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Original Research

A prospective study of switching asthma patients from a Fixed-Dose Combination (FDC) Inhaled Corticosteroid [ICS]/Long-Acting Beta Agonist [LABA] therapy delivered by Dry Powder Inhaler (DPI) to ICS/LABA delivered by pressurised Metered Dose Inhaler (pMDI)

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ABSTRACT

Background: Previous real-world studies have suggested that in comparison to a dry powder inhaler (DPI), the rate of critical errors is lower with a pressurised metered dose inhaler (pMDI), and inhaled corticosteroid/long-acting bronchodilator (ICS/LABA) delivered by pMDI is more likely to achieve asthma control.
Objectives: To evaluate the acceptability, efficacy, safety and cost-effectiveness of switching asthma patients from an ICS/LABA DPI to an ICS/LABA pMDI in a real-world population in Kuwait.
Methods: This was a 12-month, observational, nonblinded, prospective, real world study. Patients with asthma for ≥1 year with 2 or more asthma exacerbations in the last year were assigned to either switch to ICS/LABA pMDI, or to continue with ICS/LABA DPI.
Results: A total of 239 patients were treated with either ICS/LABA pMDI (Switch cohort; n = 119) or ICS/LABA DPI (Maintenance cohort; n = 120). The majority of patients (99/119; 83.2%) in the Switch cohort remained on ICS/LABA pMDI over 12 months of follow-up. Both cohorts experienced an improvement in their FEV1 levels, with mean values in the Switch group reaching normal levels (>80% predicted). On average, at 3 and 12 months, the Switch cohort had significantly better FEV1 values than patients in the Maintenance cohort (p = 0.001). At 12 months, the proportion of patients with controlled asthma increased in the Switch group, but did not change significantly in the Maintenance group.
Conclusions: In patients with asthma symptoms that are not well controlled with an ICS/LABA DPI, switching to an ICS/LABA pMDI provides an alternative choice that may improve asthma control.

1. Background

Asthma is a major global health concern associated with significant morbidity [1,2]. The Global Burden of Diseases study estimated that, in 2017, more than 272 million people were living with asthma and it accounted for over 10.6 million years lived with disability [2]. Incidence and prevalence rates are highest in children, but asthma-related morbidity, healthcare use and mortality are higher in adults [4,5]. Although in comparison with other chronic diseases mortality related to asthma is relatively low, in 2016 poorly controlled asthma was responsible for approximately 400 000 deaths worldwide [3].

Compared with other Middle Eastern countries, the prevalence of asthma in Kuwait is relatively high. Studies estimate that approximately 10–12% of adults in Kuwait are asthmatic, compared to only 4–8% in Turkey, Egypt, UAE and Saudi Arabia [6]. [[,7] Despite the increasing prevalence of asthma worldwide, improvement in management strategies and treatments and access to high quality healthcare services in Kuwait have led to substantial reductions in asthma-related hospital admission and mortality rates in this country [4,5]. Nevertheless, chronic asthma in this country is associated with significant comorbidity and impaired quality of life, and management and treatments are associated with considerable financial burden [5,6]. In a survey of 370 patients with chronic asthma conducted in a random sample of general practitioners and specialists from public and private sectors in Kuwait, fewer than half (43%) had controlled asthma [8]. Considering also that, relative to medication costs, in Kuwait the highest medical expenditure

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is associated with emergency room and inpatient visits, improving asthma control remains a clinical priority [9].

According to recent asthma guidelines, an inhaled corticosteroid (ICS) in combination with a long-acting bronchodilator (LABA) is the mainstay of therapy for adults and adolescents with chronic asthma, starting with low dose ICS and formoterol as needed at step 1 and stepping up to daily maintenance ICS, low dose ICS plus LABA, and gradually increasing the dose of ICS if the patient remains symptomatic [1]. However, inhaler technique is critical to asthma control, and the type of inhaler and patients' ability to use it correctly can have a profound effect on asthma outcomes. In general, not exhaling before inhalation, not holding the breath, insufficient inspiratory effort and dose preparation errors for dry powder inhalers (DPIs), and coordination problems with pressurised metered dose inhalers (pMDIs), are the most common inhaler technique errors that affect asthma control [10,11]. Poor inhaler technique is associated with limitations in daily activities, sleep disturbance and increased risk of hospitalisation [12].

