ORIGINAL ARTICLE

Asthma control in adult patients treated with a combination of inhaled corticosteroids and long-acting β_2-agonists: a prospective observational study

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ABSTRACT

INTRODUCTION Asthma is a highly prevalent disease that often requires maintenance therapy. Combined inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA) inhalers are one of the available maintenance treatment options.

OBJECTIVES This prospective observational study aimed to assess asthma control in patients treated with ICS/LABA inhalers and to identify factors related to optimal asthma control.

PATIENTS AND METHODS The study included 5789 asthmatic patients from Poland, treated with one of the following ICS/LABA inhalers at clinically appropriate doses: beclomethasone/formoterol, fluticasone/salmeterol, or budesonide/formoterol. The follow-up lasted 6 months (4 visits in total). The outcomes were physician-reported and patient-reported asthma control and occurrence of adverse drug reactions. A retrospective logistic regression analysis was performed to identify a potential association between age, obesity, and smoking and the level of disease control.

RESULTS A total of 4469 patients completed the study. Throughout the study period, the rate of patient-reported control of asthma increased from 24.8% to 67.7%, while physician-reported control increased from 22.6% to 66.4%. The incidence of exacerbations decreased from 23.4% to 1.9%. Less than 0.1% of the patients reported adverse drug reactions. Age, obesity (body mass index ≥30 kg/m^2), and smoking were confirmed as factors negatively affecting disease control, with combined ICS/LABA inhalers potentially reducing their effect.

CONCLUSIONS Our results confirm the efficacy and safety of combined ICS/LABA inhalers in a real-life clinical setting. They also corroborate the finding that obesity, older age, and smoking are risk factors for poor asthma control.

INTRODUCTION Bronchial asthma is a common chronic airway disease with a complex pathophysiology consisting of chronic airway inflammation and hyperreactivity leading to paroxysmal bronchospasm. The pathophysiological mechanism of asthma is reflected in the therapeutic approaches used to manage the disease, consisting broadly of bronchodilators such as inhaled long-acting β_2-agonists (LABAs) and anti-inflammatory drugs such as inhaled corticosteroids (ICSs). While they can be administered separately, inhalers combining both medications have been a promising alternative for the past several years.[1-3]

There are strong biological, economic, and practical reasons for using combined inhalers rather than the individual components alone. First of all, a combination of LABAs and ICSs shows synergistic activity.[4] Glucocorticoids influence the β_2-adrenoceptor expression and inhibit its functional desensitization, while β_2-agonists induce

translocation of the activated glucocorticoid receptor complex to the cell nucleus, thereby increasing steroid-induced transcriptional activity.[1,2,4] This finding proves the usefulness of combining ICS and LABA treatments. There is also some compelling evidence that it is even more useful to combine these treatments in a single inhaler, as discussed below.

Economically speaking, combined ICS/LABA inhalers have been reported to be more cost-effective than other maintenance treatment options (eg, ICS therapy alone).[5,6] Patients are more likely to comply with LABA than with ICS monotherapy, but LABA monotherapy is not recommended in the current guidelines of the Global Initiative for Asthma (GINA)[1] and the US Food and Drug Administration.[7] Therefore, the use of a combined inhaler allows patients to avoid outdated treatment and to improve compliance.[8]

ICS/LABA inhalers enable the emerging single inhaler maintenance and reliever therapy (MART) model, which allows combining separate controller and reliever inhalers in a single, all-purpose device. While there is ongoing debate regarding the efficacy and safety of MART, combined ICS/LABA devices are already widely available, including Symbicort® SMART (AstraZeneca, Cambridge, United Kingdom) and Fostair® MART (Chiesi Pharmaceutici Sp.A, Parma, Italy).[1,3-5,9]

Broadly speaking, the GINA guidelines recommend asthma treatment to aim at clinical control of symptoms such as wheeze, shortness of breath, and cough. Common benchmarks used to evaluate therapy include the number of exacerbations, number of emergency admissions, reliever medication use, participation in daily life activities, lung function tests (forced expiratory volume in 1 second [FEV_1]), and adverse drug reactions.[1,10]

