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Evaluation of the preference, satisfaction and correct use of Breezhaler® and Respimat® inhalers in patients with chronic obstructive pulmonary disease – INHALATOR study

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ABSTRACT

The INHALATOR study was a randomized, multicentre, open label, two-period of 7 days each, crossover study, with 7 days of washout in-between, aiming to evaluate the correct use, satisfaction and preference between Breezhaler® and Respimat® devices in patients under daily use of open Spiriva® or open Onbrize®, as monotherapy for treatment of mild or moderate COPD. Patients aged ≥40 years with a smoking history of at least 10 pack-year were included in the study. Primary endpoint was the rate of correct use of each device at the first day of treatment after reading the drug leaflet information and was evaluated under the supervision of a trained evaluator. At the end of each treatment phase, the inhaler use was re-evaluated and a satisfaction questionnaire was completed. The patients' preference for the inhaler devices was assessed at the end of the study. After exclusions due to screening failures, 140 patients were randomized: 136 received at least one dose of Breezhaler® and 135 of Respimat®. At treatment start, the rate of correct inhaler use was 40.4% (95%CI: 32.2%–48.7%) for Breezhaler® and 36.3% (95%CI: 28.2%–44.4%) for Respimat® ($p = 0.451$). After 7 days, the rates were 68.9% (95%CI: 61.1%–76.7%) and 60.4% (95%CI: 52.2%–68.7%), respectively ($p = 0.077$). According to the Feeling of Satisfaction with Inhaler Questionnaire - FSI 10 patients were more satisfied using Breezhaler® than Respimat® and 57.1% preferred using Breezhaler® ($p = 0.001$) while 30.1% preferred Respimat® ($p < 0.001$).

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by the persistence of respiratory symptoms and airflow limitation, which causes a progressive deterioration of the lung function over time [1,2]. Continuous exposure to toxic particles or gases, especially cigarette smoking, is the triggering factor for a pulmonary inflammatory response. It is known that COPD is not confined to the lungs and is currently considered a systemic disease, with important implications, namely in the cardiovascular system, metabolic diseases, skeletal muscle, cachexia and psychiatric disorders, especially depression and anxiety [3,4].

Nowadays, comorbidity control is a mandatory part of proper COPD management, as it is essential to improve patients' quality of life and to reduce exacerbations and hospitalizations. The 2017 recommendations of Global Initiative for Chronic Lung Disease (GOLD) focus on attaining an individualized assessment of symptoms and future risk of exacerbations, which are not limited to pharmacologic treatments, and should be complemented by appropriate non-pharmacologic interventions, such as encouraging and supporting smokers to quit and patient

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education [2]. The short-acting drugs are indicated for short-term relief or as rescue medication, while the long-acting bronchodilators remain the basis for the daily management of the disease. Clinical studies revealed that the continuous treatment with long-acting bronchodilators are more suitable for the treatment of any stage of COPD, relieves symptoms and reduces exacerbations in patients with COPD [5].

The long-acting bronchodilators are divided into two therapeutic classes: long-acting β_2-antagonists (LABAs) and long-acting muscarinic antagonists (LAMAs). Several clinical trials evidenced the efficacy and safety of combining both therapeutic classes, as well as their association with an improved patients' quality of life, a decreased loss of the lung function over time and a likely decrease in mortality [5]. There are several bronchodilator inhaler devices available for treatment of patients with COPD, such as, pressurised metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), soft mist inhalers and nebulisers. Nevertheless, all inhaler devices have advantages and disadvantages, which emphasises the therapeutic challenges of COPD treatment [1]. Besides the pharmacological and physical properties of the drug formulation, the success of a therapeutic effect is strongly dependent on the patients' preference and correct use/handling of the inhaler device, which in turn are the two most important factors denoted in GOLD 2017 guidelines [2,6]. The incorrect usage of inhalation devices is very common, and depends on the type of device, patients' ability to use and their adequate training [7]. Thus, the selection of the appropriate inhaler for each patient should consider patients' willingness and ability to use [8], as these factors may promote their better adherence to treatment, satisfaction and improvement of quality of life [9].

Onbrize™ via Breezhaler® is an ultra-LABA indicated for the treatment of COPD, *i.e.* it constitutes an advance of the current available LABAs that allows a single daily dose [10]. This inhaler device is available as capsules with dry powder containing the active substance indacaterol maleate. Besides being long-acting, indacaterol has a rapid onset of action, promoting rapid and sustained bronchodilation, fundamental in relieving dyspnea, the primary symptom that afflicts COPD patients. Spiriva® via Respimat® inhaler device was used as the comparator in this study, as it has been the patients' preference in several studies [1,7,11], and both inhalers contain long-acting bronchodilators and are used once a day. In addition, they were the two available long-acting bronchodilators in Brazil at the time of study design. Tiotropium is the active substance of this inhaler device, which uses the mechanical energy from the spring to generate a fine slow-moving mist from an aqueous solution. In addition, both inhaler devices were recognized as safe, effective and well tolerated [12].

The aim of this study was to evaluate the correct use of Breezhaler® device compared to Respimat® device and to evaluate the patients' preference and satisfaction between these two devices.