Randomised controlled studies comparing respiratory function with different asthma inhalers have reported similar outcomes with pMDIs and DPIs [13–17]. However, real-world data has suggested that in comparison to a DPI, the rate of critical errors is lower with a pMDI, and ICS/LABA delivered by pMDI is more likely to achieve asthma control [10,12,18]. Furthermore, pMDI was preferred by patients [19]. In comparison to randomised controlled studies, which are often designed to show equivalence or non-inferiority, real world data may more accurately reflect what is to be expected from everyday clinical practice [18,20].

The purpose of this study was to evaluate the acceptability, efficacy, safety and cost-effectiveness of switching asthma patients from an ICS/LABA DPI to an ICS/LABA pMDI in a real-world population in Kuwait, and to examine the impact of inhaler device on real-world efficacy by comparing ICS/LABA combination therapy delivered by two different inhaler devices.

2. Methods

This was a 12-month, observational, nonblinded prospective, real world study. Participating patients were recruited directly from a single center in Kuwait, the Al-Rashed Allergy Centre, which serves all health governorates in the country.

Patients between the ages of 12 and 80 years were eligible for inclusion if they met the following criteria: physician diagnosis of asthma; evidence of active asthma; asthma for ≥1 year with 2 or more asthma exacerbations in the last year; forced expiratory volume in the first second (FEV1) ≥50% and ≤90% of predicted normal (pre-bronchodilator), with a reversibility of ≥12% and ≥200 ml FEV1 after inhalation of a short-acting bronchodilator; and have had ≥3 prescriptions for ICS/LABA DPI during the baseline year. Exclusion criteria were diagnosis of any other chronic respiratory disease at any time; received maintenance oral/systemic corticosteroids during the previous year, and/or received different fixed dose combination ICS/LABA or separate ICS or LABA during the previous year, and/or pregnant and/or breastfeeding women.

The study design comprised two periods, before and after initiation of pMDI (Zero time): a Baseline Period and an Outcome Period. Baseline Period data were collected retrospectively from each patient (1-year period before the Zero Time for eligibility testing), during which patients were characterised in terms of demography, clinical characteristics and asthma severity and control. The study was initiated from the day of the patient's visit to the physician (Zero time), on which the patient was evaluated for asthma severity and the use of DPIs during the previous year. Thereafter the investigator evaluated the need to switch (if also agreed upon by the patient) from DPI to pMDI, or continue with the same treatment. Therefore, at the physicians' discretion, patients were assigned to either switch to ICS/LABA pMDI (Switch cohort), or to continue with ICS/LABA DPI (Maintenance cohort).

Treatment was assigned according to the patients' medical records and could be fluticasone propionate/formoterol (FP/FOR) pMDI 50/5 μg, 125/5 μg, or 250/10 μg (e.g. 2 puffs twice daily [bid]) in the Switch cohort, and fluticasone propionate/salmeterol (FP/SAL) DPI 100/50 μg, 250/50 μg, or 500/50 μg (e.g. 1 puff bid) in the Maintenance cohort. To minimise the risk of bias, Maintenance cohort patients were matched to the Switch cohort patients by the following variables: date (actual zero time within one week, as far as possible), sex, age (within 5 years band), smoking status, and GINA asthma control/severity. During the Outcome period, patients were evaluated for efficacy and safety at 3, 6 and 12 months.

The primary objective was to evaluate the acceptability of switching asthma patients from an ICS/LABA DPI to an ICS/LABA pMDI inhaler, defined as the percentage of ICS/LABA pMDI patients who received ≥2 prescriptions of ICS/LABA pMDI (i.e. ≥ 1 prescription in addition to that issued at switch) at 12 months and who continued on ICS/LABA pMDI. Secondary efficacy outcomes included the evolution of asthma severity according to FEV1; peak expiratory flow (PEF); Asthma Control Test (ACT) score; a composite definition of control comprising no recorded hospital attendance for asthma, including admission, Accident & Emergency (A&E) attendance, out-of-hours attendance, or Out-Patient Department (OPD) attendance, and no prescription for oral steroids, and no general physician (GP) consultations, hospital admissions or A&E attendance for lower respiratory tract infections (LRTI) requiring antibiotics; the individual components of the composite definition; and asthma symptoms. ACT (http://www.asthmacontroltest.com) is a short, simple tool for identifying patients with poorly controlled asthma. It consists of 5 items, covering five domains and categories with a 4-week recall assessing frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. Non-inferiority tests were done between switchers to pMDI and those remaining on maintenance DPI to assess whether there were differences in rate of asthma exacerbation (asthma-related unscheduled consultations, and asthma-related hospitalizations and/or hospital outpatient attendances, number of courses of acute systemic steroids, and rate of severe exacerbations). Adverse events were also evaluated. Clinical events (including laboratory abnormalities) were considered to be treatment-related if they occurred within a reasonable time after medication administration and could not be explained by concurrent disease or other drugs or chemicals. Where there was uncertainty of a relationship between the adverse event and other concurrent conditions, drugs or chemicals, the adverse event was considered to be possibly related to treatment.

