Targeting asthma control in real-life clinical practice by using ICS/LABA combination

Štefan Laššán[1], Ildikó Téglás[2], Monika Laššánová[3]
[1]Department of Pneumology, Phthisiology and Functional Diagnosis,
Slovak Medical University and University Hospital Bratislava
[2]Department of Epidemiology, Faculty of Public Health, Slovak Medical University, Bratislava,
[3]Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava

Introduction: Regular treatment with a fixed combination of long-acting β2-adrenoreceptor agonist (LABA) and inhaled corticosteroid (ICS) led to asthma control in randomized controlled trials. Is it possible to reach similar results in a real-life setting? Methods: During a 3-month multicenter prospective study, patients not meeting the criteria of total asthma control were treated for three months with a fixed combination of ICS/LABA guided by a physician. The patients were educated in proper inhaler technique and importance of adherence to treatment. **Results:** Four hundred and ninety-four patients were included with a mean age of 39.0 (SD 16.2) years and disease duration of 6.3 years (SD 7.5). During the treatment phase, a significant reduction in patients with day-time (from 93% to 23%, $p < 0.001$) and night-time symptoms (from 81% to 10%, $p < 0.001$) was observed. The mean Asthma Control Test score gradually increased from 16.7 (SD 3.8) to 23.8 (SD 1.7) ($p < 0.001$). The proportion of uncontrolled asthma patients decreased from 76% at the baseline visit to 2% at the end of the study period ($p < 0.001$). The mean dose of ICS decreased from the baseline 721 (SD 289) µg to the final 672 (SD 317) µg ($p = 0.041$) daily. According to multivariate analysis (logistic regression), an age ≥ 40 years (OR = 0.552, $p = 0.002$) and smoking (OR = 0.527, $p = 0.026$) significantly decreased asthma control. **Conclusion:** In a real-life scenario, regular treatment with ICS/LABA and improved adherence/inhaler handling resulted in a significant increase in asthma control in as little as three months.

Key words: bronchial asthma, asthma control, adherence, inhaled corticosteroid/long-acting β2-adrenoreceptor agonists (ICS/LABA).

Kontrola astmy v bežnej klinickej praxi pri liečbe fixnou kombináciou ICS/LABA

Úvod: Pravidelná liečba fixnou kombináciou inhalačného kortikosteroidu (ICS) s dlhodobo pôsobiacim β2-sympatomimetikom (LABA) spoľahlivo preukázala v randomizovaných kontrolovaných štúdiách potenciál na dosiahnutie kontroly astmy. Je možné dosiahnuť podobné výsledky v podmienkach bežnej klinickej praxe? **Metódy:** V priebehu 3-mesačnej multicentrickej prospektívnej štúdie boli pacienti nespĺňajúci kritériá úplnej kontroly astmy liečení počas 3 mesiacov fixnou kombináciou ICS/LABA pod vedením ošetrujúceho lekára. Pacienti boli edukovaní s cieľom osvojenia správnej inhalačnej techniky a s dôrazom na adherenciu k liečbe. **Výsledky:** Zaradili sme 494 pacientov s priemerným vekom 39,0 (SD 16,2) rokov, ktorí boli liečení kvôli astme v priemere 6,3 rokov (SD 7,5). Počas liečebnej fázy došlo ku signifikantnej redukcii podielu pacientov s dennými (z 93 % na 23 %, $p < 0,001$) a nočnými symptómami (z 81 % na 10 %, $p < 0,001$). Priemerná hodnota skóre v Asthma Control Teste sa postupne zvyšovala z 16,7 (SD 3,8) na 23,8 (SD 1,7) ($p < 0,001$). Podiel pacientov s nekontrolovanou astmou sa znížil zo 76 % na vstupnej vizite na 2 % pri ukončení štúdie ($p < 0,001$). Súčasne sa podarilo znížiť priemernú dávku ICS zo vstupných 721 (SD 289) µg/deň na konečných 672 (SD 317) µg/deň ($p = 0,041$). Na základe viacrozmernej analýzy (logistická regresia) sa pravdepodobnosť dosiahnutia kontroly astmy znižovala s vekom ≥ 40 rokov (OR = 0,552, $p = 0.002$) a fajčením (OR = 0,527, $p = 0,026$). **Záver:** V podmienkach bežnej klinickej praxe vedie pravidelná liečba s ICS/LABA spolu so zlepšením adherencie a zručnosti pri zaobchádzaní s inhalátorom k signifikantnému nárastu kontroly astmy už počas troch mesiacov.