While disease control is usually very good in developed countries, asthma remains an important cause of morbidity and mortality, the latter largely due to exacerbations. Despite huge progress in asthma management over the last decades, satisfactory levels of asthma control are not universal.[11,12] Apart from the few truly refractory cases, failure to achieve or maintain optimal control has been attributed to inappropriate dosing or drug selection, patient noncompliance, or deficient inhaler technique.[12-15] It remains an important issue because suboptimal levels of asthma control are a risk factor for asthma exacerbations.[16-18]

The current prospective, observational study was conducted in a large population of asthmatic patients in Poland. The study objectives were to assess the level of asthma control in patients treated with 3 different combined ICS/LABA inhalers in routine clinical practice, and to identify factors affecting the lack of or suboptimal asthma control.

PATIENTS AND METHODS The study group was a subcohort of a prospective, multicenter, noninterventional, observational study conducted between January 2, 2012, and November 16, 2012, in primary care, allergy, and respiratory medicine clinics throughout Poland. The study involved 886 physicians and 11 270 patients. The 5789 patients included in the subcohort described here were adults (over 18 years of age) who had been diagnosed with asthma at least 6 months prior to inclusion and had been treated with a combined ICS/LABA inhaler for at least 1 month prior to inclusion. The subcohort was selected from the original study based on completeness of collected surveys, some of which could not be assessed. Only patients with completed surveys were included in the subcohort. Pregnant patients, those with unstable chronic comorbidities, and those deemed unlikely to cooperate were excluded from the original cohort.

Participants gave informed consent before entering the study. The choice of treatment was based on clinical need, as per the decision of the prescribing physician, in accordance with relevant guidelines and marketing authorizations. Consequently, the inclusion into the study did not affect the choice of the prescribed drugs for any of the patients. The methodology fully complied with the provisions of the European Clinical Trials Directive 2001/20/EC.[19]

Patients entering the study had been treated with 1 of 3 combined ICS/LABA formulations commercially available in Poland in 2013, namely, beclomethasone/formoterol (Fostex®, Chiesi), fluticasone/salmeterol (Seretide®, GlaxoSmithKline), or budesonide/formoterol (Symbicort®, AstraZeneca), all prescribed at a clinically appropriate dose at least 1 month before entering the study. Switching between drugs was permitted throughout the study based on the clinical decisions of the prescriber.

Patients were followed for 6 months. The follow-up consisted of 4 total visits at 2-month intervals. During the first visit, information was obtained about age, body weight, height, smoking status, and the number of exacerbations requiring emergency interventions. This information was later analyzed to identify a potential association between these parameters and suboptimal asthma control. Clinical progress was assessed using the following data collected at each visit: current pharmacological therapy, including the dosage and number of inhalations per day; occurrence and timing of exacerbations; current level of asthma control based on the GINA 2011 criteria[1]; and current FEV_1 values. According to local regulations, any adverse drug reactions were required to be immediately reported by physicians. The Asthma Control Questionnaire (ACQ)[20] was used to obtain patient-reported data. The ACQ assesses the following 7 domains on a semiquantitative 6-point scale: nighttime symptoms, symptom severity immediately upon awaking, limitation of activity, shortness of breath, wheeze, number of puffs of bronchodilator used, and FEV_1. The final score was added up and divided by 7, yielding a number between 0 and 6. Optimal patient-reported asthma control was

TABLE 1 Clinical characteristics of the study population

Descriptive variable		Value
age, y, mean (SD)		45.7 (15.4)
sex, male, n (%)		2732 (47.7)
BMI, kg/m^2, mean (SD)		26.1 (4.3)
BMI ≥30 kg/m^2, n (%)		907 (15.7)
asthma duration, y, mean (SD)		12 (9.3)
smoking status, n (%)	active	636 (11.0)
	former	1096 (18.9)
FEV_1, %, n (%)	>95	440 (10.9)
	95–90	568 (14.0)
	89–80	937 (23.2)
	79–70	890 (22.0)
	69–60	715 (17.7)
	59–50	608 (9.0)
	<50	377 (5.6)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second

