrolment (start of run-in, visit 1); after the 4-week run-in (randomisation, visit 2) and at the end of the 12-week randomised-treatment period (visit 3, end of study). During the run-in period, patients received budesonide/formoterol (200/6 μg, corresponding to 160/4.5 μg delivered dose, Symbicort Turbuhaler) 2 inhalations twice daily. Terbutaline (Bricanyl® Turbuhaler) was supplied as rescue medication throughout. At visit 2, patients were randomised to receive treatment with budesonide/formoterol (200/6 μg) adjustable dosing or fixed dosing (2 inhalations twice daily). Patients on adjustable dosing could step down immediately to 1 inhalation twice daily or 2 inhalations at night at the discretion of the investigator. Thereafter, patients adjusted their medication dose according to the following criteria: step down to 1 inhalation morning and evening or 2 inhalations at night if they were unaware of any recent deterioration, required reliever medication on ≤2 days and had no nocturnal awakenings due to asthma during the previous week; and step up back to 2 or maximally 4 inhalations twice daily for a minimum of 7 days, if on 2 consecutive days they required reliever medication on ≥3 occasions or had nocturnal awakenings, or if their PEF was <80% of baseline (mean morning PEF on the last 7 days of the run-in). Patients who stepped up could step down after 7 days to their previous maintenance dose if symptoms were resolved. However, if not resolved within 14 days they could either step up once more from 2 to 4 inhalations twice daily or, if already on 4 inhalations twice daily, they contacted the investigator for review of their treatment.

The patients in both treatment groups were provided with an action plan for dealing with serious exacerbations or ongoing deterioration in asthma control. Patients were trained at visit 1 on the use of the Turbuhaler, and a detailed written description of its use was provided. During the study no objective measurement of compliance was made; the number of inhalations taken was based on the patient’s diary records. Patients in either group who experienced 2 exacerbations requiring oral corticosteroids had their treatment reassessed and were withdrawn from the study. Patients were free to withdraw, or could be withdrawn at the discretion of the investigator, at any time during the study.
Assessments

Patients recorded their medication usage, nocturnal awakenings and PEF measurements in a diary on a daily basis. After appropriate training at visit 1, patients measured their PEF twice daily before inhaling their medication using a PEF meter (Mini-Wright, Clement Clarke International Ltd. Essex, UK) while standing, and the best of 3 values was recorded. Patients were contacted by phone after 4 and 8 weeks of treatment to obtain information from their diary records and to identify any adverse events (AEs) occurring since the last visit at the clinic. Patients were assessed for medical history, AEs, and lung function (forced expiratory volume in 1 second [FEV₁] in the clinic at visits 1, 2 and 3). Health-related quality of life was also assessed using the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) [15].

Primary efficacy variables

The primary efficacy variables were the number of treatment successes and treatment failures. Treatment success was assessed by determining the number of patients who maintained or improved their category of asthma symptom severity according to NHLBI definitions (mild intermittent, mild persistent, moderate persistent, severe persistent) [1]. Patients were allocated to the most severe category for which they met at least one criterion.

Treatment failure was defined as one or more of the following: a serious asthma-related AE such as deterioration in asthma; emergency treatment (such as nebulised β₂-agonist therapy or glucocorticosteroid injection); a course of oral corticosteroids lasting at least 5 days; any withdrawal leading to a change in asthma medication due to lack of efficacy.

Secondary efficacy variables

Secondary efficacy variables included FEV₁, morning and night-time PEF measurements, night-time awakenings, use of reliever medication, MiniAQLQ, and number of study-drug inhalations. The percentage of best daily morning and evening PEF value was calculated for each patient relative to their respective maximum values recorded during the 4-week run-in period [16, 17].

Safety variables

The number, type and severity of AEs occurring from the first administration of study medication were recorded throughout the study.