2. Methods

2.1. Patients and research centers

The study population included ambulatory cooperative patients of both genders, aged 40 years or older, with smoking history of at least 10 pack-years, with confirmed COPD diagnosis, or assessed in a pre-screening period through simple spirometry with COPD-6™ device when not documented in medical records, and indication of inhaled bronchodilators for COPD treatment. COPD diagnosis were considered with classifications of mild or moderate according to GOLD 2010 or grades A or B according to GOLD 2011, and also when the patients presented FEV1/FVC < 0.70 or 70% post-BD and FEV1 post-bronchodilator > 50% of post-BD predicted normal value.

Key exclusion criteria included, history of asthma or symptoms suggestive of asthma prior to the age of 40, episode of upper respiratory tract infection within the previous 6 weeks and hospitalization or emergency care attendance due to COPD exacerbation in the past 3 months. Patients with history of cardiovascular disease and with prior use of Spiriva® via Respimat® or Onbrize™ via Breezhaler® or any other inhaled drug with similar devices [as but not limited to: Aerolizer® (Foradil®), Aerocaps® (Alenia®), Mantecorp inhaler used to administer the medication Fluir®, Libbs inhaler used to administer the medication Formare®], or participation in any other clinical study with inhaled medications with the mentioned devices or similar ones were also excluded.

The study took place between 18th of April 2013 (*first-patient first-visit*) and 9th of November 2015 (*last-patient last-visit*) and included the participation of the following Brazilian research centers: 3 in the State of São Paulo, 2 in Rio Grande do Sul, 2 in Minas Gerais, 1 in Rio de Janeiro, 1 in Santa Catarina, and 1 in Goiás.

2.2. Ethical approval

This study was approved by the applicable ethics committees: Comitê de Ética em Pesquisa do IAMSPE, Comitê de Ética em Pesquisa com Seres Humanos – CEP/UFSC, Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto, Comitê de Ética em Pesquisa da PUCRS, Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Comitê de Ética em Pesquisa da Irmandade da Santa Casa de Misericórdia de Porto Alegre, Comitê de Ética: Comitê de Ética em Pesquisa em Seres Humanos da Irmandade Santa Casa de Misericórdia de São Paulo, Comitê de Ética em Pesquisa em Seres Humanos Hospital das Clínicas da Universidade Federal de Goiás, Comitê de Ética em Pesquisa – COEP e Comitê de Ética em Pesquisa do Hospital Universitário São José. Moreover, the study was performed in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles of the Declaration of Helsinki. Patients had signed an informed consent (IC) form before the pre-screening period and before the study period.

2.3. Study design and treatment

INHALATOR study was a randomized, national, multicenter, open label, two-period crossover study of 7 days each, with 7 days of washout in-between, as per Fig. 1 (ClinicalTrials.gov identifier: NCT01727024).

The study included a pre-screening period (up to 10 days before visit 1) for patients without previous diagnosis of COPD, during which eligibility was assessed. The patients were consecutively enrolled in the sites during their routine visits. The patients who attended the eligibility criteria and signed the IC were randomized to one of the two treatments sequence in two periods: indacaterol (Onbrize™ 150 mcg) via Breezhaler® once daily or tiotropium (Spiriva®2.5mcg) via Respimat® once daily with two consecutive inhalations to achieve a total dose of 5mcg, for 7 days (days 1–7). After 7 days of washout (days 8–14) they invert the treatment for more 7 days (days 15–21). The randomization was carried out via proportional allocation 1:1. That is, for each patient in sequence 1, there was 1 patient in sequence 2, until completing 140 subjects. The randomization list was performed in blocks to ensure balanced numbers for sequences 1 and 2 in the study. The sequence of treatments used by the patient was assigned by IWRS according to the randomization list provided by a Contract Research Organization.

At the first day of each treatment (day 1 and 15), patients received the assigned inhaler device along with the drug leaflet. They were given time to read them prior to demonstrating their ability to use the inhaler correctly, under the supervision of one trained evaluator from the site. The evaluator would only stop the patient procedure if he judges that the incorrect use of the device may jeopardize the patient. In this case, the evaluator indicated how such step should be conducted and asked the patient to continue performing the procedure. Neither instruction nor demonstration about the device were carried out at this phase.