2.1. Statistical methods

The primary efficacy endpoint was calculated for the pMDI cohort as the proportion of included patients with a 1-year visit and who remained on ICS/LABA pMDI during the follow-up period. The evolution of FEV1 and PEF during the Outcome Period was compared between the two cohorts with a two-way repeated measures ANOVA as a mixed model. Noninferiority for exacerbations was considered to be established if the upper 95% confidence interval during the 12 month observation period did not exceed 20% of baseline values. The evolution of the asthma control variables were statistically analysed within the study cohorts using paired *t*-test, Wilcoxon signed-rank test and McNemar test with Bonferroni correction as appropriate. Considering an α (two-tailed) of 0.05 for threshold probability for rejecting the null hypothesis (Type I error rate), β of 0.20 for probability of failing to reject the null hypothesis under the alternative hypothesis (Type II error rate), and an expected proportion experiencing one or more severe asthma exacerbation of 20% in the Maintenance cohort during the 12 months period, it was estimated that 100 patients would be required to complete the study in each group. Allowing for a 20% loss to follow up meant that 120 asthma patients would need to be enrolled in each cohort.

2.2. Ethics

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments) and the Guidelines for Good Pharmacoepidemiology Practices (ISPE). This study was approved by the ethics research committee of the Ministry of Health in Kuwait (number 2017/524).

3. Results

3.1. Baseline (zero time) characteristics

A total of 239 patients with active asthma were enrolled in the study and were subsequently treated with either ICS/LABA pMDI (Switch cohort; n = 119) or ICS/LABA DPI (Maintenance cohort; n = 120). All patients completed 12 months of follow-up and were included in the efficacy and safety analyses. Patients' demographics and baseline characteristics were comparable in the two groups (Table 1). All patients were Caucasian and Arab ethnicity. The majority were female. Median age was 46.0 years and 48.0 years (range 16.0–80.0 years) in the Switch and Maintenance cohorts, respectively. Overall, approximately 80% had comorbidities other than asthma and were taking concomitant non-respiratory medications.

In the year prior to baseline, groups were comparable with regards to their respiratory-related therapy history, except for the use of anti-IgE, which was significantly higher in the maintenance cohort (38.7% vs. 2.6%; $p < 0.0001$). All patients had received asthma therapy with a fixed combination inhaled ICS/LABA. Groups were also comparable at baseline in their ongoing respiratory-related therapy, except for use of fixed combinations of ICS/LABA and anti-IgE, which were significantly higher in the Maintenance cohort (100.0% vs 38.3%, respectively and 37.8% vs. 2.6%, respectively; $p > 0.0001$ for both). A significantly higher proportion of patients in the Maintenance cohort had well-controlled asthma, indicated by ACT score ≥20 (60.8% vs. 37.0%; $p = 0.001$), and a significantly higher proportion of patients in the Switch cohort had ACT score <15, consistent with uncontrolled asthma (31.9% vs. 17.5%; $p = 0.029$). Consistent with worse asthma control, daytime and night-time asthma symptoms in the previous 7 days were reported by significantly more patients in the Switch cohort than in the Maintenance cohort (9.2% vs. 1.7%; $p = 0.011$ and 20.2 vs. 5.0; $p < 0.001$, respectively). Although there was no difference between groups in frequency of severe exacerbations during the previous 7 days, the number of patients with severe exacerbations during 1 year prior to baseline, mean frequency of severe exacerbations and number of patients requiring a course of acute systemic corticosteroids were significantly higher in the Switch group (Table 2). However, the number of patients with hospitalisations and/or hospital outpatient visits for asthma was not significantly different between groups and asthma-related unscheduled consultations were uncommon in both groups.

