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ORIGINAL RESEARCH

Patients with Asthma Prescribed Once-Daily Fluticasone Furoate/Vilanterol or Twice-Daily Fluticasone Propionate/Salmeterol as Maintenance Treatment: Analysis from a Claims Database

Ryo Atsuta · Jun Takai · Isao Mukai · Akihiro Kobayashi · Takeo Ishii · Henrik Svedsater

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ABSTRACT

Introduction: There is a paucity of data describing prescribing patterns and adherence to therapy of inhaled corticosteroids (ICS) in combination with long-acting β_2-agonists (LABA) in the Japanese population in clinical practice.

Methods: This was a non-interventional, retrospective, cohort study of patients who were prescribed medication for asthma, using data from the Japan Medical Data Center Claims Database. Data from patients aged ≥ 15 years with a prescription of asthma drugs between December 2014 and October 2015 (Day 0, the index date when asthma medication was initiated) were analysed in 12-month pre-index and post-index periods. Part 1 focused on baseline characteristics and epidemiological outcomes in the pre- and post-index period in the overall asthma population, whereas comparing medication adherence [number of prescribed days per year and proportion of days covered (PDC)] between ICS/LABA-naïve patients treated with once-daily fluticasone furoate/vilanterol (FF/VI) and twice-daily fluticasone propionate/salmeterol (FP/SAL) was the primary endpoint in Part 2.

Results: Of the available patient data (N = 2,953,652), 28,699 patients were identified as having asthma. ICS/LABA was the main asthma treatment prescribed; 11,167 (38.9%) patients were continuous ICS/LABA users. In ICS/LABA-naïve asthma patients, treatment with once-daily FF/VI was associated with

Ryo Atsuta and Jun Takai contributed equally.

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R. Atsuta
Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan

Present Address:
R. Atsuta
Akihabara Atsuta Allergy and Respiratory Medicine Clinic, Tokyo, Japan

J. Takai · I. Mukai (✉) · A. Kobayashi · T. Ishii
GSK, Tokyo, Japan
e-mail: isao.mukai@gsk.com

Present Address:
J. Takai
Division of Medical Biochemistry, Tohoku Medical and Pharmaceutical University, Miyagi, Japan

T. Ishii
Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

H. Svedsater
GSK, Brentford, UK

higher medication adherence compared with twice-daily FP/SAL; mean [standard deviation (SD)] number of prescribed days per year was 97.8 (115.9) for FF/VI versus 80.5 (92.7) for FP/SAL ($p = 0.04$), mean (SD) PDC was 26.7% (31.5) for FF/VI versus 21.9% (24.8) for FP/SAL ($p = 0.04$). FF/VI was also associated with a lower rate of treatment discontinuation and no difference in use of short-acting beta$_2$-agonists or oral corticosteroids compared with FP/SAL.

Conclusions: ICS/LABA was the major prescribed asthma treatment in Japan. Medication adherence was greater with FF/VI, which may indicate that patients are more likely to adhere to once-daily FF/VI versus twice-daily FP/SAL.

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Study Registration: GSK Study No. 207264, GSK Study Register site: https://www.gsk-clinicalstudyregister.com/search/?search_terms=207264.

Keywords: Adherence; Asthma; Claims database; Japan; Retrospective

INTRODUCTION

Asthma prevalence in Japan has increased in recent years, with a 1.5-fold increase per decade since 1985 [1, 2]. The aim of asthma treatment is to enable patients to have normal respiratory function with no symptoms and to lead a life that is unhindered by their condition [1]. Inhaled corticosteroids (ICS) are used for the long-term management of mild asthma, due to the relatively low risk of side effects [1]. Since the clinical application of ICS concomitantly with long-acting β_2-agonists (LABA) became available for the treatment of asthma, the use of this combination has increased in Japanese clinical practice [3, 4]. In a Japanese National Health and Wellness Survey carried out in 2013, the proportion of ICS-using asthma patients also using LABA was 67% [4].

ICS/LABA treatment has been shown to provide good asthma control. According to a randomised, stratified, double-blind, parallel-group study of 3421 patients with uncontrolled asthma, use of ICS/LABA for one year enabled asthma to be well controlled in approximately 80% of patients [5]. However, poor adherence to prescribed asthma medication is a major barrier to positive treatment outcomes [6], and is a significant issue in asthma treatment; 30–70% of patients with asthma may be non-adherent to therapy [7]. While most ICS/LABA combinations need to be taken twice daily, it has been reported that adherence to once-daily inhaled medication is better than with twice-daily inhaled medication [6, 8].