The evaluator recorded the patients' ability to correctly perform

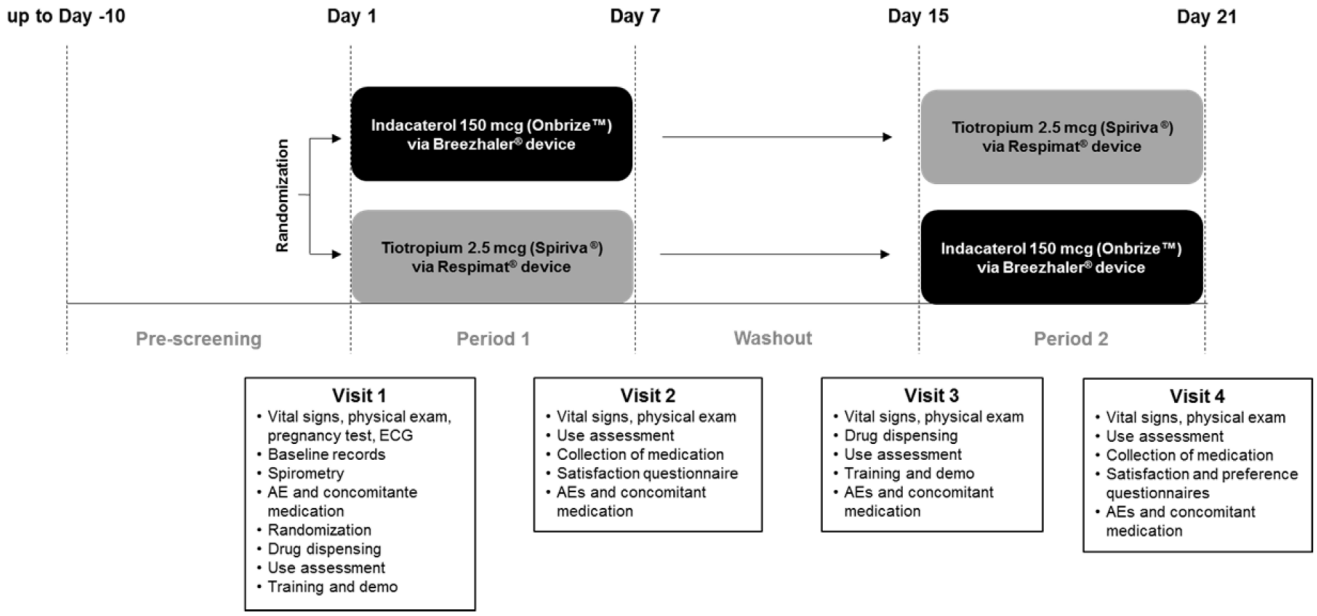

Fig. 1. Study design.

each of the 23 steps required for each device, accordingly to a checklist assessment (for more details on the inhaler devices checklists, see Supplementary Information 1 – Table SI1-1 and SI1-2, respectively for Breezhaler® and Respimat®). These 23 steps were artificially construct based on the drug leaflets as part of the method development for this study to ensure comparability in the measurement of errors. There are not 23 steps in the drug leaflets. Steps were classified as 'correctly completed'/'yes' or 'not correctly completed'/'no'. In addition, three critical steps were identified for Breezhaler® and 2 for Respimat® (for more details see sub-section *Endpoints and assessments*). These critical steps were defined by the researches involved in the study design based on the instructions for use from the drug leaflet, thus evaluating what would be the points of attention of use of the devices in the real life of the patients. At the end of the assessment of patients' use, the evaluator provided a demonstration and training on how to use the assigned inhaler device properly. At the end of each treatment period (day 7 and 21), patients' correct inhaler use were re-assessed by the evaluators.

After this procedure, at each period, patients completed a satisfaction questionnaire (*FSI-10 Feeling Satisfaction with Inhaler Questionnaire*) for each inhaled device used in the period, with 5-point Likert scale (ranging from 1 = 'hardly at all' to 5 = 'very') for each questionnaire item [13]. The satisfaction questionnaire evaluated the patients' opinions about convenience, difficulty, transportation and handling of the device.

At the end of the study, patient were asked to select the inhaler device of their preference to continue the treatment.

2.4. Endpoints and assessments

The primary endpoint of this study was the rate of correct use of Breezhaler® and Respimat® devices on the first day of each treatment, defined as the proportion of patients without critical error during the use of each device, after the patient read the inhaler instructions in the drug leaflet as mentioned in "study design and treatment" section. Errors were considered critical if they hampered the total administration of the drugs or their lung deposition, which in turn could compromise the efficacy of the treatment. For Breezhaler® device, the following errors were considered critical: 'Insert the capsule into the device' (item 5), 'Buttons were fully released before inhalation' (item 13) and 'Fully breath out, not inside the inhaler' (item 14). For Respimat®, the critical errors were: 'To slowly and fully release air from the lungs and set the lips around the mouthpiece, without covering air entries' (item 18) and 'While deeply and slowly breathing in by mouth press application button, continue to breath in as slowly as possible during the longer time possible' (item 20).

The secondary endpoints were the rate of correct use of Breezhaler® and Respimat® devices and the mean score of the Satisfaction Questionnaire of Inhaled Device after 7 days of daily use of each device. At the end of the study, the patients' preference rate and difficulty felt to use each inhaler device were also recorded.

Other assessments included patients' characteristics at baseline and safety records of all adverse events (AEs), serious AEs (SAEs), with their grade of severity and relationship with study medication.

2.5. Statistical methods and populations for analyses

A sample of 133 patients has greater than 80% power to detect a paired difference of 10% between the proportions of correct use of both inhaler devices, with a significance level of 0.05. Considering a rate of invalid or missing data for about 5%, 140 patients would be recruited.

Descriptive statistics: namely mean, standard deviation (SD), median and range (minimum and maximum) for quantitative variables, and counts and percentages for quantitative variables were computed. Missing values were not replaced and percentages were calculated based on non-missing values.

The primary endpoint was analyzed through the Generalized Estimation Equation method and considering the effects of period, sequence and inhaler device in the model. Additionally the rates of correct use of devices were compared on day 1 and day 15 using the chi-square test and the change in the use of the devices (used correctly the 1st device on day 1 and used wrongly the 2nd device on day 15 or vice versa) was analyzed through McNemar's test. The rates of correct use considered all non-missing values and the *Last observation carried forward* (LOCF) method was used as sensitivity analysis. In addition, 95% confidence intervals were estimated.