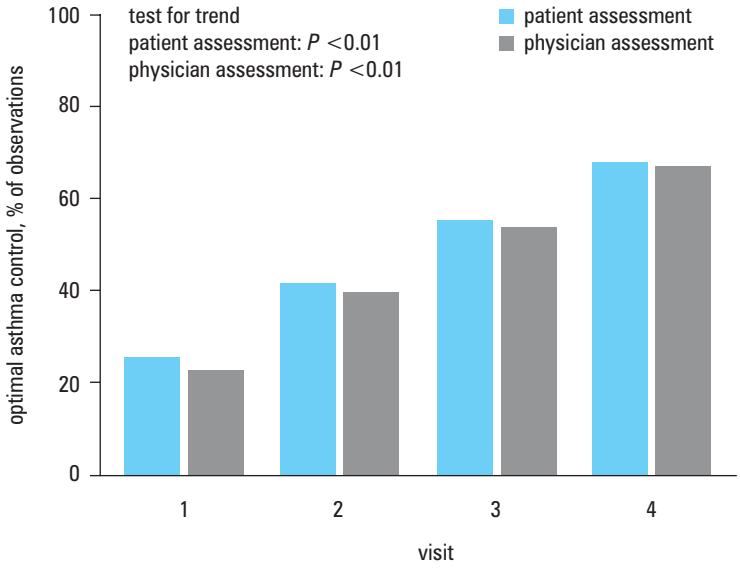

FIGURE 1 Frequency of optimal asthma control at subsequent follow-up visits. Data are presented as percentage of observations.

TABLE 2 Drug regimens prescribed in the study population at subsequent follow-up visits

Follow-up visit	Beclomethasone/ formoterol	Fluticasone/ salmeterol	Budesonide/ formoterol
visit 1	4077 (70.4)	998 (17.2)	714 (12.3)
visit 2	5122 (89.8)	355 (6.2)	228 (4.0)
visit 3	3968 (88.8)	300 (6.7)	200 (4.5)
visit 4	3994 (89.4)	282 (6.3)	193 (4.3)

Data are presented as number (percentage) of patients.

defined as an ACQ score of less than 0.75, while the physician-reported counterpart corresponded to the absence of daytime or nighttime symptoms, normal exercise tolerance, normal lung function tests, and absence of exacerbations.

Statistical analysis The Pearson χ^2 test was used to determine the statistical significance of differences between categorical variables at subsequent study visits, with a P value of less than 0.05 considered to be statistically significant. An odds ratio (OR) was calculated to visualize the concordance of patient- and physician-reported asthma control. Before this analysis, both variables were dichotomized according to the following rule: optimal vs nonoptimal asthma control.

Logistic regression analyses (univariate and multivariate) were used to evaluate the association between patient-reported asthma control (a 2-state dependent variable) and demographic and clinical factors (age, sex, obesity, current and previous smoking, duration of asthma). Obesity was defined as a body mass index (BMI) of 30 kg/m^2 or higher. Again, a P value of less than 0.05 was considered significant. Variability arising from the multicenter design of the study was accounted for in the multivariate analyses.

RESULTS Out of the 5789 patients, 4469 completed the study by attending all 4 visits. The clinical characteristics of the study population are shown in TABLE 1.

At the first visit, patient-reported asthma control (ACQ <0.75) was observed in 24.8% of the patients. This proportion gradually increased throughout the follow-up period, with asthma control noted in 41.4% at the second visit, 55.2% at the third visit, and 67.7% at the fourth visit. All differences in asthma control between visits were significant (P <0.001). Physician-reported asthma control was observed in 22.6% of the patients at the first visit, 39.5% at the second visit, 53.6% at the third visit, and 66.4% at the fourth visit (FIGURE 1). All differences were significant (P <0.001). Patient-reported and physician-reported assessments of asthma control were concordant (OR, 18.9; 95% confidence interval [CI], 16.1–22.3; P <0.001).

Asthma exacerbations were reported retrospectively by 23.4% of the patients at the first visit, by 6.2% at the second visit (2 months), by 2.8% at the third visit (4 months), and by 1.9% at the fourth visit (6 months). Differences between subsequent visits were significant (P <0.0001). Less than 0.1% of the patients reported adverse drug reactions (burning sensation in the mouth and throat and sporadic coughing fits).

