DOES THE FREQUENCY OF SWITCHING INHALERS REPRESENT A PREDICTIVE FACTOR OF EXACERBATION IN ASTHMA?

Principe Stefania[1], Battaglia Salvatore[1], Arena Cinzia[1], Benfante Alida[1], Scichilone Nicola[1]

[1]Dep. Dipartimento Universitario di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), Division of Respiratory Medicine, "Paolo Giaccone" University Hospital, University of Palermo; Palermo; Italy

Corresponding author:

Nicola Scichilone, University of Palermo, Piazza delle Cliniche 2, Palermo, Italy. Phone: +39-091-6552146; e-mail: nicola.scichilone@unipa.it

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ABSTRACT

Objective: Management of asthma aims to control symptoms and reduce the risk of exacerbations. This includes monitoring of inhaler technique and level of adherence to treatment. Both factors could be influenced by high frequency of switching inhaler devices. We explored whether switching inhalers is an independent predictive factor of exacerbations.

Methods: Data were collected from 2015 to 2017 from the outpatient clinic of asthma at the University of Palermo, Italy. This observational study consisted of 2 phases: Phase 1, included subjects of at least three visits in the previous year who reported the frequency of inhalers switched; Phase 2 included subjects of at least two visits during the second year and the rate of switches and exacerbations was recorded. We included adult (24 to 84 years old) mild/moderate asthmatics under regular inhaled treatment; uncontrolled asthma was defined as poor symptom control, exacerbations (≥2/year) requiring oral corticosteroids (OCS), or serious exacerbations (≥1/year) requiring hospitalization.

Results: A total of 109 records were retrieved for the analysis. A significant correlation between the rate of switches in Phase 1 and exacerbations in the Phase 2 was found ($p=0.001$). Age and the rates of exacerbations in Phase 1 were also independently associated with a higher number of exacerbations in Phase 2 ($p<0.0001$). The multivariate regression model showed that the numbers of switches, as well as exacerbations in Phase 1, were independently correlated to the number of exacerbations in Phase 2 ($p=0.003$).

Conclusions: The higher frequency of switching inhalers independently affects the risk of exacerbations in asthma. These results imply that changing inhaler requires careful management in daily clinical practice.

Keywords: Asthma, switch, inhaler, device, exacerbation

INTRODUCTION

Asthma is a chronic disease that can affect people of all ages. Its prevalence is increasing worldwide, thus becoming a serious global health problem (1). Although some countries have experienced a decline in hospitalizations and deaths from asthma, the lack of symptom control remains a challenge for physicians (2). The severity of clinical symptoms, such as wheeze, cough, shortness of breath and chest tightness, is related to the severity of bronchial obstruction, perceived differently between individuals and in relation to different phases of the disease, fluctuating between periods of worsening or acute exacerbations and stable conditions (3).

Management of asthma should include the assessment of symptom control and future risk of adverse outcomes, as well as proper evaluations of factors affecting asthma control, such as incorrect inhaler technique and poor adherence (4), and comorbidities that could contribute to symptom burden and worsening of quality of life. Before making changes to patients' therapy, their inhaler technique and adherence to treatment should be checked regularly (5). Treatment compliance is fundamental for optimal control of the disease; the underuse of long-term asthma therapy causes an increase in exacerbation and worsening towards the most severe stages of the disease (6). This is the reason why the pharmaceutical industry is engaged in promoting new and easier devices to facilitate administration of the drug, implement adherence to treatment and minimize collateral effects. Inhaled therapy is based on different devices such as Metered Dose Inhaler (MDI), Dry Powder Inhaler (DPI) and Soft Mist Inhaler (SMI ™ Respimat ®). Although technological progresses have dramatically decreased the risk of critical errors when using the device, the *ideal* inhaler is still far from reality (7). Techniques needed for MDI and DPI administrations are different: to activate the MDI, the patient presses down on the top of the canister, during a deep inspiration, and