Table 1
Baseline characteristics (zero time).

	ICS/LABA pMDI Switch cohort (n = 119)	ICS/LABA DPI Maintenance cohort (n = 120)	P
Male, n (%)	53 (44.5)	48 (40.0)	1.00
Female, n (%)	66 (55.5)	72 (60.0)	
Mean age, years (range)	46.8 (16.0–80.0)	46.4 (16.0–80.0)	1.00
Mean BMI, kg/m^2 (range)	32.9 (19.6–54.7)	31.6 (16.8–63.6)	1.00
Smokers, n (%)	16 (13.4)	17 (14.2)	1.00
Comorbidity other than asthma, n (%)	100 (84.0)	98 (81.7)	0.732
Concomitant non-respiratory medications, n (%)	95 (79.8)	94 (78.3)	0.874
Respiratory medications, n (%)			
Fixed combination ICS/LABA	44 (38.3)	119 (100)	<0.0001
Short-acting β2 agonist	79 (68.7)	72 (60.5)	0.135
Leukotriene receptor antagonist	36 (31.3)	39 (32.8)	1.00
Long-acting muscarinic antagonist	17 (14.8)	23 (19.3)	1.00
Anti-IgE	3 (2.6)	45 (37.8)	<0.0001
Inhaled corticosteroids	3 (2.6)	6 (5.0)	1.00
Theophylline	2 (1.7)	3 (2.5)	1.00
Asthma control			
ACT score, n (%)			
Controlled (score 20–25)	44 (37.0)	73 (60.8)	0.001
Partially controlled (score 15–19)	37 (31.1)	26 (21.7)	0.295
Uncontrolled (score <15)	38 (31.9)	21 (17.5)	0.029
Exacerbations and symptoms in previous 7 days[a]			
Severe exacerbations, n (%)	28 (23.5)	17 (14.2)	0.071
Mean number (range)	1.6 (1.0–7.0)	1.2 (1.0–5.0)	0.052
Daytime symptoms, n (%)	11 (9.2)	2 (1.7)	0.011
Mean number (range)	3.1 (1.0–7.0)	4.0 (1.0–7.0)	0.010
Night-time symptoms, n (%)	24 (20.2)	6 (5.0)	<0.001
Mean number (range)	1.8 (1.0–7.0)	2.0 (1.0–7.0)	<0.001
Mean PEF, L/min (range)	303.5 (109.0–560.0)	326.7 (119.0–769.0)	0.584
Mean FEV_1, % predicted (range)	63.2 (42.0–106.0)	67.2 (37.0–103.0)	0.053

PEF: peak expiratory flow; FEV_1: forced expiratory volume in 1 second
[a] Mean number of events within the previous 7 days before baseline.

3.2. Primary endpoint

The majority of patients (99/119; 83.2%; 95%CI 80.1–86.3) in the Switch cohort remained on ICS/LABA pMDI over the entire 12 months of follow-up. In comparison, 6 patients (5%) in the Maintenance cohort switched from their current DPI to an alternative treatment.

3.3. Secondary endpoints

Patients in both the Switch and Maintenance cohorts had no asthma-related unscheduled consultations during the 12 months outcome period. For the remaining efficacy endpoints observed during the 12-month outcome period, the pMDI was non-inferior to DPI, as the upper limit of the 95% CI of the difference in the mean number of events for each outcome did not exceed the established margin of 20% (Table 3).

During the outcome period, at the 3-months and 12-months study visits, patients in both cohorts experienced an improvement in their FEV1 levels, with mean values in the Switch group reaching normal levels (>80% predicted) (Table 4). On average, during the outcome period (3- and 12-months), patients in the Switch cohort had significantly better FEV1 values than patients in the Maintenance cohort ($p = 0.001$). The mean values for PEF also improved in both cohorts with no statistically significant difference between groups. Although at baseline a significantly higher proportion of patients had well controlled asthma in the Maintenance cohort compared to the Switch cohort, throughout follow-up asthma control among patients in the Switch cohort improved significantly, so that at 3 and 12 months follow-up differences between cohorts were no longer statistically significant.