The drug administered to each individual patient was not necessarily the same throughout the study period. A detailed breakdown of prescribed ICS/LABA inhalers throughout the study period is presented in TABLE 2.

The univariate logistic regression analysis revealed that older age, obesity, and smoking were positively correlated with a lower probability of optimal asthma control at the first visit (FIGURE 2). These results were confirmed by the multivariate logistic regression analysis (TABLE 3), in which, independent of the ICS/LABA formulation, older age yielded an OR for patient-reported asthma control of 0.979 per year of age added. For obese

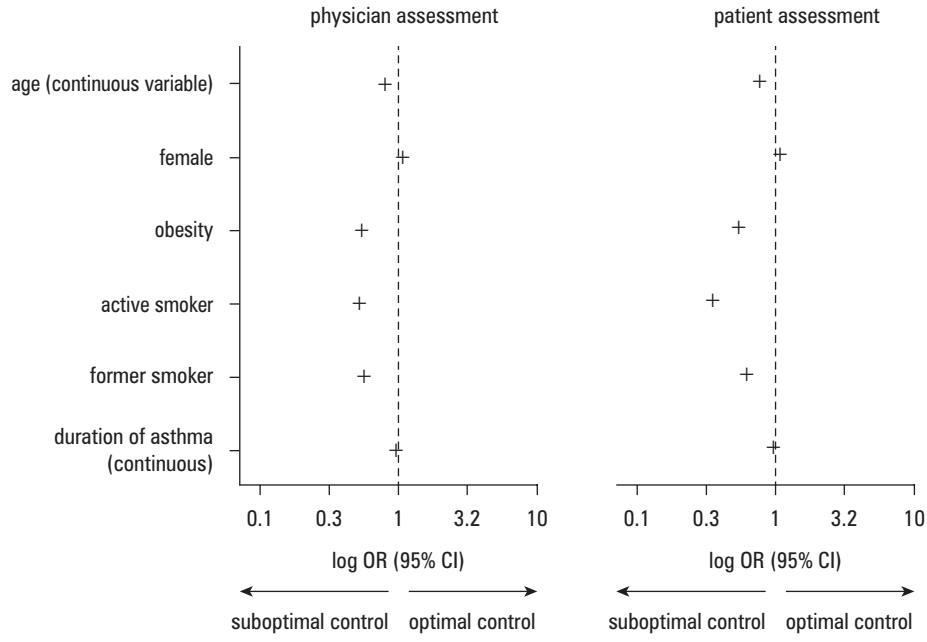

FIGURE 2 Analysis of the relationship between optimal asthma control reported by physicians (absence of asthma symptoms during the day and at night, no limitations in physical activity, no functional pulmonary disorders, no asthma exacerbations) and patients (Asthma Control Questionnaire score <0.75), and the group of independent variables in a logistic regression model; data presented as odds ratio (OR) and 95% confidence interval (CI) in a logarithmic scale

TABLE 3 Interactions between factors affecting the likelihood of achieving optimal asthma control and the type of control drug in the logistic regression model

Effect of risk factors		Risk factors of suboptimal asthma control		
		age (continuous variable)	obesity	smoking
		OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)
depending on the formulation used (interactions)	beclomethasone/formoterol (n = 4090)	1.003 (1.001–1.006)	0.568 (0.436–0.739)	0.363 (0.245–0.538)
	fluticasone/salmeterol (n = 998)	0.988 (0.984–0.993)	0.598 (0.363–0.983)	0.255 (0.129–0.506)
	budesonide/formoterol (n = 714)	0.984 (0.978–0.990)	0.351 (0.168–0.733)	0.754 (0.376–1.514)
irrespective of the formulation used		0.979 (0.974–0.984)	0.521 (0.415–0.655)	0.358 0.263–0.488)

a dependent variable: optimal asthma control defined as the Asthma Control Questionnaire score of less than 0.75.