Kľúčové slová: astma bronchiale, kontrola astmy, adherencia, inhalačné kortikosteroidy/dlhodobo pôsobiace β2-sympatomimetiká (ICS/LABA).

KORESPONDENČNÍ ADRESA AUTORA: Monika Laššánová, M.D., Ph.D., monika.lassanova@fmed.uniba.sk
Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University
Sasinkova 4, 811 08 Bratislava, Slovakia

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Introduction

The majority of current national as well as international guidelines emphasize that the primary goals of asthma management are symptom control and future risk reduction (1, 2). Moreover, the preferred stepwise approach for adjusting pharmacological treatment of asthma depends on the current level of asthma control (1, 2). Although such a strategy is effective in the majority of patients (3), experience from everyday practice indicates a discrepancy between the results of randomized controlled trials and clinical practice. In the setting of unselected asthma populations, observational, cross-sectional surveys show, in general, a high frequency of symptoms and activity limitation related to asthma (4, 5, 6). In addition, patients have a tendency to overestimate the level of their asthma control (6).

Along with a proper choice of medication and treatment of comorbidities, an essential role is played by patient education. Our efforts were directed at modification of lifestyle and improvement of adherence to the disease management regimen (7). Inhaled corticosteroids (ICS) are the cornerstone of pharmacological asthma therapy. According to the current Global Initiative for Asthma (GINA) guidelines, ICS represent the first-line medication intended for the regular treatment of all symptomatic asthma patients (GINA 2018). However, there is a large group of patients who require combination therapy to achieve asthma control. The addition of long-acting β2-adrenoreceptor agonists (LABA) to ICS significantly improves symptoms and lung functions in comparison to the same or even higher dose of ICS (8, 9). Within this context, the GINA document recommends taking advantage of this combination in treatment Steps 3-5 (2).

The purpose of our 3-month prospective study was to investigate the treatment of bronchial asthma with a fixed ICS/LABA combination paired with an intervention aimed at a proper inhaler technique. Better adherence to the treatment regimen would lead to a significant improvement in the initial level of asthma control in uncontrolled asthma patients. A secondary objective was to identify risk factors affecting the achievement of asthma control.

Tab. 1. *Criteria for total asthma control according to the study protocol*

Characteristic	Total asthma control
Day-time symptoms	None
Limitation of activities	None
Night-time symptoms/awakenings	None
Use of reliever/rescue medication	None
Lung functions (FEV1 and FEV1/FVC ratio)	Normal
Exacerbations	None
ACT score	25

FEV1 = Forced expiratory volume at first second
FVC = Forced vital capacity
ACT = Asthma Control Test (10)

Materials and Methods

Subjects

Adult asthma patients (≥ 18 years) who had at least a 6-month history of bronchial asthma diagnosed according to the national guidelines were recruited by the investigators (1). All enrolled patients failed to meet the pre-defined criteria for total asthma control despite regular asthma treatment for at least 3 months. The criteria for total asthma control (shown in Table 1) were based on a composite outcome measure resulting from lung function assessment (using spirometry), the frequency of symptom occurrence, use of rescue therapy, history of exacerbations, and Asthma Control Test (ACT) score (10). The exacerbation frequency data referred to the previous 3-month period and the usage of rescue therapy applied in the week before the baseline visit. Exacerbation events were defined according to the GINA 2017 document. The study was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The patients signed an informed consent form before being enrolled in the study.

Study Design and Interventions

Our study was a 3-month, multicenter, open-label, prospective real-life study in adult patients with bronchial asthma who did not meet the criteria for total asthma control (Table 1). A total of 40 selected outpatient offices which specialized either in clinical immunology/allergology or pneumology/phthisiology in the Slovak Republic participated in the study. The goal of our study was to reflect the settings of routine clinical practice.