Statistical analysis

All randomised patients, with the exception of those with missing diary data, were included in the analysis. All data were analysed by descriptive and non-parametric statistics. Proportions were compared using the Fisher Exact test, while the Cochran-Mantel-Haenszel test was used for odds ratios. Mean values between the two treatment groups were compared using the two-sample (unpaired) t-test. Contingency tables containing the asthma severity before and after treatment were analysed using Bowker’s test for symmetry [18]. A 5% two-sided level of significance was used throughout. Data were analysed using the statistical package SAS V8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 142 patients enrolled in the study, 69 patients on adjustable dosing and 58 patients on fixed dosing were eligible for analysis. Only 1 patient (fixed-dosing group) was withdrawn prematurely from the study due to a lack of efficacy and 1 because of an AE not related to treatment (adjustable-dosing group). The remaining 13 patients (7 on adjustable and 6 on fixed dosing) failed to record any or most of their diary records (≤34 days) during the randomised-treatment period. One patient in the adjustable-dosing group discontinued after 69 days because of exacerbation of his asthma condition, however, data from this patient were included in the efficacy analysis. No patients were withdrawn from the study as a result of suffering 2 exacerbations of their asthma requiring oral corticosteroids. The patient demographic and baseline characteristics were generally well balanced between the treatment groups (table 1). There was no difference in asthma symptom severity (NHLBI severity level) between the two groups; in each group approximately 40% were categorized as having mild-persistent and 40% as having moderate-persistent asthma symptoms. Frequency of awakenings at night was also similar between groups. Patients in the adjustable-dosing group were slightly younger on average than patients in the fixed-dosing group, although the difference between groups was not significant. However, there was a significantly smaller proportion of males in the adjustable-dosing group and significantly less use of rescue medication during the run-in by patients randomised to receive adjustable dosing (0.16 vs. 0.21 inhalations/day, p = 0.038).

Patients in the adjustable group effectively modified the number of inhalations of budesonide/formoterol in response to symptoms. Fifty-six patients (81%) reduced their maintenance dose at least once during the treatment period. Thirty-six patients (52%) used a decreased maintenance dose on more than 50% of the days, and 23 (33%) on more than 90% of days. Fifty patients (72.5%) reduced their dose during the first 2 weeks. Thirteen patients (18.8%) never reduced their dose and 4 patients (6%) stepped up their medication on one occasion during the study to 4 inhalations twice daily. Most patients on fixed dosing completed the study using 2 inhalations twice daily and reductions in dose or missing doses were rare; the average recorded medication dose in this group during the randomised-treatment period was 3.9 inhalations/day and close to that which was expected. The average number of daily inhalations of study medication was also significantly lower in the adjustable-dosing group than in the fixed-dosing group (3.0 vs. 3.9, p < 0.0001).

After 12 weeks of treatment, the severity of asthma symptoms decreased in both groups (table
At the end of treatment, patients in the adjustable-dosing and fixed-dosing groups (96% and 95%, respectively) maintained or improved their asthma symptom severity status compared with their status at the start of treatment. Although there was a trend for an improvement in both groups, a statistically significant shift to a lower symptom severity status was only obtained in the adjustable-dosing group ($p = 0.004$ vs. $p = 0.11$ in the fixed-dosing group).

Twelve patients (17.4%) in the adjustable-dosing group and 14 (24.1%) in the fixed-dosing group had one or more episodes of treatment failure; the difference between groups was not statistically significant ($p = 0.35$). More patients on fixed dosing had multiple treatment failures compared with adjustable dosing (figure 2). The individual treatment failures were classified as follows: asthma-related serious AE, 2 (both fixed group); emergency treatment, 26 (14 fixed, 12 adjustable); use of oral/systemic corticosteroids, 7 (6 fixed, 1 adjustable).

