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ORIGINAL ARTICLE

Real-life effectiveness of inhaler device switch from dry powder inhalers to pressurized metred-dose inhalers in patients with asthma treated with ICS/LABA

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ABSTRACT

Background and objective: **Mixed inhaler device use for asthma is associated with worse inhaler technique and outcomes. Given that relievers are commonly prescribed as pressurized metred-dose inhalers (pMDI), changing preventers from dry powder inhalers (DPI) to pMDI may improve asthma outcomes. This study aimed to assess the persistence and effectiveness of switching from DPI to pMDI for inhaled corticosteroid and long-acting β_2-agonist combination therapy (ICS/LABA).**

Methods: **This was a historical cohort study using Ajou University Hospital (Korea) patient records. Persistence of switch was defined as receiving ≥1 pMDI and no DPI after the switch. Effectiveness of switch was assessed as the proportion without severe asthma exacerbation and the proportion achieving risk domain asthma control (RDAC; no asthma-related hospitalization, antibiotics without upper respiratory diagnosis or acute course of oral corticosteroids) and overall asthma control (OAC; RDAC and ≤ 200 µg salbutamol/≤500 µg terbutaline average daily dose) comparing 1 year after and before the switch.**

Results: **Within 85 patients who switched from DPI to pMDI and persisted for a year, higher proportion were free from asthma exacerbation after the switch (mean difference in proportion = 0.129, 95% CI: 0.038–0.220). Switching to pMDI was also associated with better RDAC (75.3% vs 57.7%, *P* = 0.001) and OAC (57.7% vs 45.9%, *P* = 0.021). From the entire 117 patients who switched to fixed-dose combination (FDC)/ICS LABA pMDI, 76.1% (95% CI: 69.0–100.0%) patients persisted in the following 6 months.**

Conclusion: **Switching to and persisting with pMDI was associated with decreased asthma exacerbations and improved asthma control. The majority of patients persisted with the switch to pMDI for ICS/LABA treatment.**

SUMMARY AT A GLANCE

Switching from a dry powder inhaler (DPI) to a pressurized metred-dose inhaler (pMDI) for fixed-dose combination inhaled corticosteroids/long-acting β_2-agonist (FDC ICS/LABA) asthma treatment led to decreased asthma exacerbations and was associated with better asthma control. The majority of patients persisted with the change.

Key words: asthma, dry powder inhaler, medication persistence, metred-dose inhaler, treatment efficacy.

INTRODUCTION

Asthma is a chronic inflammatory airway disease representing a considerable global healthcare burden.[1,2] In South Korea, asthma had a prevalence of 4.7% in 2008,[3] and posed significant economic burden through both direct (healthcare resource usage) and indirect costs (loss of productivity),[3,4] ranking as the fourth most burdensome disease in terms of disability-adjusted life years.[5]

Korean and International asthma guidelines recommend fixed-dose combination (FDC) of inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) for patients with persistent asthma when ICS treatment is insufficient.[6,7] Current inhaler devices available for ICS/LABA combination therapy include dry powder inhalers (DPI) and pressurized metred-dose inhalers (pMDI). Regardless of the device, optimal inhaler technique is crucial for efficient drug delivery to the lungs.

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To deliver relievers, pMDI are most common among patients with asthma, yet for maintenance treatment, both DPI and pMDI are used. DPI and pMDI require different techniques, and mixed prescription of a DPI reliever and a pMDI preventer may lead to increased errors and subsequent negative impact on asthma outcomes.[8–11] Changing maintenance therapies from DPI to pMDI, that is matching of reliever and preventer device, may therefore improve clinical outcomes in asthma patients prescribed FDC ICS/LABA as preventer.

A systematic review of the Cochrane Airways Group trial database showed pMDI to be as effective as other types of inhaler devices, including DPI, with regard to ICS treatment outcomes for asthma.[12] This was supported by a real-world observational study in UK general practice setting which showed FDC ICS/LABA delivered as pMDI to have significantly higher odds in achieving asthma control and treatment success than DPI.[13]

This study aimed to investigate the asthma treatment outcomes in 1 year after switching from a DPI to a pMDI device for FDC ICS/LABA compared to the year before the switch within a real-life specialist asthma care setting in South Korea. This study also aimed to determine the short-term (6 months) persistence of the switch within these patients.