Within the study period, all enrolled patients underwent a total of five visits according to the protocol. The initial baseline visit was followed by a subsequent „visit 1" and „visit 2" at two-week intervals. „Visit 3" and „visit 4" were carried out at 4-week intervals. At the „baseline visit", the physician recorded the following: complete clinical history, demographic data, disease symptoms, data on comorbidities (according to available medical records), exacerbation history, and current asthma treatment including the frequency of reliever medication use. Every patient underwent spirometry testing with subsequent interpretation of lung function tests (11), and completed an ACT questionnaire. The physician objectively assessed the level of asthma control and decided on the patient's eligibility for enrollment in the study, according to the inclusion criteria. Finally, treatment with a fixed-dose combination ICS/LABA fluticasone propionate/salmeterol xinafoate in dry powder inhaler DiskusTM (FSC) was prescribed with an intention to achieve and maintain asthma control. All patients were instructed by a physician and/or a trained nurse on the principles of proper inhaler handling and the importance of treatment adherence. At all following visits (i.e., „visits 1-4"), data collection according to the protocol was performed in order to recognize possible changes in the level of asthma control (including pulmonary function testing, ACT questionnaire, reliever medication use, and occurrence of symptoms) and medication adherence (an interview aimed at verification of days covered with the recommended use of prescribed asthma medication). The patient's physician ultimately decided on FSC dosage for the period until the next visit.

Statistical methods

Discrete (qualitative) variables were specified utilizing absolute and relative frequency (n, %). The continuous variables were analyzed using arithmetic mean and standard deviation (SD). The significance of the type of variable and the numbers of groups compared was tested through the

Tab. 2. *Baseline characteristics of subjects (n = 494)*

Characteristic	
Sex (n, %)	
Male	238 (48%)
Female	256 (52%)
Mean Age, years (SD; median)	
All	39 (16; 37)
Male	37.9 (16.5; 37)
Female	40.1 (15.9; 37.5)
Mean age at the time of asthma diagnosis, years (SD; median)	
All	32.5 (16.6; 31)
Male	31.8 (17.1; 29)
Female	33.2 (16.2; 32)
Mean asthma duration, years (SD; median)	
All	6.3 (7.3; 4)
Male	6.0 (6.5; 4)
Female	6.6 (7.9; 4)
Active smokers (n, %)	72 (14.6%)
Family history of asthma occurrence (n, %)	256 (51.8%)
Positive allergic status (n, %)	
Inhaled allergens	165 (33.4%)
Drugs/medication	58 (11.7%)
Food	37 (7.5%)
Insect bite	5 (1%)
Occurrence of day-time symptoms at baseline (n, %)	459 (93%)
Occurrence of night-time symptoms at baseline (n, %)	401 (81%)
Limitation of daily activities (n, %)	330 (67%)
Pulmonary function testing at baseline (n, %)	
Mean prebronchodilator FEV1 (l)	2.4
% predicted	77
Without ventilatory disorder	105 (21%)
Mild obstructive ventilatory disorder	184 (37%)
Moderate obstructive ventilatory disorder	156 (32%)
Severe or very severe obstructive ventilatory disorder	31 (6%)
Combined ventilatory disorder	18 (4%)
Asthma medication at baseline (n, %)	
ICS alone	58 (11.7%)
ICS + LABA	416 (84.2%)
Montelukast	31 (6.3%)
Tiotropium bromide	5 (1%)
Theophylline	34 (6.8%)
Systemic corticosteroids	9 (1.8%)
Antihistamines	215 (4.4.%)
Comorbidities	
Allergic rhinitis	38%
Chronic bronchitis or chronic obstructive pulmonary disease	29%
Cardiovascular disease	16%
Atopic dermatitis	9%
Gastrointestinal and metabolic disorders	7%
Thyroid gland disorders	2%
Tuberculosis	1%
Rheumatologic disorders	1%
Depression	0.6%
Chronic idiopathic urticaria	0.2%
Other	9%

ICS = inhaled corticosteroids
LABA = long-acting β2-adrenoreceptor agonist
FEV1 = forced expiratory volume at first second

t-test, analysis of variance or Chi-square test of independence. The dependence of qualitative variables was measured using a Spearman correlation coefficient, with an appropriate test of significance of the coefficient being calculated as well. Multivariable logistic regression was used to calculate the odds ratio (OR), with a 95% Confidence Interval (CI), and by a test of significance for specified parameters. The significance level was set at the level $\alpha = 0.05$. For the subsequent logistic regression analysis, we used the parameters from the baseline logistic regression with a significance of $p < 0.1$.