Frequency of nocturnal awakenings was low in both groups, but significantly lower in the adjustable-dosing group than in the fixed-dosing group (0.057 vs. 0.067/night, $p = 0.006$). Compared with run-in values the use of rescue medication was reduced by 0.15 inhalations/day in the adjustable-dosing group and was increased by 0.20 inhalations/day in the fixed-dosing group; though use of rescue medications was infrequent in both groups there was a significant difference in favour of adjustable dosing (0.15 vs. 0.23 inhalations/day, $p < 0.0001$). Mean FEV$_1$ (percentage predicted normal) increased from 78% to 81% in the adjustable-dosing group and from 80% to 83% in the fixed-dosing group during the study (visit 1 to visit 3, figure 3). There were no significant differences between treatment groups at any clinic visit. Daily peak flow values, given as percentages, were essentially unchanged during the treatment period in both groups; there were no significant differences between groups at any time during the study. The mean MiniAQLQ total scores increased during run-in (indicating an improved health-related quality of life) from 4.82 to 5.44 in the

### Table 1

<table>
<thead>
<tr>
<th>Demographic and baseline characteristics.</th>
<th>all (n = 127)</th>
<th>adjustable dosing (n = 69)</th>
<th>fixed dosing (n = 58)</th>
<th>p-value (adjustable vs. fixed dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: years, mean [median] (range)</td>
<td>46.0 [45.7] (12–78)</td>
<td>44.7 [41.6] (13–74)</td>
<td>47.6 [47.7] (12–78)</td>
<td>0.15*</td>
</tr>
<tr>
<td>Gender: Males, n (%)</td>
<td>62 (48.8)</td>
<td>28 (40.6)</td>
<td>34 (58.6)</td>
<td>0.028**</td>
</tr>
<tr>
<td>Weight: kg, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>73.4 (17.2)</td>
<td>72.7 (18.0)</td>
<td>74.3 (16.4)</td>
<td>0.31*</td>
</tr>
<tr>
<td>Males</td>
<td>81.2 (15.1)</td>
<td>79.6 (17.7)</td>
<td>82.4 (12.8)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Females</td>
<td>66.1 (15.9)</td>
<td>67.9 (16.8)</td>
<td>62.8 (11.9)</td>
<td>0.27*</td>
</tr>
<tr>
<td>Height: cm, mean (SD)$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>168.5 (9.1)</td>
<td>167.2 (8.5)</td>
<td>170 (9.7)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Males</td>
<td>174.3 (7.3)</td>
<td>172.8 (8.5)</td>
<td>175.3 (6.1)</td>
<td>0.17*</td>
</tr>
<tr>
<td>Females</td>
<td>162.9 (7.0)</td>
<td>163.3 (6.1)</td>
<td>162.3 (8.4)</td>
<td>0.57*</td>
</tr>
<tr>
<td>FEV$_1$: % predicted normal (SD)</td>
<td>79.2 (18.1)</td>
<td>78.4 (17.1)</td>
<td>80.3 (19.4)</td>
<td>0.41*</td>
</tr>
<tr>
<td>Relative PEF: % (SD)$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>91.3 (35.3)</td>
<td>88.8 (29.2)</td>
<td>94.2 (41.7)</td>
<td>0.52***</td>
</tr>
<tr>
<td>Evening</td>
<td>92.1 (39.6)</td>
<td>90.9 (35.7)</td>
<td>93.3 (41.9)</td>
<td>0.74***</td>
</tr>
<tr>
<td>Awakenings per night: % (SD)$^c$</td>
<td>5.08 (2.0)</td>
<td>5.02 (1.9)</td>
<td>5.15 (2.6)</td>
<td>0.82***</td>
</tr>
<tr>
<td>Asthma symptom severity: n (%)$^d$</td>
<td></td>
<td></td>
<td></td>
<td>0.48*</td>
</tr>
<tr>
<td>Mild intermittent</td>
<td>19 (15.0)</td>
<td>9 (13.0)</td>
<td>10 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Mild persistent</td>
<td>49 (38.6)</td>
<td>27 (39.1)</td>
<td>22 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>53 (41.7)</td>
<td>29 (42.0)</td>
<td>24 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Severe persistent</td>
<td>6 (4.7)</td>
<td>4 (5.8)</td>
<td>2 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