releases a single metered dose of the medication, which contains the medication either dissolved or suspended in the propellant. On the contrary, DPI delivers medication to the lungs in the form of a dry powder; in this case, the medication needs to be loaded or activated inside the inhaler and the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation. MDIs have high rates of incorrect handling (7–71%), because of patient-device coordination (8–10). DPIs require minimal patient-device co-ordination but are usually flow-dependent (11,12). Therefore, apart from choosing the best inhaler for a specific patient, effort should be made to minimize the occurrence of handling mistakes and avoid doctor and/or patients' wrong behaviors. Moreover, to our knowledge multiple inhalers and mixed prescriptions may lead to prolonged errors and have a negative impact on asthma outcome (13–15). Taken together, switching the device may add confusion to the patient, thus affecting correct inhalation technique and adherence to treatment. On this basis, we speculate that switching inhaled therapies negatively influences the control of the disease by lowering the level of adherence to treatment. Our hypothesis is therefore that, in a real-life setting, the frequency of switching among inhaler devices is associated with the rate of exacerbations, thus representing a predictive factor of asthma instability. The current investigation aims to investigate whether the number of switches (i.e. changes) of devices for inhaled therapy is an independent factor influencing exacerbation rate in asthmatic patients. Moreover, the study investigated other potential factors influencing the frequency of exacerbations.

MATERIALS AND METHODS

Design

During Phase 1, the following parameters were evaluated: age, sex, smoking history, comorbidities (rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression, and anxiety), lung function measurements (FEV_1), the inhaler device used (DPI or MDI), the number of switches of inhaler devices, and the number of exacerbations. In Phase 2, the rates of switches and exacerbations were also recorded. The study design is showed in Figure 1. Exacerbation was defined as an acute or sub-acute worsening in symptoms from the patients' usual status that required an increase of reliever medications (SABA 4 times/day for 3 consecutive days) and/or the use of short courses of oral corticosteroids (OCS) for at least 3 consecutive days as reported by the patient. We focused on DPI and MDI only since they incorporate the majority of patients (16). We assumed that switching devices was carried out only after a step-up or step-down approach, meaning modifying dosage and/or compound, was conducted.

Data collection

This is a retrospective study. Data were collected from records available from 2015 to 2017 at the outpatient clinic of asthma, Division of Pulmonology, University Hospital of Palermo, Italy. The clinical charts of adult asthmatic patients visited in the year 2016 were also checked for potential inclusion. To be retained for the analysis, subjects had to have an ascertain diagnosis of mild to moderate asthma according to the GINA document (17). To comply with the aim of the study, we arbitrarily decided that enrolled patients should have attended the clinic at least 3 times in one year (Phase 1), in order to detect potential switches of device. To be included in the study, subjects also had to have attended the clinic at least twice in the following year (Phase 2), in order to investigate the rate of exacerbations. We

defined “switch” of device the occurrence of changes in the type of device prescribed as registered in the clinical chart of each patient (i.e. MDI vs DPI or *vice versa*). Regular use of inhaled therapy and lung function examinations were mandatory for the inclusion in the study. Subject who did not comply with the inclusion criteria were excluded from the analysis.

Statistical analysis

The statistical analysis was performed using R Programme (18). Data are reported as mean and standard deviation (SD) or median and range, depending on whether they were normally distributed. Differences in means between two groups were analyzed using the Student’s t-test or the Mann Whitney U test, as appropriate. Differences in means among groups were analyzed using the Kruskal-Wallis rank-sum test, with the appropriate post hoc test. Differences in proportions were analyzed using the chi-squared. Spearman's rank correlation coefficient was used to assess the linear correlation between the explored variables.

A linear multiple regression model was used to assess factors affecting exacerbations during the second year (dependent variable). The stepwise regression was used to select the best-fitting model. Variables correlated with the dependent variable in the univariate analysis were entered in the model as independent variables. The model was corrected for gender and the model was tested for assumptions. To better describe the effect of switching therapies, the sample was subdivided into non-switchers (i.e. no switch in therapy in Phase 1) and switcher (i.e. one or two switches in therapy in Phase 1). Data reported had a confidence level of 95%. Differences at probability values of $p<0.05$ were considered to be significant.