The global score of satisfaction was computed considering a total of 10 items of FSI-10 questionnaire (maximum total score of 50, with higher values indicate higher satisfaction) [13] and devices were compared by a mixed model, considering the period, sequence and inhaled device as fixed effects and patient within sequence as random effect. Preference rate for each device at the end of study was evaluated by testing a sample for proportions.

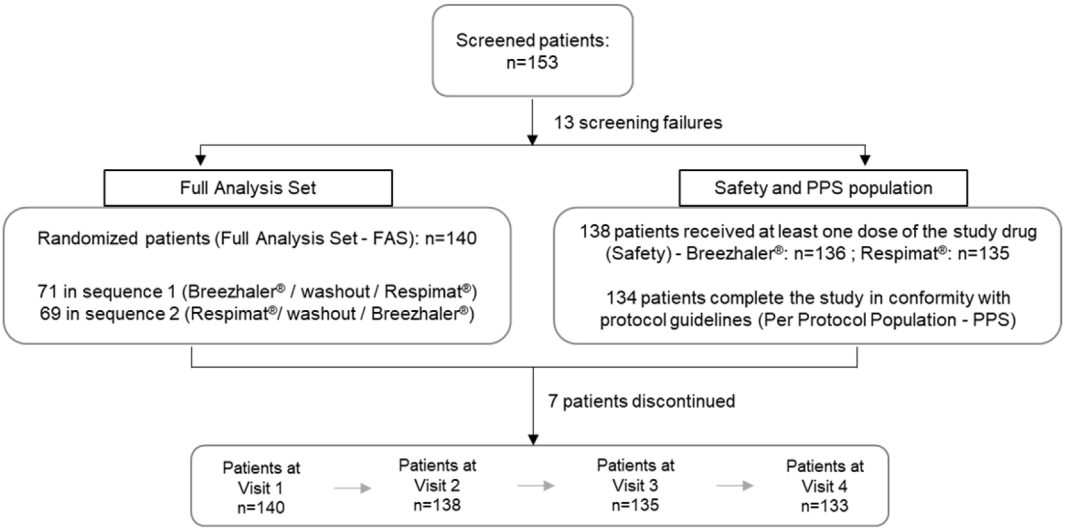

Fig. 2. Patients disposition.

Populations for analyses of correct use of devices, satisfaction and preference were full analysis set (FAS - all randomized patients) and per protocol population (PPS - patients who complete the study in conformity with protocol guidelines) as sensitivity analysis for the primary endpoint. Safety population (all randomized patients who have received at least one dose of the study medication) was used in the adverse events analysis.

Statistical analyses were performed using SAS® (version 9.4; SAS Institute Inc, Cary, USA) software package.

3. Results

3.1. Baseline characteristics

A total of 10 Brazilian sites screened 153 patients of whom 140 were randomized, 138 patients were in safety population and 134 in PPS. Fig. 2 summarizes the study patient distribution in more details. Mean age of patients in the FAS population was 63.5 years (48–85 years old), more than half were male (55.7%) and the majority of the patients were Caucasian (82.1%). Approximately 57.1% were active smokers (mean smoking time of 45.5 years) Table 1 summarizes patients and disease characteristics.

The mean duration of disease was 1.6 years. More than 30% of the patients reported medical history of vascular disorders (55.4%), respiratory, thoracic and mediastinal disorders (44.6%), social circumstances (41.0%, mainly menopause), metabolism and nutrition disorders (36.0%) and surgical and medical procedures (33.1%)

Overall compliance was similar between Breezhaler® and Respimat® with mean time of exposure of 7.8 days (range: 5–10 days and 3–18 days, respectively) and mean number of days that patients had not taken the medication was 0 days.

3.2. Use of the devices

Correct use and critical errors comparison are summarized in tables Table SI2-1 Table SI2-2.

Overall, 4.9% and 4.2% of the patients reported difficulties in the use of Breezhaler® and Respimat®, respectively. The difficulties reported for Breezhaler® were mainly related with the insertion of the capsule into the device and the ones reported for Respimat® were related with the handling of the inhaler device.

Table 1
Baseline patients' characteristics (FAS population).

	Total (n = 140)
Age, years	
Mean (SD)	63.5 (8.2)
Female, n (%)	62 (44.3%)
BMI (kg/m^2)	
Mean (SD)	26.1 (4.8)
Race, n (%)	
Caucasin	115 (82.1%)
Black	15 (10.7%)
Asian	1 (0.7%)
High level school, n (%)	17 (12.1%)
Duration of disease, years	
Mean (SD)	1.6 (4.5)
Use of the bronchodilator, n (%)	29 (21.0%)
Smoker, n(%)	80 (57.1%)
Smoking time, years	
Mean (SD)	45.6 (7.9)
Ex-smoker, n(%)	60 (42.9%)
Smoking time, years	
Mean (SD)	40.6 (12.3)
Systolic blood pressure (mmHg)	
Mean (SD)	128.6 (16.4)
Diastolic blood pressure (mmHg)	
Mean (SD)	79.3 (7.8)
Heart rate (bpm)	
Mean (SD)	75.3 (10.1)
FEV1 post-BD (L)	
Mean (SD)	1.9 (0.6)
FVC post-BD (L)	
Mean (SD)	3.2 (0.9)
FEV1/FVC post-BD	
Mean (SD)	54.5 (19.8)

FAS: full analysis set; SD: standard deviation; Min-max: minimum – maximum; BMI: Body mass index; BD: bronchodilator.