METHODS

Study design

This was a historical cohort database study consisting of two cohorts: a total switch cohort and an effectiveness cohort (Fig. 1).

The effectiveness cohort aimed to assess the effectiveness of switching from DPI to pMDI. This cohort consisted of a 1-year baseline period for patient characterization prior to the index date (date of first pMDI prescription) and a 1-year outcome period for endpoint measures. The total switch cohort aimed to evaluate the persistence of switch from previous DPI to pMDI prescription. This cohort consisted of a 1-year baseline and a 6-month outcome period.

This study was approved by the Institutional Review Board of Ajou University Hospital, Republic of Korea with registration number AJIRB-MED-MDB-16-019. This study was registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance website with registration number EUPAS12279.

Data source

This study utilized records from the Electronic Medical Record Database of Ajou University Hospital (Allergy and Clinical Immunology Department), South Korea from 31 July 2010 to 31 July 2016. The database contains detailed and extensive longitudinal data of patients with moderate/severe asthma.

Inclusion and exclusion criteria

This study included patients with asthma aged 12–80 years at the index date. Patients must had at least 1 year of available medical records prior to FDC/ICS LABA prescription, the first prescription of FDC ICS/LABA pMDI was within the study period, had actively treated asthma (≥2 prescriptions of FDC ICS/LABA DPI at baseline) and belonged to the same ICS daily FP (fluticasone propionate) equivalent dose category on their last baseline DPI and first pMDI at index date (the prescribed ICS dose, based on GINA definition; low: >100–250 μg, medium: >250–500 μg or high: ≥500 μg).

Patients were excluded if they had FDC ICS/LABA pMDI prescription prior to the study, received maintenance oral corticosteroids (OCS) during the baseline period or received multiple FDC ICS/LABA or separate

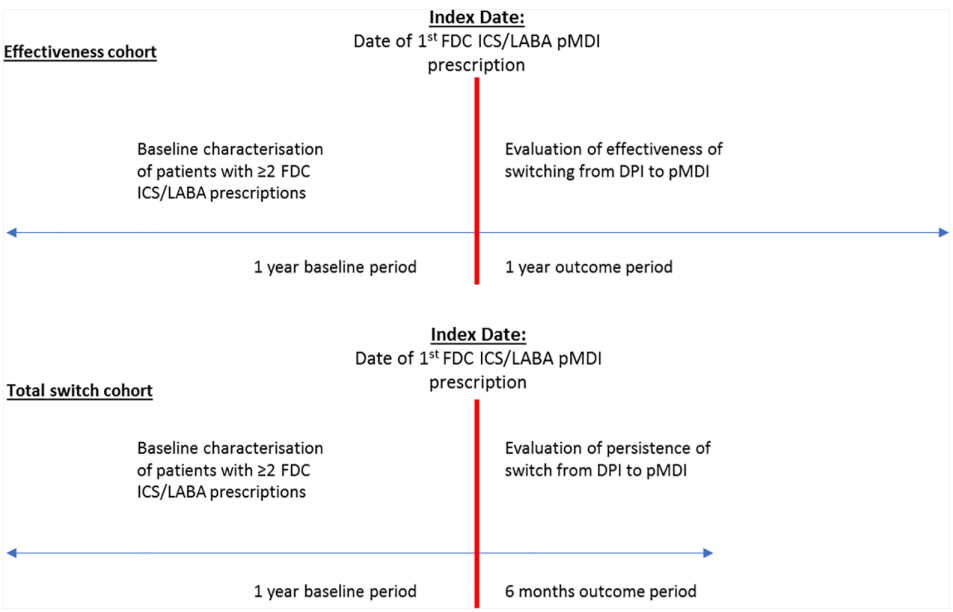

Figure 1 Study design of the effectiveness cohort and the total switch cohort. DPI, dry powder inhaler; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metred-dose inhaler.

ICS or LABA prescriptions on the date of the FDC ICS/LABA prescription.