RESULTS

A total of 1324 clinical charts were checked, and data from 109 asthmatic patients fulfilled the inclusion criteria for the investigation. Reasons for exclusion were lack of clinical or functional information, or less than the required visits (at least 3 in Phase 1 and 2 in Phase 2). The most frequent missing variables were FEV_1% predicted, the recorded number of exacerbations and the type of device used. Table 1 shows the main demographic and clinical information of the study group. At baseline, 57 patients used a DPI and 49 an MDI, while at the last visit 60 patients used a DPI and 46 an MDI. During Phase 1, 38 subjects (35% of the study population) changed their current device (16 subjects from DPI to MDI, and 22 subjects from MDI to DPI): 31 subjects once, 7 subjects twice. A total of 54 patients experienced at least one exacerbation during Phase 1: mean 0.94±1.30, range 0 to 6 exacerbations in the whole sample. During Phase 2, 45 subjects had at least one exacerbation: mean 0.72 ±1.19 exacerbations, ranging from 0 to 7 in the whole sample. 55 patients had no exacerbation in the first year, 64 patients had no exacerbation in the second year.

Both in Phase 1 and 2, the number of exacerbations was higher in patients with higher number of switches as illustrated in Figure 2 and 3, respectively. In details, in Phase 1 the mean number of exacerbations was 0.77±1.2, 0.94±1.26, and 2.57± 1.51 in patients with 0, 1 and 2 switches, respectively (p=0.003). In Phase 2, the mean number of exacerbations was 0.52±0.79, 0.58± 0.89 and 3.29± 2.43 in patients with 0, 1 and 2 switches, respectively (p=0.001).

Both age and the number of exacerbations in Phase 1 positively correlated with the number of exacerbations of Phase 2 (rho 0.24; p=0.01 and rho 0.45; p<0.0001, respectively). None of the explored comorbidities was shown to influence the occurrence of exacerbation in Phase 2.

Moreover, switchers and non-switchers showed different correlation slopes between the exacerbations during Phase 1 and the number of exacerbations during Phase 2 (Figure 4), with the slope of switcher (patients with 1 or 2 switches) being steeper compared with that of non-switcher. On the contrary, the number of exacerbations during Phase 2 was not correlated with lung function (FEV_1% pred. or FEV_1/FVC ratio), or with the initial dose of ICS in Phase 1. Similarly, the number of exacerbations during Phase 2 did not differ by the type of device, or by the type of ICS used in Phase 1.

The multivariate regression model confirmed that the number of switches and the number of exacerbations during Phase 1 were independent correlates of the number of exacerbations during Phase 2 (model details in Table 2). On the contrary, age, sex, FEV_1 % pred, the type of device and the ICS used in Phase 1 were not independent correlates.

DISCUSSION

The current study was designed to test the hypothesis that the frequency of switching inhaler devices is an independent risk factor for exacerbations in asthma. To the aim of the study, we enrolled mild to moderate adult asthmatics regularly attending the outpatient clinic of asthma and having multiple visits during the evaluation period, according to the inclusion criteria. Findings supported our hypothesis and, as expected, the rate of exacerbations was also shown to influence the future risk of exacerbations. A possible explanation of changing devices in asthmatics is related to the improper inhalation technique; indeed, most patients with asthma still do not manage the device properly. It has been reported that 4–94% of patients make errors during inhalation (19). Luczak-Wozniak et al (20) in a prospective cohort study including asthmatic patients pointed out the importance of ongoing training for patients treated with regular inhalers, because the mishandling in the inhalation technique is, in the majority of cases, repetitive and very common. Furthermore, a qualitative interview aimed to assess asthma inhalers characteristics and patients expectations, the PASAPQ scores (patient satisfaction and preference questionnaires) indicated that all patients were at least "somewhat satisfied" with their inhalers, regardless of technique, but only the 12% of patients used a correct inhaler technique; therefore, the satisfaction, perception of inhaler devices, or choice in device selection are not related to a correct use of devices. Patients with correct inhaler technique were more aware of their asthma and expressed motivation to achieve optimal asthma control (21).

We cannot exclude that some of the switches that occurred in Phase 1 aimed to improve the disease control in asthmatics with uncontrolled respiratory symptoms. Therefore, patients who had switches during the Phase 1 could theoretically represent a more severe population of asthmatics, prone to more exacerbations in the future. Switching in that case would be a

marker of more difficult to control asthma rather than a specific cause.

Moreover, an increase in inhaler changes reduces drug intake and lung deposition (22), provoking a worsening of disease control (9). Therefore, it is plausible to assume that a higher number of switching inhalers influences asthma instability. This is also supported by observations from several studies showing that asthmatic patients with proper self-management behavior or constantly using the same inhaler device are characterized by fewer symptoms and a better level of disease control (23–26).