3.3. Primary endpoint

At the beginning of treatment, the rate of correct use for FAS population was 40.4% [95% CI: 32.2%–48.7%] for Breezhaler®, and 36.3% [95% CI: 28.2%–44.4%] for Respimat® (Fig. 3 and Table SI2-3). The rate of correct use for FAS population for Breezhaler® and Respimat® at the beginning and at the end of treatment are shown in Fig. 3 and Table SI2-3.

In each day, the rates of correct use were compared between devices and the differences were not statistically significant (this result is in accordance with the abovementioned for multivariate analysis: there

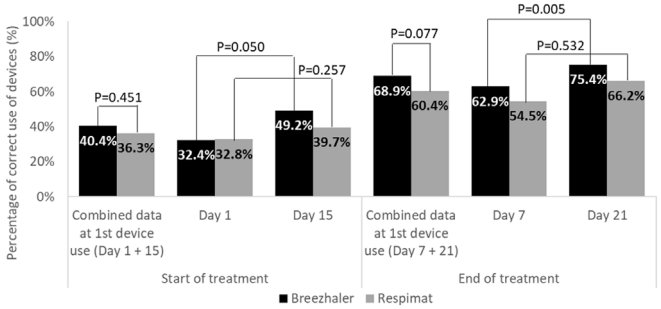

Fig. 3. Percentage of correct use of Breezhaler® and Respimat® devices at the start of treatment and at the end of treatment.

was no device effect neither at the beginning nor at the end of the treatment).

For each device, the comparison of the rate of correct use on day 1 versus day 15 (start treatment) and day 7 versus day 21 (end of treatment) were performed. In both devices, there was an increase of correct use between the first and second period (this result is in accordance with the abovementioned for multivariate analysis).

The results were similar in the analysis with missing values replacement (LOCF) and for PPS population (data not shown).

3.4. Satisfaction

The satisfaction results are shown in Fig. 4.

3.5. Preference

The preference results are shown in Fig. 5. At the end of the study, patients were asked which device they would prefer to continue the treatment and more than half of the patients (57.1%) chose Breezhaler®, 30.1% chose the Respimat® and 12.8% expressed no preference for either device. The proportion of patients who preferred Breezhaler® was statistically superior to the Respimat® (p = 0.001).

3.6. Adverse events

There were reported 19 adverse events: 7 occurred in patients who were using Breezhaler®, 12 in patients using Respimat®.

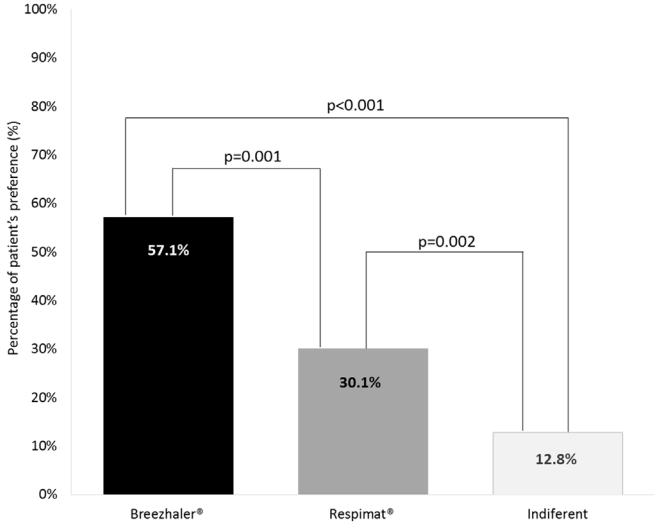

Fig. 5. Preference by device in patients with mild to moderate COPD.

Seven patients (5.1%, 95% CI: 1.4%–8.9%) using Breezhaler® and 12 patients (8.2%, 95% CI: 3.6%–12.9%) using of Respimat® registered at least one AE, tough no significant difference was found between both inhaler devices (p = 0.315). An AE attributed to Breezhaler® (nervous system disorders: dizziness) and 3 AEs attributed to Respimat® (nervous system disorders: saliva altered, heart disease: palpitations, and diseases of the skin and subcutaneous tissue: skin lesion) were considered to be related with the medication. There were neither serious adverse events nor deaths during the study.