Results

Four hundred and ninety-four adult asthma patients were enrolled in the study with a nearly equal proportion of males and females. Baseline characteristics of the subjects are shown in Table 2. The mean age at the time of asthma diagnosis was 32.5 (SD 16.6) years. The mean disease duration was 6.3 years (SD 7.5, median 4 years). There were no significant differences in age at diagnosis or the duration of the disease ($p = 0.379$, $p = 0.418$, respectively) between males and females. Over a half of the patients (52%) had a positive family history of asthma, particularly the younger ones. However, their proportion decreased with increasing age ($\rho = -0.197$, $p < 0.001$). Of the 494 patients, 74 (15 %) were active smokers irrespective of gender ($p = 0.271$). With increasing age, an increasing proportion of smokers was observed ($\rho = 0.101$, $p = 0.028$).

We assessed comorbidities according to available medical records with a focus on ten diseases: allergic rhinitis; either chronic bronchitis or chronic obstructive pulmonary disease (COPD); cardiovascular diseases; atopic dermatitis; gastrointestinal and metabolic diseases; thyroid gland disorders; rheumatic diseases; depression; and chronic idiopathic urticaria. The majority of patients suffered from at least one comorbid condition, with 27% having no recorded comorbidity, 49% having at least one, and 25% at least two comorbidities. The most frequent comorbidities were allergic rhinitis (38%) and chronic bronchitis or COPD (29%).

The impact of therapy and education on asthma control

Day-time and night-time asthma symptoms

At the baseline visit, 93% of the patients reported day-time symptoms related to asthma and 81 % reported night-time symptoms. Over the study treatment period, the occurrence of day and night symptoms decreased markedly ($p < 0.001$) (Fig. 1).

Fig. 1. *Occurrence of day-time and night-time symptoms (n = 494)*

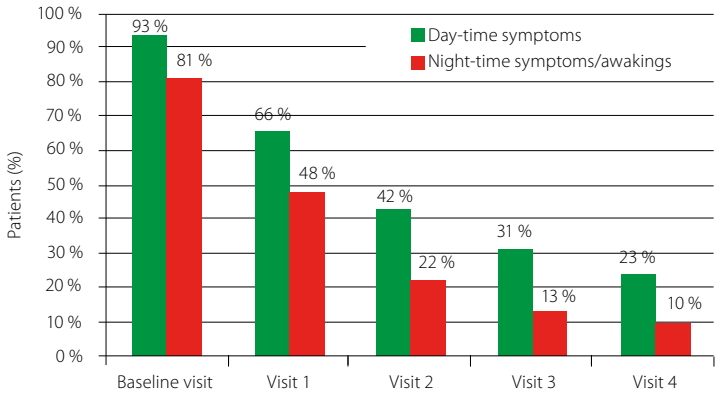
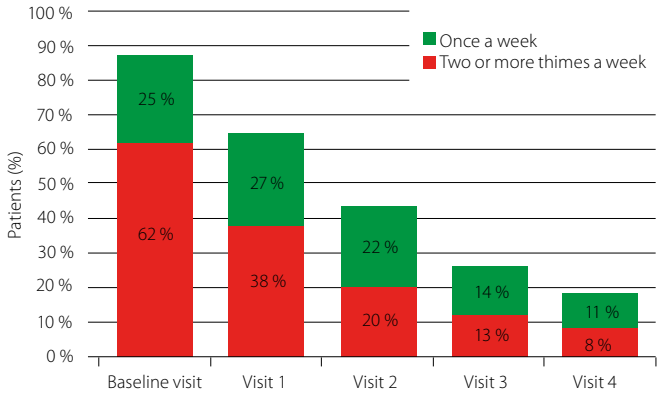


Fig. 2. *Use of reliever medication (n = 494)*



Limitation in daily activities

A similar trend was observed for limitation in the patients' daily activities. The proportion of patients with a limitation in daily activities gradually decreased from 67% at the baseline visit to 5% at the end of the study period ($p < 0.001$).