Additional inclusion criterion for the effectiveness cohort was that patients must have ≥1 prescription of FDC ICS/LABA pMDI (in addition to the index prescription) and no FDC ICS/LABA DPI during the outcome period. Patients with index date between 31 July 2011 and 31 July 2015 were included.

The total switch cohort included patients with index date between 31 July 2011 and 31 January 2016. Patients must have at least one prescription of FDC ICS/LABA during the 6-month outcome period (in addition to the index prescription).

Clinical outcomes

The primary outcome of this study was the proportion of patients free from severe asthma exacerbation after compared to before the switch within the effectiveness cohort. Severe exacerbation was defined based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force 2015 definition[14]: any asthma-related hospitalization or emergency hospital attendance or prescription of acute course of OCS. Other respiratory-related outcomes investigated included previously validated[15] database measures of asthma control: risk domain asthma control (RDAC) and overall asthma control (OAC), as described and defined in Table 1.

The secondary outcome was the persistence of change to pMDI within the total switch cohort. This was defined as the percentage of patients who, at 6 months post-index date, received ≥1 prescriptions of ICS/LABA pMDI (in addition to that issued at their index date prescription) and no prescription for an ICS/LABA DPI over the same period. Persistence of change was claimed if the proportion of patients who persisted with the change was ≥70% which was considered a clinically significant limit.[16]

Exploratory subgroup analysis for primary and secondary outcomes was performed, stratified by the type of FDC ICS/LABA pMDI prescribed: FP/formoterol (FP/FORM; Flutiform, Recipharm, Crewe, UK) or beclomethasone dipropionate/FORM (BDP/FORM; Foster, Chiesi Pharmaceuticals Parma, Italy).

Sample size calculation

For the primary outcome, a sample size of 163 has 90% power to detect a non-inferior difference in proportions of patients with no exacerbations of −0.125 using a paired McNemar's chi-square test with a 0.025 one-sided significance level, assuming the proportion of discordant pairs was 0.242.[16]

For the secondary outcome of persistence, a sample size of 100 per change cohort would be sufficient to construct a 95% one-sided CI with an upper bound of less than 30% to power the evaluation of ICS/LABA pMDI persistence of change based on an expected change-back probability of approximately 20%.[16]

Statistical analysis

Statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics were compared using Student's t-tests or Mann–Whitney U-tests for continuous variables and chi-square test for categorical variables.

Primary statistical outcome was difference in paired binomial proportion with 95% CI of patients free from asthma exacerbation. Other respiratory outcomes were analysed with Wilcoxon signed-rank test with continuity correction, exact McNemar's test or marginal homogeneity test as appropriate. For the secondary outcome of persistence of change, one-sided 90% CI for binomial proportions were calculated.

RESULTS

A total of 2288 patients prescribed with FDC ICS/LABA were identified. Following inclusion and exclusion, the effectiveness cohort consisted of 85 patients who switched and remained on pMDI for at least 1 year, of whom 47 switched to BDP/FORM pMDI and 38 switched to FP/FORM pMDI. The total switch cohort consisted of 117 patients who switched from DPI to pMDI, of whom 65 switched to BDP/FORM and 52 to FP/FORM. The patient selection flow chart for the both cohorts is presented in Figure 2.

Baseline characteristics of the 85 patients in the effectiveness cohort are presented in Table S1 (Supplementary Information). This cohort consisted of 49.4% male patients with mean age of 52.9 years.

Baseline characteristics of the 117 patients in the total switch cohort are presented in Table S2 (Supplementary Information). Similar baseline characteristics were observed between patients who persisted (n = 89 patients) and patients who returned to DPI (n = 28 patients). The persisting group was slightly, but not significantly younger (mean age: 53.4 vs 56.7 years). The only significant difference was the higher proportion of patients with leukotriene receptor antagonist prescription in the persisting group (86.5% compared to 67.9% in non-persisting group, P = 0.05).

Effectiveness of switch to pMDI

Prevention of exacerbation

The mean difference in proportion of patients free from severe asthma exacerbation was 0.129 (95%CI: 0.038–0.220) (Table 2). Stratification by the FDC ICS/LABA pMDI prescribed, both FP/FORM (difference in proportions: 0.211, 95% CI: 0.081–0.340) and BDP/FORM (difference in proportions: 0.064, 95%CI: −0.060 to0.188) showed similar results (Table 2).