Abbreviations: CI, confidence interval; OR, odds ratio

individuals (BMI ≥30 kg/m^2), the OR was 0.521 compared with nonobese individuals, while smokers had an OR of 0.358 compared with nonsmokers. Factors affecting the likelihood of achieving optimal asthma control were similar irrespective of the ICS/LABA formulation. The only exception was the effect of age on achieving asthma control in patients treated with beclomethasone/formoterol; an OR of 1.003 indicated a better chance of controlling asthma with advanced age (TABLE 3).

DISCUSSION

Participants in this study were deemed to be a representative sample of asthmatic patients in Poland with a well-established diagnosis. The cohort demonstrated varying degrees of asthma control at baseline, with less than a quarter of the cohort showing patient-reported and physician-reported asthma control. Provided that these patients had been diagnosed with asthma at least 6 months prior to the study, these levels of control should be regarded as poor. Similar values are seen in different geographic regions generally inadequate asthma control. An epidemiological study of 3079 adult asthma patients from New England, United States, reported well-controlled asthma only in 30% of study participants.[12] While these data may not be representative of general asthma control levels in Poland, they provided an excellent background for a meaningful observational study.

ICS/LABA therapy was shown to progressively improve asthma control in our study group. By the last visit, 67.7% of patients achieved ACQ-defined asthma control, and 66.4% had optimal physician-reported control. The current study thus supports the concept that ICS/LABA therapy, combined with systematic clinical care, regular doctor office visits, and education in terms of proper inhalation technique, leads to improvement in asthma control both in terms of subjective and objective measures of disease activity.

Our results are in line with the observations of Kuna et al,[21] who demonstrated a long-lasting efficacy of a fixed-dose combination of beclomethasone and formoterol in the control of uncontrolled asthma in a real-life setting. The study included as many as 16 000 patients with asthma. Its findings were discussed in an editorial article by Jassem and Niedoszytko,[22] who emphasized that among several factors determining appropriate asthma control also the patient's

preference in the choice of an inhaler should be taken into account.

In our study, it was allowed to change the administered drugs from visit to visit; therefore, a systematic comparison of the 3 ICS/LABA inhalers was not undertaken. Nevertheless, the proportion of patients taking beclomethasone/formoterol increased from 70.4% at the first visit to 89.4% at 6 months.

Both beclomethasone and formoterol are well-established, efficient, and safe therapeutics, considered to be reference drugs in their respective classes. Using them in a single inhaler should logically provide at least all of their individual benefits. As discussed earlier, the biological synergy and improved compliance when using an ICS/LABA combination should further enhance clinical results.

According to O'Byrne and Jaeschke,[23] the dramatic improvement in asthma treatment has been due to the increased use of ICSs. The authors underlined that an ICS together with a LABA in the same device allows a good management of the vast majority of patients. They also pointed out that these drugs should be used regularly also when patients feel good. It was the case with our patients.

The beclomethasone/formoterol combination used in this study is characterized by an idiosyncratic feature that sets it apart from the other inhalers. The Modulite® technology (Chiesi Pharmaceutuci Sp.A, Parma, Italy) used in its production process yields a hydroxyfluoroalkane (HFA)-propelled pressurized metered-dose inhaler (pMDI) formulation characterized by extrafine particle sizes. Clinical evidence, including the results of a phase III clinical trial, demonstrated noninferiority in terms of the safety and efficacy of a combined Modulite® HFA beclomethasone/formoterol pMDI compared with other single ICS/LABA inhaler combinations.[24,25] The Modulite® HFA beclomethasone/formoterol pMDI offered rapid onset of bronchodilation due to the presence of formoterol,[26] opening up the possibility for its use as part of the MART strategy, likely as budesonide/formoterol (SMART strategy). Finally, theoretically, inhaler technique may be of lesser significance if an extrafine inhaler is used, as the drug may potentially be effectively delivered without high inspiratory flow rates. However, this hypothesis remains to be confirmed by experimental data.[27,28]