Interestingly, the demonstration that age was associated to a higher number of exacerbations during the second year of follow-up confirms what has been already reported in previous studies (27). Wieshammer et al (28), demonstrated that the error rate of the inhalation technique using DPI, in patients previously trained by physicians, increased with age and with the severity of airway obstruction. Although often considered a disease of young ages, asthma prevalence in older populations does not differ from that of younger populations (29). The importance of recognizing asthma as a disease that also occurs in older populations is justified by the fact that the mortality rate is higher in these subjects (30). In addition, Molimard et al (10) and Battaglia et al. (31) showed that clinical trials include selected populations that are not representative of the real-life population in clinical settings. Elderly patients should be asked to show their inhalational technique at each visit, and the possibility to change the device should be strictly monitored during follow-up training. The introduction of a large-volume spacer might be a valuable treatment alternative (32) that can reduce the number of switches and consequently the risk of future exacerbations. The collaboration between general practitioners (GPs) and pulmonologists may also help to improve the management of asthmatics (33).

This study has some limitations, mainly related to the retrospective nature of the investigation with difficulties in retrieving clinical information. We lack information on the level of adherence and on the reasons for the inhaler switches, as well as on the level of asthma control at the time of the visit. Larger and multicenter studies are therefore advocated to confirm the current findings. On the other hand, the strength of the current study is that objective measures to explore the relationships between the tested variables and the outcomes were employed. In addition, the study population may be considered representative of a real-life outpatient setting and the model is representative of a long-term follow-up, which is fundamental for obtaining correct disease management and asthma re-assessment. In this scenario, educational interventions are mandatory in order to optimize the inhaler use for each patient, to improve the inhaler techniques and to increase the adherence to inhaled treatment, since the incorrect use could negatively affect the asthma outcomes, thus increasing the risk of future exacerbations. Since additional confusion may result from using different inhaler devices, clinicians should be encouraged to prescribe the same device for both controller and reliever medications.

In conclusion, this investigation demonstrates that the higher frequency of inhaler switches in mild and moderate asthmatics affects the risk of exacerbations independent of factors such as age or asthma instability, or changing in dose medications. Based on these findings, the change of the type of inhaler should be limited to the inevitable cases, and efforts should be made in clinical practice to limit the switching of inhalers to avoid the risk of future exacerbations.

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TABLES:

Table 1: Baseline characteristics of the study sample at Phase 1. Data are expressed in number of patients, mean ± standard deviation or median and range for non-normal distributions. DPI: Dry Powder Inhaler; MDI: Metered Dose Inhaler.

	Switchers (n=38)	**Non Switchers (n=71)**
Age (n=109)	57.9±14.4	56.52 ±15.7
Sex (M/F)	27/11	50/21
Smoking History: (Never smokers/Ex smokers/Smokers)	21/3/14	47/7/17
Initial device: (DPI/MDI/others)	17/18/3	43/28/0
FEV1 (l)	2.30 ± 0.94	2.2 ± 0.45
FEV1 (%pred)	92.57 ± 20.83	88.12 ± 23.72
FEV1/FVC	72.35 ± 9.72	71.15 ± 10.23
Exacerbations Phase 1	1.24 ± 1.44	0.77 ± 1.19

Table 2: Factors affecting exacerbations in Phase 2 (stepwise regression). Adjust. R^2 for the final model: 0.386.

	Estimate (B)	**Std. Error B**	**95% C.I.**	**P value**
Constant	0.279	0.116	0.049 to 0.509	0.018
Exacerbations Phase 1	0.330	0.076	0.178 to 0.481	<0.001
Switches	2.064	0.438	1.195 to 2.934	<0.001

FIGURE LEGEND:

Fig. 1: Study design.

Fig. 2: Number of exacerbations during the first year stratified by numbers of switches. Boxes represent median and the 25th and 75th percentiles.

Fig. 3: Number of exacerbations during the second year stratified by numbers of switches. Boxes represent median and the 25th and 75th percentiles.

Fig. 4: Correlation between the number of exacerbations during Phase 1 and the number of exacerbations during Phase 2 in patients that switched and non-switched inhalers: switch "no" = zero switch; "yes" = 1 or 2 switches during the first year. Data are graphical presented using jitter points to avoid overplotting. The switchers show steeper slope: in non-switcher y = 0.310 + 0.272*x; in switcher y = 0.302 + 0.628*x.