Other respiratory outcomes

Significantly higher proportions of patients achieved RDAC (75.3% vs 57.7%, P = 0.001) and OAC (57.7% vs 45.9%, P = 0.021) in the outcome period compared to the baseline period (Table 3). Stratification by FDC ICS/LABA type showed significantly better RDAC (81.6% vs 55.3%, P = 0.002) and OAC (60.5% vs 42.1%, P = 0.020) in patients who changed to FP/FORM in the outcome compared to the baseline. However, no

Table 1 Other respiratory outcomes and their definitions

Outcome	Definition[†]
RDAC[15]	Absence of: Asthma-related hospital admissions AND Asthma-related A&E attendance AND An acute course of OCS AND Asthma-related antibiotics without upper respiratory diagnosis
OAC[15]	RDAC as defined above AND ≤200 μg Salbutamol/≤500 μg terbutaline average daily dose
Severe asthma exacerbation (ATS/ERS 2015)	Occurrence of the following: Asthma-related hospital admissions OR Asthma-related A&E attendance OR An acute course or OCS
Acute respiratory event	Occurrence of the following: Asthma-related hospital admissions OR Asthma-related A&E attendance OR An acute course of OCS OR Asthma-related antibiotics without upper respiratory diagnosis
Treatment stability	RDAC as defined above AND No additional or change in therapy, denoted by either: an increase in ICS dose of ≥50% of that of prescribed at index date addition of theophylline or an LTRA or LABA
Asthma-related hospitalization	Rate of asthma-related hospital inpatient admissions
Average daily SABA usage	Average daily SABA dosage during outcome year (in μg) calculated by $\frac{\text{Number of inhalers used} \times \text{doses per inhaler}}{365} \times \text{strength}$ Categorized as >0 to ≤200, >200 to ≤400, >400 to ≤800, >801 μg daily SABA dosage
Average daily ICS dose	Average daily ICS (fluticasone equivalent) dosage during outcome year (in μg) calculated by $\frac{\text{Number of inhalers used} \times \text{doses per inhaler}}{365} \times \text{strength}$ Categorized as 0, >0 to ≤250, >250 to ≤500, >500 μg daily ICS dosage (low, medium and high as per GINA guidelines)
Oral thrush	Diagnostic code for oral thrush OR Prescription of antifungal therapy

[†]Asthma related was defined as accompanied by either: (i) primary diagnosis of asthma, (ii) primary diagnosis of lower respiratory tract infection and secondary diagnosis of asthma and (iii) primary diagnosis of lower respiratory tract infection and previous asthma diagnosis.

A&E, Accident & Emergency; ATS/ERS, American Thoracic Society/European Respiratory Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OAC, overall asthma control; OCS, oral corticosteroid; RDAC, risk domain asthma control; SABA, short-acting β_2-agonist.

statistically significant improvement in RDAC (70.2% vs 59.6%, P = 0.200) or OAC (55.3% vs 48.9%, P = 0.500) was observed after switching to BDP/FORM.

Within the outcome year, there were significantly lower proportion of patients who had severe asthma exacerbations (15.3% vs 28.2% with ≥1 exacerbation, P = 0.030), number of acute respiratory events (24.7% vs 42.3% with ≥1 events; P = 0.006) and ICS average daily dose (74.1% vs 89.4% at >500 μg; P < 0.001) compared to the baseline year (Table 3).

Persistence of change to pMDI

Persistence of change in the following 6 months was observed in 76.1% (95% CI: 69.0–100.0%) (Table 4), fulfilling the predetermined limit for persistence of 70%. Stratified based on the prescribed FDC ICS/LABA, similar rates of persistence were observed in both change to FP/FORM (75.0%; 95% CI: 64.1–100.0%) and BDP/FORM (76.9%; 95% CI: 67.4–100%) (Table 4).

DISCUSSION

This was a historical cohort study assessing the persistence and effectiveness, in terms of proportion of patients free from asthma exacerbations, of switching from a DPI to a pMDI for FDC ICS/LABA within the South Korean specialist asthma care setting.