Asthma control at 1 year pre- and post-switch, where control was defined by a composite proxy of "no recorded hospital attendance for

Table 2
Asthma control during the 1 year prior to switch (patients reporting events and number of events).

	ICS/LABA pMDI Switch cohort (n = 119)	ICS/LABA DPI Maintenance cohort (n = 120)	P
Asthma-related unscheduled consultations			
n (%)	2 (1.7)	1 (0.8)	0.622
Mean number (range)	2.0 (1.0–3.0)	2.0 (2.0–2.0)	0.557
Asthma-related hospitalisations and/or hospital outpatient visits			
n (%)	116 (97.5)	119 (99.2)	0.369
Mean number (range)	3.8 (1.0–12.0)	6.1 (3.0–21.0)	<0.0001
Courses of acute oral corticosteroids			
n (%)	3 (2.5)	5 (4.2)	0.722
Mean number (range)	3.0 (2.0–4.0)	1.6 (1.0–3.0)	0.501
Courses of acute systemic corticosteroids			
n (%)	62 (52.1)	45 (37.5)	0.027
Mean number (range)	1.9 (1.0–5.0)	1.8 (1.0–5.0)	0.015
Severe exacerbations			
n (%)	97 (81.5)	74 (61.7)	<0.001
Mean number (range)	3.0 (1.0–12.0)	2.6 (1.0–20.0)	<0.001

Table 3
Non-inferiority tests for variables related to asthma control.

Outcome (mean [range])	ICS/LABA pMDI Switch cohort (n = 119)	ICS/LABA DPI Maintenance cohort (n = 120)	P[a]
Number of asthma-related unscheduled consultations, person-years	0.0 (0.0–0.0)	0.0 (0.0–0.0)	NA
Number of asthma-related hospitalisations and/or hospital outpatient attendances, person-years	2.1 (0.0–15.0)	7.3 (0.0–29.0)	<0.001
Number of courses of acute oral corticosteroids, person-years	0.0 (0.0–0.1)	0.1 (0.0–0.4)	<0.001
Number of severe exacerbations, person-years	0.3 (0.0–8.0)	0.0 (0.0–8.0)	0.0074

[a] P-value noninferiority test.

asthma, including admission, A&E attendance, out-of-hours attendance or OPD attendance, AND no prescriptions for oral steroids, AND prescriptions for any antibiotic where the reason for the prescription is a lower respiratory tract infections" is shown in Table 5. In the Switch group all of the prespecified individual outcomes improved, leading to a significant increase in the proportion of patients with controlled asthma. However, in the Maintenance group, although there were improvements in some of the individual outcomes, there were also significant increases in the annual number of asthma-related attendances at the OPD and asthma-related hospitalisations and/or hospital outpatient attendances, and consequently there was no significant change in the proportion of patients with the composite definition of controlled asthma. Notably daytime and night-time symptoms were considerably improved in both groups.

3.4. Adverse events

During the study period, two adverse events (dehydration and fatigue) were reported by one patient each in the switch cohort. Although neither were considered serious, because they were judged to be possibly related to treatment, according to the study protocol dosing was discontinued in these patients. No adverse events were reported in the Maintenance cohort.

Table 4
Asthma control at 3 and 12 months.

	ICS/LABA pMDI Switch cohort (n = 119)	ICS/LABA DPI Maintenance cohort (n = 120)	P
3 months			
ACT score, n (%)			
Controlled (score 20–25)	71 (59.7%)	79 (66.4%)	0.848
Partially controlled (score 15–19)	35 (29.4%)	28 (23.5%)	0.911
Uncontrolled (score <15)	13 (10.9%)	12 (10.1%)	1.00
Mean PEF, L/min (range)	368.6 (134.0–802.0)	352.6 (74.0–697.0)	1.00
Mean FEV_1, % predicted (range)	84.7 (41.0–126.0)	75.4 (36.0–115.0)	0.001
12 months			
ACT score, n (%)			
Controlled (score 20–25)	87 (73.7%)	84 (70.6%)	1.00
Partially controlled (score 15–19)	22 (18.6%)	29 (24.4%)	0.851
Uncontrolled (score <15)	9 (7.6%)	6 (5.0%)	1.00
Mean PEF, L/min (range)	364.1 (126.0–661.0)	326.6 (89.0–726.0)	0.128
Mean FEV_1, % predicted (range)	83.9 (27.0–123.0)	74.3 (31.0–118.0)	0.001