4. Discussion

In this randomized, multicenter, open label and crossover study there was no statistical difference between the proportion of patients who did not make critical errors during the evaluation of the inhalation technique using Breezhaler® or Respimat®. However, a high prevalence of inappropriate use of the devices was observed in both groups. Regarding the preference of the device, a majority of the patients

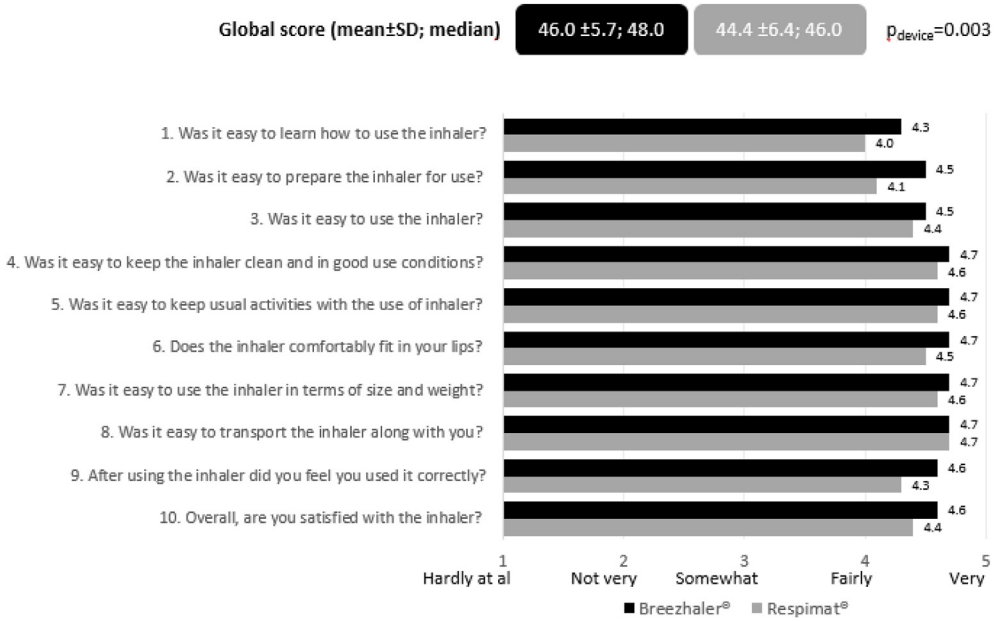

Fig. 4. Satisfaction questionnaire by device in patients with mild to moderate COPD.

preferred the Breezhaler® over Respimat®, 57.1% versus 30.1% respectively.

The primary endpoint was aimed to evaluate the critical errors during inhalation technique using Breezhaler® and Respimat®. At this stage, patients were evaluated based on their first use of the inhaler devices, after reading their respective leaflet information without any further instruction. For both inhalers, the proportion of patients that accomplished the critical steps correctly increased from day 1 to day 7, which was particularly denoted in the case of Breezhaler® where the learning effect over time was statistically significant. This was also observed for the remaining, non-critical steps of the inhalers' evaluation. These results are in agreement with the study of Schulte et al. that evaluated the correct usage of several dry powder inhalers [6]. Likewise, this reinforces the importance of patients' training and adaptation to the inhaler in reducing usage errors during the inhaler's assembling [14–17]. Nevertheless, it is important to emphasize that there is no consensus for which checklist is most appropriate to evaluate the correct use of inhaled devices. Different checklists are used in several studies, but all take into account the characteristics described in the monographs of the products. Thus, despite the lack of consensus, data from various studies can be adequately comparable [15,18–20].

Both inhalers have been developed taking into account the key features to design an ideal inhaler. Therefore, as previously stated by Ram et al. it was considered that the inhalers herein studied were clinically equivalent [18], and thus the study assessments depend on the patients' use and perception of the inhaler. All of the adverse events herein reported as related to the devices have already been described in their respective clinical trials, which in general only include patients that know how to use the inhaler correctly.

The fact that, in our study, more patients were satisfied and preferred to use Breezhaler® instead of Respimat®, may contribute to improve their treatment compliance, which in turn could lead to a long-term efficacy outcome [1,21]. Recently, two studies have reported the handling and patient satisfaction between Respimat® and Breezhaler®, though using different instruments: the Handling Questionnaire [22], and the Patient Satisfaction and Preference Questionnaire (PASAPQ) [23]. Dal Negro et al. demonstrated in a study with 333 patients that Respimat® was more liked than Breezhaler® either for patients or nurse perception [22]. However, it is important to note some different points between this study and ours. In our study, we assessed the correct rate of device use without committing any errors considered as critical and without prior guidance regarding device use. On the other hand, Dal Negro et al. evaluated all patients after instruction explanation by an expert nurse and the patient could have already used the device prior to the evaluation. In other study, Miravittles et al. did not reveal any statistical differences between both inhaler devices regarding patient overall satisfaction, including the inhaler's performance and convenience in a Spanish population. The preference between both devices were very similar ($p = 0.70$)[23]. In addition, in Miravitlles et al. only patients who had previously used one of the devices were included (between 3 and 6 months). All together, these data emphasises the importance that different scenarios and populations can exert on the perception and satisfaction between inhaled devices.

The cross-over design used in this study contributed to minimize the bias involved in each treatment assessment, as each patient evaluated both inhaler devices. The randomized cross-over design is considered the design of choice for evaluating the patients' preference for two devices [21]. The multicentre character minimized the potential selection bias and allowed a better geographical representativeness. The FSI-10 questionnaire has been previously validated for Asthma and COPD [24,25], though it does not account for the determination of a minimally important difference [13]. Still, the results herein obtained have shown that both inhalers were well accepted by the patients, the mean score of all FSI-10 items was ≥ 4.0, with at least statistical significant differences favouring Breezhaler® (a difference of 1.6 out of 50 points between devices). Furthermore, in the case of clinically equivalent devices with similar safety profiles, the treatment selection should take into consideration patients' preferences and satisfaction, as they may influence treatment compliance [6,26].