Results from the effectiveness cohort suggested that switching to a pMDI for ICS/LABA therapy resulted in a significantly lower proportion of patients who had at least one asthma exacerbation in the year after the switch. Switching to pMDI was also associated with significantly better RDAC and OAC. Based on the result from the total switch cohort, majority of the patients was observed to persist with the change to pMDI.

This study utilized real-life data from a high-quality hospital database with well-characterized asthma patients. Classic randomized control trials investigating the efficacy of inhaler devices tend to enrol very selective groups of patients.[11,17,18] In real-life practice setting, factors such as imperfect inhalation techniques and non-adherence to treatment are common,[18–22]

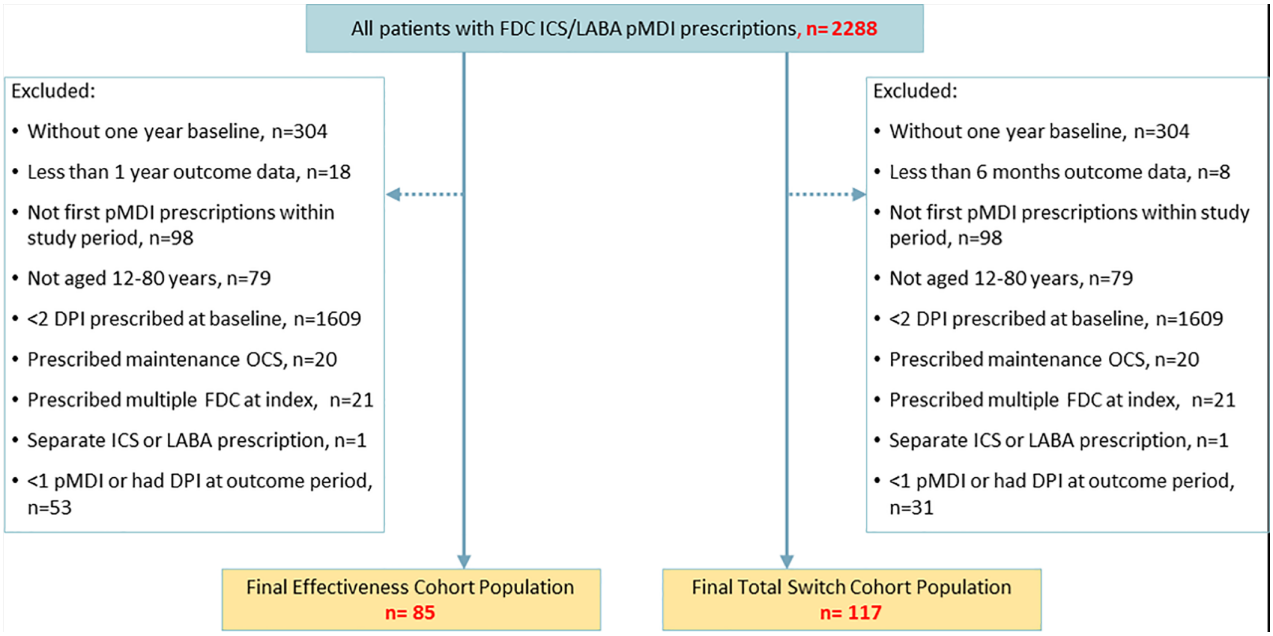

Figure 2 Patient selection flow chart for the effectiveness cohort and total switch cohort. FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroid; pMDI, pressurized metred-dose inhaler.

Table 2 Mean difference in proportion of patients free from severe asthma exacerbation following change to FDC ICS/LABA pMDI from FDC ICS/LABA DPI

Patient group	Mean difference (CI)[†]	Non-inferiority met (Yes/No)
Overall ($n = 85$)	0.129 (0.038, 0.220)	Yes
FP/FOR ($n = 38$)	0.211 (0.081, 0.340)	Yes
BDP/FOR ($n = 47$)	0.064 (−0.060, 0.188)	Yes

[†]Paired difference of binomial proportions with 95% CI.