4. Discussion

Delivery of asthma medications by inhalation achieves high concentrations in the airways with improved efficacy and better tolerability than systemic treatments [1]. However, using an inhaler is a skill that needs to be learned. Errors in inhaler technique are common, leading to poor asthma control, limitation of daytime activities and sleep, and reduced quality of life. Studies have shown that poor inhaler technique is common with all inhaler types, but in comparison with a DPI, a pMDI may be associated with fewer critical errors that result in poor clinical outcomes [10]. Asthma guidelines recommend that inhaler technique should be re-evaluated frequently and an alternative device should be considered for patients who cannot use the inhaler correctly after several repeats of training. This approach might avoid unnecessary intensification of pharmacological therapy, which is the usual recommended strategy for poorly controlled asthma [1]. In addition, use of multiple different inhaler types (e.g., for reliever and prophylactic therapies) should be avoided.

In this observational prospective real-world evidence study, we showed that switching from an ICS/LABA DPI to a ICS/LABA pMDI was non-inferior in respect of asthma control compared to maintenance therapy with an ICS/LABA DPI. The decision to switch was made by the physician in consultation with the patient and the patient was taught how to correctly use the new inhaler. The majority of patients (83%) in the Switch cohort remained on ICS/LABA pMDI over the entire 12 months follow-up period, indicating that the switch was generally well accepted by the patients. This is an important observation; previous studies have shown that switching asthma inhaler device without patient consent and engagement may negatively impact the doctor-patient relationship and adherence to therapy, and reduce asthma control [21, 22].

During the study 1-year outcome period, the pMDI was shown to be non-inferior to DPI (for a pre-defined threshold of non-inferiority set at a difference of no more than 20%) for all the efficacy outcomes assessed: asthma-related hospitalisations and/or hospital outpatient visits, exacerbations, and number of courses of acute oral corticosteroids. There were no asthma-related unscheduled consultations during the outcomes

Table 5
Comparison of asthma control at 1 year before switch versus 1 year outcome period.

	ICS/LABA pMDI Switch cohort (n = 119)		ICS/LABA DPI Maintenance cohort (n = 120)	
	Year before	Outcome period	Year before	Outcome period
Asthma control[a], n (%)	1 (0.8)	16 (13.4) p < 0.001	1 (0.8)	3 (2.5) p = 0.157
Individual outcomes, mean				
Number of exacerbations (person-years)[b]	2.4	0.9 p < 0.001	1.6	0.8 p < 0.001
Number of severe exacerbations (person-years)	2.5	1.3 p < 0.001	1.6	1.1 p < 0.001
Number of asthma-related attendances at the outpatient department (person-years)	3.7	2.1 p < 0.001	6.0	7.3 p < 0.001
Number of asthma-related hospitalisations and/or hospital outpatient attendances (person-years)	3.7	2.1 p < 0.001	6.1	7.3 p < 0.001
Number of asthma-related accident & emergency (A&E) attendance (person-years)	2.3	0.8 p < 0.001	1.6	0.7 p < 0.001
Number of prescriptions of any antibiotic where the reason for the prescription is a lower respiratory tract infections (person years)	1.1	0.5 p < 0.001	0.7	0.3 p < 0.001
Number of courses of acute systemic steroids (person years)	1.0	0.3 p < 0.001	0.7	0.4 p < 0.001
Number of daytime symptoms (person-years)	37.8	0.3 p = 0.005	32.0	0.5 p < 0.001
Number of night-time symptoms (person-years)	46.5	0.2 p = 0.005	35.2	0.6 p < 0.001

P value is for within group comparison of 1 year before to outcomes period. Rates are expressed as person-years, which is total number of occurrences/total number of patients.

To report p values used paired *t*-test for continuous variables with normal distribution, Wilcoxon signed rank test for continuous variables with non-normal distribution and McNemar test for categorical variables. To adjust the p values Bonferroni correction was used.

[a] Proxy for asthma control defined as no recorded hospital attendance for asthma, including admission, accident & emergency (A&E) attendance, out-of-hours attendance or outpatient department (OPD) attendance, AND no prescriptions for oral steroids, AND prescriptions for any antibiotic where the reason for the prescription is a lower respiratory tract infections.