The primary outcome of the previously mentioned phase III trial was postdose morning peak expiratory flow.[24,25] However, objective lung function parameters are thought not to reflect small airway function.[28-30] The nature and severity of symptoms reported by patients offer much more clinical information than the usual ventilatory parameters. Symptomatic differences between patients with similar respiratory test results can be attributed to differences in airflow as well as inflammation in the small bronchi and associated air trapping. These changes in the small airways translate into poorer asthma control.[31] Therefore, the administration of a drug offering better penetration of the bronchial tree and enhanced pulmonary deposition could lead to symptomatic improvement without necessarily affecting objective parameters. Since the goal of this noninterventional study was to corroborate the efficacy of combined ICS/LABA inhalers in general, the study design did not allow for a formal assessment of the superiority of any of the preparations investigated. As argued before, however, the visit-to-visit increase in the use of Modulite® HFA beclomethasone/formoterol pMDI relative to the other studied formulations in itself constitutes evidence for its clinical usefulness, although circumstantial.

The current study confirms that obesity, smoking, and advanced age as important risk factors for poor asthma control. Nevertheless, the preparations investigated demonstrated some potential to offset the detrimental effects of these risk factors. Age was the only one of these factors to be beneficially affected by all the formulations. However, these results should be interpreted with caution. Firstly, the CIs for ORs for obesity and smoking are very wide and demonstrate significant overlap with the baseline OR CIs, limiting the potential validity of the resulting conclusions. Secondly, age was analyzed as a continuous variable, with ORs being calculated "per year". This implies that the potential to offset the increased risk of poor asthma control with increasing age (ie, the risk associated with being 1 year older) does not change with age itself, which needs not be the case. Suboptimal treatment outcomes in patients with risk factors for poor asthma control have been suggested to be associated with insufficient drug deposition in the small airways.[32,33] It is important because the small airways seem to be particularly affected both in smoking and obese asthmatics. Apart from the disturbances in ventilatory function of the lungs in this group of patients, the tendency of the small airways to closure has been also emphasized. It could explain the greater efficacy of extrafine particle ICS formulations with high deposition rate in the peripheral airways in achievement and maintenance of asthma control compared with other formulations.[34,35] Nevertheless, some authors question that or go even further arguing for the absence of a correlation between smoking and the efficacy of combined ICS/LABA treatment.[36]

The study limitations are those inherent in the design of observational studies, namely, selection bias, potential confounding factors, and the lack of randomization. Hence, the reported efficacy of ICS/LABA inhalers could not be compared with a control group (eg, patients not using combined ICS/LABA inhalers). Due to the lack of randomization, the demographic and clinical characteristics of this group could have been markedly different. For similar reasons and some others already mentioned above, a formal comparison between the different preparations was not undertaken. Finally, the limitations of the risk factors have been

discussed above. Observational studies based on a less strict protocol than that required for randomized controlled trials, but otherwise well designed, prospective, and with adequate sample size provide reliable results. Therefore, our results can be complementary to randomized clinical trials concerning asthma management.

The evidence discussed supports combined ICS/LABA therapy as a worthwhile treatment option. It has not only been formally confirmed through randomized clinical trials and other studies (including this one), but also confers practical advantages for the patient. The use of a single inhaler improves compliance, which is essential in the treatment of asthma. It also reduces the risk of selective noncompliance with long-term steroid therapy.[1,9,26,33] Basic scientific evidence supports the use of combined therapy by demonstrating synergy at the molecular level.[6,37] Combined ICS/LABA inhalers offer a well-tolerated and effective maintenance therapy considered to be a gold standard for treating advanced asthma. Combined ICS/LABA inhalers with extrafine particles offer favorable small airway penetration, which is a particularly good therapeutic option in obese and smoking asthmatics.[38]

In conclusion, combined ICS/LABA therapy significantly improves both subjective and objective clinical measures of asthma while maintaining an excellent safety profile. The increase in use of the HFA-beclomethasone/formoterol preparation during the study may suggest that it is an attractive therapeutic option in asthma management.

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Contribution statement BR contributed to the design and global supervision of the study, data analysis, and the writing of the manuscript. PM gathered and discussed the data, performed statistical analysis, and made tables and graphs. JG contributed to data analysis and interpretation and critically revised the manuscript. TD contributed to the concept and design of the study, discussed the data, and wrote the manuscript.

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