FEV$_1$ = forced expiratory volume in 1 second; PEF = peak expiratory flow

$^a$ Wilcoxon test (Mann-Whitney U test)

$^b$ Fisher’s exact test

$^c$ Two-sample t-test (unpaired)

$^d$ Differences are largely due to gender-related physiognomic characteristics

$^a$ Calculated as value on first day of treatment divided by maximum value recorded during run-in

$^b$ Calculated as the percentage of nights with nocturnal awakenings during run-in

$^c$ According to NHLBI severity level [1]

### Table 2

<table>
<thead>
<tr>
<th>Change of asthma condition (NHLBI severity level [1]) under treatment.</th>
<th>Adjustable dosing</th>
<th>Fixed dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Condition improved</td>
<td>23</td>
<td>33.3</td>
</tr>
<tr>
<td>Condition unchanged</td>
<td>43</td>
<td>62.3</td>
</tr>
<tr>
<td>Condition deteriorated</td>
<td>3</td>
<td>4.3</td>
</tr>
</tbody>
</table>
adjustable group (p = 0.046) and from 5.01 to 5.55 (p = 0.055) in the fixed-dosing group. At the end of treatment, MiniAQLQ scores were at similar levels to the end of run-in (5.40 adjustable dosing, 5.52 fixed dosing). There were no significant differences between the two treatment groups.

Both treatments were well tolerated. There were 77 AEs in total (35 adjustable dosing, 42 fixed dosing, no significant difference). Of these 13 (5 adjustable dosing, 8 fixed dosing) were considered as possibly related to treatment: hoarseness (4 adjustable dosing, 5 fixed dosing); thrush (1 fixed dos-
(hypertension and acute hearing loss); the others were an asthma exacerbation and a nephrotic syndrome. There were no asthma-related hospital admissions.

**Discussion**

This study showed that asthma symptom severity, judged according to NHLBI severity levels [1], was significantly improved in patients who received an adjustable maintenance dosing regimen with inhaled budesonide/formoterol. Compared with fixed dosing, improvements with adjustable dosing were attained with less maintenance medication overall, fewer nocturnal awakenings and less frequent use of rescue medication.

Numerous studies have proven the efficacy and importance of ICS in asthma management. In asthma, the underlying inflammation must be treated continuously in order to control the condition. Guidelines for asthma treatment emphasize that once control is achieved, the maintenance dose of medication should be reduced to the minimum necessary to maintain a therapeutic benefit, thus reducing the risk of adverse effects [1]. In the present study, the overall amount of budesonide and formoterol inhaled was significantly reduced compared with fixed dosing by using adjustable dosing. Although high doses of ICS provide sufficient asthma control in patients with unstable asthma [8], in those patients with clinically stable asthma, ICS can be reduced, especially if patients are not hyperresponsive [9]. Once asthmatic patients are stabilized, low doses of budesonide plus formoterol are as effective as a high dose of budesonide alone [12]. In patients with persistent asthma that is sub-optimally controlled with an ICS alone, but whose asthma improves after adding a LABA, the ICS may be reduced by more than 50% without eliciting a significant loss of asthma control; however, total elimination of ICS may result in a significant deterioration in asthma control [19]. The adjustable-dosing regimen used in the present study enabled patients to utilize an appropriately low maintenance dose when their symptoms were controlled, while allowing them to rapidly increase their dose at signs of worsening to maintain control. Being able to step up the dose promptly at early signs of worsening is an important aspect of an adjustable-dosing regimen and may help prevent exacerbations.