However, it is worth to mention that this study has some limitations, such as its unblinded design. In addition, the evaluation of the patients' inhalation technique was based on the investigator's observation without using any measurement to validate the complete drug inhalation. The authors acknowledge that the efficacy of the drug may interfere with patient satisfaction with the device, however, the primary objective of the study was to evaluate the correct use and satisfaction rather than efficacy between devices. The two studied devices, Breezhaler® and Respimat® contain indacaterol and tiotropium, respectively [10,12]. This difference between them may be a bias, comparing distinct products. Another relevant point is the preparation of the Respimat® device. The fitting of the cartridge is considered a critical error for an adequate inhalation technique. Since this step is necessary only on the first day of use of the device, the correct use rate on subsequent days may be slightly overestimated since one of the critical steps is no longer necessary.

The success of COPD treatment goes beyond simple prescription of effective drugs with good safety profile. It also depends on factors such as patients' information about the disease, cost of medication, and good adherence to treatment. The inhalation route is preferred for the treatment of obstructive pulmonary diseases because of its better risk-benefit ratio compared to the oral route [27]. However, some studies indicate that more than 70% of patients make a mistake when using inhaled devices. Of these errors, slightly more than 10% of the patients commit at least one serious error that compromises the effectiveness of the treatment [28]. A recent real life assessment, performed in almost 3000 COPD patients, has shown that critical errors are associated with increased risk of severe exacerbations and were less common with Breezhaler® when compared with other inhalers [29]. In addition, the lack of knowledge of many health professionals regarding the technique of proper use of the devices is one of the major factors of its misuse by patients [30]. The ease and satisfaction of patients in using the inhaler are aspects that can be associated with greater adherence and reduction in the number of use errors and should be taken into consideration by physicians and other health related professionals who treat patients with obstructive lung diseases [6,26].

5. Conclusion

In this study, patients with COPD in Brazil showed a greater preference and satisfaction with Breezhaler® over Respimat®. This is an important information since treatment compliance might be improved according to patients' preference. Even so, it is relevant to note that about one-third of patients preferred Respimat®, reinforcing the importance of personalized treatment and the need of adaptation to the needs of the patient. In addition, the correct use of the inhaler devices, with and without critical errors, increase over time denoting a learning effect by the patient. The importance of patients' training and adaptation to the inhaler in reducing usage errors, together with the choice of a device that satisfies the patient may be a strategy to ensure better clinical outcomes.

ClinicalTrials.gov identifier

NCT01727024.

Contributions

Oliveira, Pizzichini, Costa, Fritscher, Vianna, Teixeira, Stirbulov and Rabahi were involved in the data collection and trial conduction. Pinho was involved in the study management and monitoring. All the authors critically revised the manuscript and approved the final version.

Conflicts of interest

Oliveira, Costa, Vianna, Teixeira, Stirbulov and Rabahi declare no potential conflicts of interest. Fritscher reports participation in clinical trials and lectures from Aché, AstraZeneca, Boehinger Ingelheim, GlaxoSmithKline and Novartis. Pizzichini reports participation in activities from Aché, AstraZeneca, Boehinger Ingelheim, Chiesi, GlaxoSmithKline and Novartis. Pinho reports she is a formal employee of Novartis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.10.006.