Use of reliever medication

Eighty-seven percent of the patients reported rescue medication use during the week preceding the baseline visit. During the study period, the proportion of patients requiring rescue medication at least once a week decreased to 19% at the final visit ($p < 0.001$). Similarly, the proportion of patients requiring reliever medication ≥ twice a week decreased from 62% at the baseline visit to 8% at the final visit 4 ($p < 0.001$) (Fig. 2).

Exacerbations

Within a period of 3 months before the baseline visit, 61% of the patients suffered from an acute flare-up of asthma. Between the baseline visit and visit 1 (two weeks), an asthma flare-up occurred in 20% of the patients. However, between visit 1 and visit 2 (two weeks) an exacerbation occurred only in 6% of the patients. At the end of the study, less than 3% of the patients had an asthma flare-up.

Pulmonary function testing

Spirometry testing at the baseline visit indicated that 79% of the patients had a ventilatory disorder. From this group, 41% of the patients suffered from moderate-to-very severe obstruction or combined ventilatory disorder. As shown in Fig. 3, the proportion of patients who achieved normal lung functions according to spirometry increased to 85% by the end of the study.

Evolution of Asthma Control Test score

The mean ACT score at the baseline visit was 16.7 (SD 3.8). During follow-up, the score increased continually to 23.8 (SD 1.7) at the final visit 4 ($p < 0.001$). At the end of the treatment period, 55% of patients achieved the highest ACT score (25) (Fig. 4).

Pharmacological asthma treatment

According to the study protocol, FSC therapy was prescribed in dosages based on the physician's clinical judgment. The mean daily dose of FCS prescribed at the baseline visit was 721 (SD 289) µg. However, as asthma control improved in the course of the treatment, the dose of FSC dropped to 672 (SD 317) µg at the final visit ($p = 0.041$). Modification of FSC dosage during the study period was not required for nearly two thirds of the patients. This implies that the majority of subjects remained guideline concordant on initial FSC daily dose with respect to the 12-week duration of the study. Other medications frequently used included oral antihistamines (44% at the baseline and 39% at the final visit 4), topical corticosteroids (10% and 12%, respectively), montelukast (6% and 10%, respectively), oral theophylline with slow release (7% and 8%, respectively), systemic corticosteroids (1.8% and 1%, respectively), and inhaled tiotropium bromide (1% and 1%, respectively).

Impact of comorbidities on treatment success rate

At the baseline visit, there was no correlation between the ACT score and the number of comorbidities ($p = 0.299$). Total asthma control at the final visit 4 was achieved by 57% and 60% of patients with no or one comorbidity, compared to 41% of patients with ≥ 2 comorbidities ($p = 0.019$).

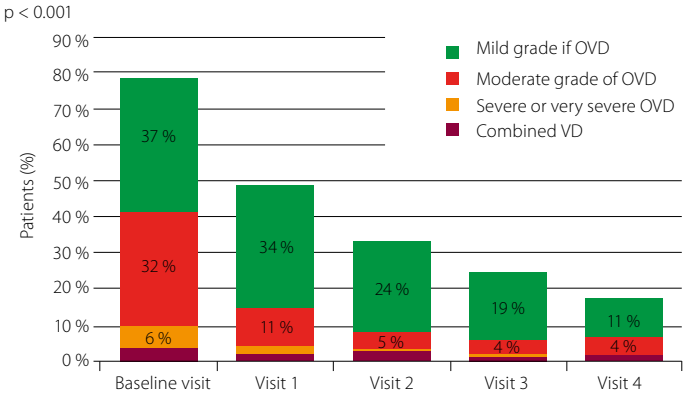
Multivariate analysis

A multivariable logistic regression was used for evaluation of the significance of the impact of various initial parameters for asthma control (according to the ACT score). Given the high number of these variables, we also carried out a subsequent logistic regression analysis. The probability of achieving a higher level of asthma control significantly decreased due to the patient's age ≥ 40 years (OR = 0.552, $p = 0.002$) and smoking (OR = 0.527, $p = 0.021$). On the contrary, achieving asthma control was more likely in patients with a documented presence of hypersensitivity to inhalation allergens (OR = 1.736, $p = 0.019$).