The results of this study suggest that for most patients on adjustable dosing the overall maintenance dose of budesonide/formoterol can be reduced without compromising efficacy. While roughly one half of all patients in the adjustable-dosing group could reduce their dose for half of the time, symptom severity was significantly improved, and there were slight improvements in almost all efficacy and safety parameters measured compared with fixed dosing (non-significant: fewer AEs, fewer treatment failures; significant: less need for rescue medication, less frequent nocturnal awakenings). As our study population was clinically stable prior to starting the randomised-
treatment period, we would not have expected significant changes in these parameters during the study; indeed FEV₁, peak flow values and health-related quality of life were maintained at similar levels in both groups throughout. The reasons for the small but significant differences in use of rescue medication and nocturnal awakenings in favour of adjustable dosing is uncertain, but does not appear to be related to an imbalance of asthma severity level between the groups; this was similar in both groups at the start of treatment. Nocturnal awakenings also occurred at a similar level in both groups during run-in. Although patients in the adjustable-dosing group used fewer inhalations of rescue medication during run-in (0.16 vs. 0.21 inhalations/day) the difference between groups actually widened during the treatment phase (0.15 vs. 0.23 inhalations/day). There is evidence that better asthma control can be achieved by using self-management plans [20]. Therefore, we can hypothesize that the patients on adjustable dosing might be more compliant and able to react faster to a worsening of asthma than patients on fixed dosing.

Current guidelines for asthma [21, 22] emphasize the need for education and written action plans to complement the use of pharmacological treatments in the treatment of asthma. Patients must be provided with proper instructions for adjusting their medication dose; however, it is important that they do not take the freedom to adjust the dose as a “green light” for non-adherence. With appropriate precautions, self-management of asthma using adjustable maintenance dosing of budesonide/formoterol may become a preferable treatment to fixed dosing for asthma management. Unlike fixed dosing, adjustable maintenance dosing is consistent with current guideline goals for asthma management, allowing treatment to be tailored to individual patient needs with an appropriately low dose to maintain control. Taken as a whole the results of the present study do not by themselves substantiate a greater improvement in asthma control for adjustable dosing over fixed dosing, however, they do demonstrate a highly significant reduction in medication use, which may have important cost implications. Health economic studies and other larger studies investigating the effects of budesonide/formoterol adjustable dosing on underlying airway inflammation and airway hyperresponsiveness are warranted.

Correspondence:
Jörg D. Leuppi, MD, PhD
Respiratory Medicine
Department of Internal Medicine
University Hospital
Petersgraben 4
CH-4031 Basel
E-Mail: jleuppi@ubhs.ch

CONTRIBUTING CENTRES
Study coordination: Prof M. Tam, MD, Respiratory Medicine, University Hospital Basel; L. Meyer, RN (study nurse).

Outpatient clinics: Brutsche MH, MD PhD, University Hospital Basel; Köhler E, MD, Cantonal Hospital Liestal; Leuppi JD, MD PhD, University Hospital Basel; Pons M, MD, Hospital Cívico, Lugano; Quadri F, MD, Hospital San Giovanni, Bellinzona; Sauty A, MD, University Hospital CHUV, Lausanne; Scherer T, MD, Lung Centre Hirrlingen, Zürich; Thorens J-B, MD, Hospital La Tour, Meyrin.

Respiratory practitioners: Berny J-Y, MD, Genève; Besse F, MD, Martigny; Bodmer R, MD, Genève; Cottu R, MD, Neuchâtel; Forrer J, MD, Basel; Garrone S, MD, Montreux; Hold G, MD, Interlaken; Kaeser P, MD, Neuchâtel; Koeffny A, MD, Genève; Kopp C, MD, Münchenstein; Lagler U, MD, Zürich; Leser C, MD, Kempraten SG; Lindt R, MD, Lyss; Maillard H, MD, Altdorf UR; Martin-Braschler H, MD, Gossau SG; Meisels C, MD, Thun; Nicolet-Chatelain G, MD, Nyon; Ritscher D, MD, Zürich; Roulin J-P, MD, Fribourg; Siebenschein R, MD, Wettingen; Tscham M, MD, Laufen; Vonmoos S, MD, Neuchâtel; Waber U, MD, Schönbühl-Urtenen; Weiss S, MD, Bern; Züllig A, MD, Wädenswil.

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