BDP, beclomethasone dipropionate; DPI, dry powder inhaler; FDC, fixed-dose combination; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metred-dose inhaler.

negatively impacting inhaler treatment outcomes.[17,22–25] The current study indicated that within Korean real-life practice setting, pMDI was comparable to DPI in preventing asthma exacerbations, and led to better asthma control, despite the potential for imperfect adherence and inhaler technique. In addition, while this study was retrospective in nature, data were collected prospectively and thus the patients were not influenced by recall bias.

Inherent to retrospective studies, this study is unable to account for confounding factors not recorded in the database.[17] The current study is unable to determine the extent to which improper adherence, inhaler techniques, the general asthma trend within the population and other potential confounding factors such as inhaler technique education influenced the outcome of switching.

The patient records utilized in this study were collected for routine clinical purposes instead of research purposes. The validity and completeness of individual patient records cannot be assessed and thus omission and errors may exist. To allow analysis, patients were included only if they had continuous data available across the entire baseline and outcome periods.

The current study looked solely at the use of FDC ICS/LABA inhalers and did not include/exclude patients by chronic obstructive pulmonary disease (COPD) or other respiratory disease diagnoses. The authors note that some asthma drugs were prescribed albeit with COPD diagnosis due to the strict reimbursement system in Korea. However, there was no significant difference in the prevalence of baseline COPD in patients who persisted and those who did not persist with the switch. Thus, it is deemed unlikely that this limitation would have caused significant changes in our findings.

The results of the current study confirm our findings in a parallel, similar study[26] measuring persistence and effectiveness of switching from DPI to pMDI using records from the national Korean Health Insurance Review and Assessment (HIRA) Service Database.[27] The study also reported non-inferiority of switching to pMDI in terms of proportion of patients free from asthma exacerbation in 1 year following the switch compared to 1 year prior the switch.

Stratification by the FDC ICS/LABA type showed that, despite the much lower sample size, switching from DPI to FP/FORM pMDI was still associated with significantly better asthma control. Previous studies have reported FP/FORM to be efficacious in improving asthma control and decreasing asthma exacerbations in clinical trial settings[28] as well as in a prospective non-interventional post-authorization safety study setting.[29] This study supports the effectiveness of FP/FORM pMDI in the context of real-world setting.

In clinical practice, when switching inhalers, patients should be carefully guided. Switching of inhalers without proper communication with patients has been

Table 3 Comparison of respiratory outcomes before and after switch to pMDI

	Measure[†]	Baseline ($n = 85$)	Outcome ($n = 85$)	*P*-value
Primary outcome: free from asthma exacerbation	Yes, *n* (%)	61 (71.8)	72 (84.7)	0.010[‡]
Number of severe asthma exacerbations	Mean (SD)	0.53 (1.2)	0.41 (1.2)	0.500[§]
Number of severe asthma exacerbations (categorized)	0	61 (71.8)	72 (84.7)	0.030[¶]
	1	13 (15.3)	3 (3.5)	
	2	7 (8.2)	5 (5.9)	
	3	3 (3.5)	1 (1.2)	
	4+	1 (1.2)	4 (4.7)	
Risk domain asthma control	Yes, *n* (%)	49 (57.7)	64 (75.3)	0.001[‡]
Overall asthma control	Yes, *n* (%)	39 (45.9)	49 (57.7)	0.021[‡]
Acute respiratory events (continuous)	Mean (SD)	0.8 (1.4)	0.5 (1.2)	0.272[§]
Acute respiratory events (categorized)	0	49 (57.7)	64 (75.3)	0.006[¶]
	1	22 (25.9)	9 (10.6)	
	2	7 (8.2)	6 (7.1)	
	3	6 (7.1)	2 (2.4)	
	4+	1 (1.2)	4 (4.7)	
Asthma-related hospitalization rate	Mean (SD)	0.1 (0.4)	0.1 (0.7)	0.100[§]
SABA inhaler average daily dose (μg)[‡‡]	Mean (SD)	243.0 (358.7)	203.7 (348.8)	0.470[§]
SABA inhaler average daily dose (categorized, in μg)[‡‡]	0	47 (55.3)	54 (63.5)	0.300[¶]
	>0–200	14 (16.5)	7 (8.2)	
	>200–400	7 (8.2)	9 (10.6)	
	>400–800	7 (8.2)	8 (9.4)	
	>800	10 (11.8)	7 (8.2)	
ICS average daily dose (fluticasone equivalent in μg)[‡‡]	≥100–250	0 (0.0)	11 (12.9)	0.001[¶]
	>250–500	9 (10.6)	11 (12.9)	
	>500	76 (89.4)	63 (74.1)	
Treatment stability	No	—	70 (82.4)	N/A
	Yes	—	15 (17.7)	
Oral thrush	No	84 (98.8)	85 (100.0)	N/A
	Yes	1 (1.2)	0 (0.0)	