Discussion

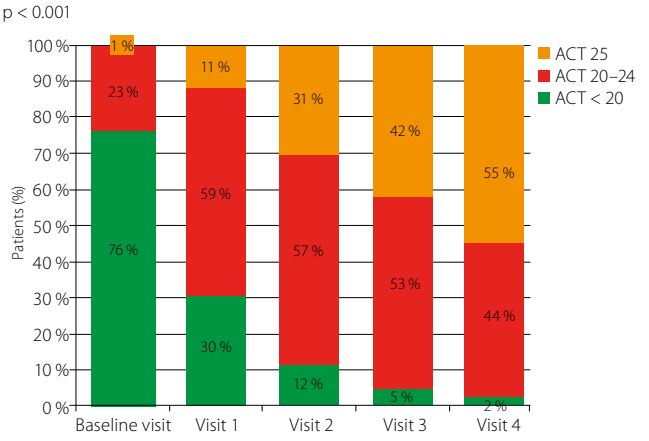
Our results demonstrated that for the majority of patients with uncontrolled asthma a guideline-defined asthma control can be achieved. Due to a common failure to reach goals in the management of asthma in routine clinical practice, we included all of the available possibilities for improving the treatment results. Guidelines based interventions rely on a choice of an appropriate antiasthmatic drug with a high therapeutic potential, in combination with education and emphasis on adherence for improvement. We showed that such interventions could lead to clinical success as early as in three months. The results of treatment became evident in all established efficacy indicators including the occurrence of day-time and night-time symptoms, limitation in activities, use of reliever medication, exacerbations, spirometry results, and ACT score. At the end of the treatment

Fig. 3. *Spirometry findings over the study period (n = 494)*



OVD = obstructive ventilatory disorder, VD = ventilatory disorder

Fig. 4. *Spirometry findings over the study period (n=494)*



ACT = Asthma Control Test (NATHAN et al., 2004)

period, we found a decrease in the proportion of patients reporting day-time symptoms from 93% to 23%, night-time symptoms from 81% to 10%, limitation in common activities from 67% to 5%, and use of rescue medication ≥ twice a week from 62% to 8%. In line with clinical success, we observed improved lung functions (an increase in the proportion of patients with normal spirometry finding from 17% to 83%) and an increase in the mean ACT score (from 16.7 to 23.8). Moreover, 55% of patients achieved the maximum ACT score. Achieving asthma control was hindered by active smoking and the age ≥ 40 years. On the contrary, patients with extrinsic asthma had a better chance for treatment success by using a fixed-dose ICS/LABA combination.

In our study, we chose a combination of pharmacological and non-pharmacological approaches in order to achieve an improvement in asthma control in outpatient population. Results of numerous long-term clinical trials confirm the potential of FSC for achieving asthma control more rapidly and with a higher probability than ICS monotherapy. The GOAL study showed early signs of treatment success during the initial dose escalation phase, where total control was achieved in 42% and a good control in 71% of patients treated with FSC. With continued long-term regular treatment, the proportion of patients with well-controlled disease increased during the open-label phase to 78% (3). Despite the differences between the designs of the GOAL trial and our real-life study, the results regarding asthma control seem to be similar. Moreover, from a clinical point of view, it is highly encouraging that it is possible to achieve well-controlled asthma in a majority of patients as early as after three months with regular treatment with ICS/LABA (12, 13). Our observations fully confirm such conclusions. At the end of the 3-month period, only 2% of patients still had uncontrolled asthma according to the ACT score. Similarly, as in randomized clinical trials, the likelihood for achieving asthma control with ICS/LABA combination was also confirmed in real-life surveys (2, 12). Recently, a prospective, non-interventional study of a fixed dose ICS/LABA combination therapy across a spectrum of community-based asthma patients in a real-life setting showed a clinically relevant improvement in asthma status (asthma control according to ACT scores, lung function, quality of life according to AQLQ scores and severe exacerbations) in a diverse population during a one-year period (14).