[b] Proxy for exacerbation defined as unscheduled hospital admissions/A&E attendance for asthma, AND/OR use of oral steroids.

period in either group. It is notable that, compared to the DPI Maintenance cohort, at the time of switch, there was a significantly higher proportion of patients with uncontrolled asthma in the Switch cohort, and in the year prior to baseline, a significantly higher proportion of patients in this group received courses of acute systemic corticosteroids and had severe asthma exacerbations. Switching was at the discretion of the physician and reasons for switching were not recorded. However, after evaluation of inhaler technique, poor asthma control due to incorrect inhaler technique is an indication for considering switching to an alternative device, and we speculate this might have been an important reason for considering a switch in this study. In support of this observation, patients who switched to pMDI were significantly more likely to achieve overall asthma control during the 1-year after the switch of inhaler device. During the outcome period, at the 3-months and 12-months study visits, patients in both cohorts experienced an improvement in their FEV1 and PEF levels, with average FEV1 in the switch cohort reaching normal levels (>80% predicted). Compared to the one year prior to baseline, the proportion of patients in the Switch cohort with controlled asthma increased significantly in the outcome period (0.8%–13.4%, p < 0.001). All asthma outcomes improved, including annual number of asthma exacerbations, asthma-related attendances at the OPD, asthma-related hospitalizations and/or hospital outpatient attendances, asthma-related A&E attendance, prescriptions of any antibiotic for a lower respiratory tract infection, courses of acute systemic steroids, and daytime and night-time symptoms. The significant reduction in the number of asthma exacerbations along with decreased healthcare resource utilization over the outcome period among patients in the Switch cohort suggest that pMDIs may be cost-effective. In contrast, asthma-related attendances at the OPD and asthma-related hospitalizations and/or hospital outpatient attendances endpoints increased during follow-up in the Maintenance DPI cohort and consequently overall improvement in asthma control was not statistically significant in this group. Both treatments were well tolerated.

There are potential limitations to this study. Firstly, we did not only compare two inhaler devices, but also two different ICS/LABA combinations, FP/FOR in the pMDI and FP/Sal in the DPI. Therefore, it is possible that differences in drug regimen may, at least in part, account for differences in outcomes between groups. Previous comparative studies and a Cochrane analysis have reported similar efficacy with these combinations in terms of asthma control and lung function [23–26]. However, formoterol has a faster bronchodilatory effect than salmeterol, which may have a positive effect on patient preference and adherence to therapy [25,27]. Secondly, the study compared new users of a pMDI in the Switch cohort to continuing users of a DPI in the Maintenance cohort. Therefore, the study would have excluded patients who had previously discontinued ICS/LABA DPI treatment because of adverse effects or lack of efficacy, and selected for a group in whom the DPI therapy was tolerated and effective. Indeed, there were no incident adverse events reported in this group during the outcomes period. Although this selection bias may result in an over-estimation of the ICS/LABA DPI efficacy, for the same reason it also increases confidence in the efficacy of the ICS/LABA pMDI, since that was demonstrated to be at least non-inferior to the DPI. Conversely, there was a selection bias in the switch group, which contained a higher proportion of patients with poor asthma control prior to baseline, which could increase the likelihood of clinical improvement in this group.

Thirdly, although difficulty with inhaler technique and poor asthma control may have been indications for switching to pMDI, we did not collect data on adherence or the reason for switch from DPI to pMDI and cannot draw any definitive conclusions in that regard. Lastly, since this study was conducted in a single medical practice in Kuwait, possible differences between asthma management practices and treatment standards among physicians of different backgrounds can affect the generalizability of the study results across a diversity of sites and countries.

5. Conclusion

The results of this study demonstrate that in real-world clinical practice, when switching from a ICS/LABA DPI to an alternative device is considered, ICS/LABA pMDI is an effective and well tolerated inhaler device. In patients with asthma symptoms that are not well controlled with an ICS/LABA DPI, after evaluation of inhaler technique, switching to an ICS/LABA pMDI provides an alternative choice that may improve asthma control.

Credit author roles

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publication. Dr Webb is a professional medical writer and provided writing assistance for the first draft of the manuscript with financial support from Mundipharma Middle East FZ-LLC. All authors reviewed, contributed to, and approved successive drafts and the final manuscript. The authors report no other conflicts of interests relating to this study.

Declaration of competing interest

The authors report no other conflicts of interests relating to this study.

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