[†]Measures are presented as *n* (%) unless stated.
[‡]Exact McNemar's test.
[§]Wilcoxon signed-rank test with continuity correction.
[¶]Marginal homogeneity test.
[‡‡]Based on the numbers of inhalers used by the patients over a year.
ICS, inhaled corticosteroid; pMDI, pressurized metred-dose inhaler; SABA, short-acting β_2-agonist.

Table 4 Persistence of switch at 6 months after switch to pMDI within the total switch cohort

	Overall		FP/FORM		BDP/FORM	
Persistence of change	*n*	% (one-sided 95% CI)	*n*	% (one-sided 95% CI)	*n*	% (one-sided 95% CI)
No	28	23.9 (0.0, 31.0)	13	25.0 (0.0, 36.0)	15	23.1 (0.0, 33.6)
Yes	89	76.1 (69.0, 100.0)	39	75.0 (64.1, 100.0)	50	76.9 (67.4, 100.0)

BDP, beclomethasone dipropionate; FORM, formoterol; FP, fluticasone propionate; pMDI, pressurized metred-dose inhaler.

reported to lead to treatment failure.[30] This was further supported in a qualitative interview study in which patients who received a non-consented inhaler device switch reported worsened perception of asthma control and patient–physician relationship.[31] Our study did not observe a higher proportion of patients with exacerbations following change of inhaler device. In this study, inhaler device switch occurred during consultations, highlighting the importance of proper physician–patient communication during the switch of inhaler devices.

The results of this study need to be confirmed in either a larger database study, or a prospective study that accounts for additional important factors such as adherence and inhaler techniques. It is of interest to investigate if switching to the same device type for reliever and maintenance therapy indeed leads to a lower rate of inhaler technique errors.

The persistence of switch suggests that pMDI was well received by majority of the patients. However, due to the different requirements for correct use of either devices, there may be variability in each patients' compatibility with either device due to factors such as age.[11,32] Inhaler switching in this study was not driven by any specific reason; several patients were switched due to their age or their preferred inhaler device. To enable better and individualized patient management, further studies are required to investigate the reasons for patients' decisions to persist or to return to the previous inhaler device.

In conclusion, this study showed that in real-life specialist asthma setting, changing to pMDI for FDC ICS/LABA led to a significantly lower proportion of patients who had severe exacerbations, and was associated with better asthma control, compared to the year before when patients were on DPI prescriptions. The majority of patients were also found to persist with this switch for at least 6 months.

The results of this study, together with our findings from the Korean Health Insurance and Review Assessment Service database,[26] provide evidence supporting the switch from DPI to pMDI to deliver FDC ICS/LABA maintenance therapy.

Data availability statement: The data set supporting the conclusions of this article was derived from the Electronic Medical Record Database of Ajou University Hospital (Allergy and Clinical Immunology Department). The authors received ethics approval for purely observational research by the IRB of Ajou University Hospital. The authors do not have permission to give public access to the study data set. Data can be requested from the Ajou University Hospital IRB and access is subject to their approval.

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Abbreviations: A&E, Accident & Emergency; BDP, beclomethasone dipropionate; DPI, dry powder inhaler; FDC, fixed-dose combination; FORM, formoterol; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OAC, overall asthma control; OCS, oral corticosteroid; pMDI, pressurized metred-dose inhaler; RDAC, risk domain asthma control; SABA, short-acting β_2-agonist.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Table S1 Baseline characteristics of patient in effectiveness cohort.
Table S2 Baseline characteristics of patient in total switch cohort.