Additionally, regular long-term treatment evidently decreases the extent of airway hyper-responsiveness, which is reflected in a reduction in the underlying asthmatic inflammation (15). Furthermore, the stability of maintaining asthma control increases with treatment duration (12). Asthma patients treated with a control-driven approach do not usually require escalation of maintenance pharmacological treatment and their main daily ICS doses are lower than with ICS monotherapy (3, 9, 15). In our group of patients, we noticed a clear tendency towards a stepwise lowering of the ICS dose with improving the level of asthma control. On the other hand, we must acknowledge that patients with no FSC dose modification during the 3-month duration of the study (67 %) were treated in accordance with the current guidelines (3).

Poor adherence is one of the key reasons for the failure in achieving the goals of asthma management. Globally, in asthma patients, adherence is lower than in other chronic diseases, and ranges from 28% to 43% (16). The overall adherence to the asthma treatment plan can also be enhanced by regular visits to a healthcare provider (16). As shown in the prospective phase of the observational PRISMA study, regular monitoring involving outpatient visits by patients with complex management of disease, along with pharmacological therapy, made an apparent contribution to improving asthma control. During a one-year period, total asthma control (ACT score 25) was achieved in 22.2% of the patients and good control in 58.7%, which approaches the proportion of patients with an ACT score ≥ 20 in our study (17). Our study suggests that frequent visits and patient motivation to adhere to treatment significantly contributed to success in the management of asthmatic patients. An improper use of an inhaler device is one of the most frequent reasons for insufficient asthma control (18). Thus, we added training in inhaler skills and adherence to the program of scheduled visits. Other important factors found to decrease the treatment success include active smoking and the presence/number of certain relevant comorbidities (19, 20). Similar to the observational ASIT study (20), in our study smoking and concurrence of ≥ 2 comorbidities showed an adverse impact on the likelihood of achieving asthma control. Therefore, an intervention directed at smoking cessation and aggressive treatment of comorbidities should be an integral part of the care of asthma patients. Although we did not perform an analysis of the impact of particular comorbidities, we could conclude that a subgroup of patients with chronic bronchitis or COPD would have had a lower treatment success rate. This could indicate that age and smoking are universal adverse prognostic factors in a multivariate analysis. We found a re-

latively high proportion of enrolled patients with chronic bronchitis or COPD as comorbid conditions (29%). However, the two diagnoses were not confirmed by performing bronchial reversibility testing with respect to a real-life design close to everyday clinical practice and possible additional workload for participating physicians. Generally, the proportion of patients with features of both asthma and chronic bronchitis/COPD is unclear and woud have been influenced by the initial inclusion criteria used for the studies from which the data were drawn. In epidemiological studies, the reported prevalence rates for asthma-COPD overlap have ranged between 15% and 55%, with variation by gender and age, and the wide range reflects the different criteria that have been used (2). Another cross-sectional observational study using a stepwise approach according to the GINA/GOLD guidelines identified only 9.2% of COPD patients as having asthma-COPD overlap (21). It is well known that asthma/COPD overlap syndrome is associated with a more severe course of the disease, lower related quality of life, and more frequent exacerbations (22).

Our study had several limitations. These included the real-life design and absence of a control group. In addition, a three-month follow-up does not provide a sufficient possibility to monitor the maintenance of long-term asthma control and its impact on the frequency of flare-ups and other serious events as well.

Conclusion

In a majority of uncontrolled asthmatic patients, significant improvement of disease control represents an achievable goal thanks to an appropriate pharmacological strategy coupled with interventions aimed at a proper inhaler technique and adherence. Along with treatment of the underlying disease, it is important to pay close attention to comorbidities and smoking cessation.

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