References

[1] R. Hodder, D. Price, Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat® Soft Mist™ inhaler, Int. J. Chronic Obstr. Pulm. Dis. 4 (2009) 381–390.
[2] Global Initiative for Chronic Obstructive Lung Disease (GOLD), GOLD 2017 Global strategy for the diagnosis, management and prevention of COPD [Internet], [cited 2018 Oct 9]. Available from: https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/.
[3] G. Hillas, F. Perlikos, I. Tsiligianni, N. Tzanakis, Managing comorbidities in COPD, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 95–109.
[4] V. Vijayan, Chronic obstructive pulmonary disease, Indian J. Med. Res. 137 (2013) 251–269.
[5] J.S. Cohen, M.C. Miles, J.F. Donohue, J.A. Ohar, Dual therapy strategies for COPD: the scientific rationale for LAMA + LABA, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 785–797.
[6] M. Schulte, K. Osseiran, R. Betz, M. Wencker, P. Brand, T. Meyer, et al., Handling of and preferences for available dry powder inhaler systems by patients with asthma and COPD, J. Aerosol Med. Pulm. Drug Deliv. 21 (4) (2008 Dec) 321–328.
[7] R. Hodder, P.R. Reese, T. Slaton, Asthma patients prefer Respimat soft mist inhaler to turbuhaler, Int. J. Chronic Obstr. Pulm. Dis. 4 (2009) 225–232.
[8] B.L. Laube, H.M. Janssens, F.H. de Jongh, S.G. Devadason, R. Dhand, P. Diot, et al., What the pulmonary specialist should know about the new inhalation therapies, Eur. Respir. J. 37 (6) (2011 Jun) 1308–1331.
[9] F. Lavorini, G.A. Fontana, Inhaler technique and patient's preference for dry powder inhaler devices, Expet Opin. Drug Deliv. 11 (1) (2014 Jan) 1–3.
[10] Ministério da Saúde, Relatório de Recomendação da Comissão Nacional de Incorporação de Tecnologias no SUS - CONITEC - 39, Indacaterol para o tratamento da Doença Pulmunar Obstructiva Crônica, 2016 May 10.
[11] W. Schurmann, S. Schmidtmann, P. Moroni, D. Massey, M. Qidan, Respimat Soft Mist inhaler versus hydrofluoroalkane metered dose inhaler: patient preference and satisfaction, Treat. Respir. Med. 4 (1) (2005) 53–61.
[12] M.G. Matera, C.P. Page, M. Cazzola, Novel bronchodilators for the treatment of chronic obstructive pulmonary disease, Trends Pharmacol. Sci. 32 (8) (2011 Aug) 495–506.
[13] M. Perpiñá Tordera, J.L. Viejo, J. Sanchis, X. Badia, N. Cobos, C. Picado, et al., [Assessment of patient satisfaction and preferences with inhalers in asthma with the FSI-10 Questionnaire], Arch. Bronconeumol. 44 (7) (2008 Jul) 346–352.
[14] H.J. Patel, An update on pharmacologic management of chronic obstructive pulmonary disease, Curr. Opin. Pulm. Med. 22 (2016) 119–124.
[15] L. Zambelli-Simões, M. Martins, C. Possari, G. Carvalho, A. Coelho, S. Cipriano, et al., Validation of scores of use of inhalation devices: valoration of errors, J. Bras. Pneumol. 41 (2015) 313–322.
[16] M. Souza, A. Meneghini, E. Vianna, M. Borges, Técnica e compreensão do uso dos dispositivos inalatórios em pacientes com asma ou DPOC, J. Bras. Pneumol. 35 (2009) 824–831.
[17] P. Oliveira, A. Menezes, A. Bertodi, F. Wehrmeister, S. Macedo, [Assessment of inhaler techniques employed by patients with respiratory diseases in southern Brazil: a population-based study], J. Bras. Pneumol. 40 (2014) 513–520.
[18] F.S. Ram, C.R. Carvallho, J. White, Clinical effectiveness of the Respimat® inhaler device in managing chronic obstructive pulmonary disease: evidence when compared with other handheld inhaler devices, Int. J. Chronic Obstr. Pulm. Dis. 6 (2011) 129–139.
[19] R. Bournival, R. Coutu, N. Goettel, C. Yang, A. Cantin-Lafleur, C. Lemieux, et al., Preferences and inhalation techniques for inhaler devices used by patients with chronic obstructive pulmonary disease, J. Aerosol Med. Pulm. Drug Deliv. 31 (2018) 1–11.
[20] V. Knipel, S. Schwarz, F. Magnet, J. Storre, C. Criée, W. Windisch, et al., Checklists for the assessment of correct inhalation therapy, Pneumologie 71 (2017) 96–105.
[21] P. Anderson, Patient preference for and satisfaction with inhaler devices, Eur. Respir. Rev. 14 (2005) 109–116.
[22] R. Dal Negro, M. Povero, Acceptability and preference of three inhalation devices assessed by the Handling Questionnaire in asthma and COPD patients, Multidiscip. Respir. Med. 11 (2016) 7.
[23] M. Miravitlles, J. Montero-Caballero, F. Richard, S. Santos, J. Garcia-Rivero, F. Ortega, et al., A cross-sectional study to assess inhalation device handling and patient satisfaction in COPD, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 407–415.
[24] E. Zervas, K. Samitas, M. Gaga, Assessment of satisfaction with different dry powder inhalation devices in Greek patients with COPD and asthma: the ANASA study, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 1845–1855.
[25] C. Öztürk, A. Kaya, C. Bilgin, L. Yücesoy, B. Ikidag, M. Demirel, et al., Evaluation of inhaler technique and patient satisfaction with fixed-combination budesonide/formoterol dry-powder inhaler in chronic obstructive pulmonary disease (COPD): data on real-life clinical practice in Turkey, Tuberk. ve Toraks 60 (2012) 301–313.
[26] K. Nielsen, L. Okamoto, T. Shah, Importance of selected inhaler characteristics and acceptance of a new breath-actuated powder inhalation device, J. Asthma 34 (1997) 249–253.
[27] G.O.L.D. Global, Iniciative for Chronic Obstructive Lung Disease - global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (updated 2015), Available from: www.goldcopd.com.
[28] M. Molimard, C. Raherison, S. Lignot, F. Depont, A. Abouelfath, N. Moore, Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care, J. Aerosol Med. 16 (2003) 249–254.
[29] M. Molimard, C. Raherison, S. Lignot, A. Balestra, S. Lamarque, A. Chartier, et al., Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients, Eur. Respir. J. 15 (2017) 2.
[30] R. Stelmach, P. Robles-Ribeiro, M. Ribeiro, J. Oliveira, A. Scalabrini, A. Cukier, Incorrect application technique of metered dose inhalers by internal medicine residents: impact of exposure to a practical situation, J. Asthma 44 (2007) 765–768.