Prescribing patterns for ICS/LABA have not been well described in clinical practice in Japan, and nor has adherence to once-daily fluticasone furoate/vilanterol (FF/VI) versus twice-daily ICS/LABA. FF/VI has demonstrated long-lasting improvements in lung function in patients with asthma, with 24-h efficacy [9]; in addition, the majority of patients find the delivery device very easy to use, with high levels of patient satisfaction reported [10].

The Japan Medical Data Center (JMDC) Claims Database is one of the largest publicly available epidemiological prescription databases in Japan [11]. It provides standardised data and has been used extensively in previous publications, including for studies evaluating treatment adherence [12, 13].

Our present analysis of data from the JMDC Claims Database aimed to: in Part (1) describe the characteristics, medical facility and healthcare resource utilisation, short-acting β_2-agonist (SABA) use and oral corticosteroid (OCS) use of patients with asthma who received a prescription for ICS/LABA; and in Part (2) compare the medication adherence [measured in this study by the number of prescribed days per year and the proportion of days covered (PDC)] between ICS/LABA-naïve patients with asthma who received prescriptions for FF/VI (once-daily) versus those who received prescriptions for fluticasone propionate/salmeterol (FP/SAL; twice-daily).

METHODS

Study Design

This was a non-interventional, retrospective, cohort study of patients with asthma (GSK Study

No. 207264 (GSK Study Register site: https://www.gsk-clinicalstudyregister.com/search/?search_terms=207264) who were prescribed medication for asthma, using medical (outpatient and inpatient) and pharmacy claims data from the JMDC Claims Database, which collects information from approximately 100 health insurance companies in Japan. The study was conducted in two parts. Part 1 was conducted as descriptive analysis and a feasibility check (i.e., confirming sufficient patient numbers, comparable characteristics of patients on FF/VI and FP/SAL, etc.) for progression to Part 2.

The study design is depicted in Supplementary Fig. S1. Data from all patients who had claims with asthma during the period from December 2014 to October 2015 were extracted from the JMDC database. Only data from patients who met all of the inclusion criteria and none of the exclusion criteria were used. In Part 1, the index date (Day 0) was defined as the date of first prescription of any asthma drug. For each patient in Part 2, the date of first initiation of ICS/LABA between December 2014 and October 2015 was designed as the index date (labelled as Day 0); patients must have received asthma drugs at least once prior to Day 0 to exclude de novo patients. FF/VI became available in December 2013, though December 2014 was chosen to ensure that drug usage had become more established.

There were two analysis periods of interest for the purpose of this study: a pre-index period (Day − 364 to Day 0) and a post-index period (Day 1 to Day + 365). The follow-up (post-index) period was 12 months for all patients in Part 1 and Part 2; a 1-year observation period was set to minimise seasonal bias. Baseline characteristics were measured during the pre-index period. For the evaluation of healthcare resource utilisation, OCS use, SABA use, asthma exacerbations and medication adherence, one years' data was extracted during the post-index period from Day 0.

Compliance with Ethics Guidelines

The study used anonymised data, therefore, no patient consent was requested, as this is not required for such studies in Japan. Ethical approval was obtained from the Ethics Review Committee at the Kitamachi Clinic (1-1-3 Kichijojikitamachi, Musashino city, Tokyo 180-0001).

Eligibility Criteria

The key inclusion and exclusion criteria are detailed in Fig. 1. Patients aged ≥ 15 years, with a claim of asthma (World Health Organization International Classification of Diseases [ICD]-10, items J45 or J46) and a prescription of asthma drugs [including ICS with or without LABA, leukotriene receptor antagonists (LTRAs), theophylline and SABA] at Day 0, and continuous enrolment in the JMDC Claims Database for one year before and one year after Day 0, were included. Patients were required to have at least one additional prescription of asthma drugs, other than Day 0, in Parts 1 or 2.

Study Cohort

Part 1: data from all patients who met all eligibility criteria were included. The patient cohorts by treatment are defined in Fig. 2. The overall asthma population included all patients who met all of the inclusion criteria. The ICS-monotherapy, ICS/LABA and non-ICS populations included patients who used the same drug class in the post-index period versus the pre-index period without switching. Patients switching drug category were excluded from the analysis.

Part 2: the ICS/LABA-naïve FP/SAL Diskus (DK) and FF/VI populations included all patients who had no prior ICS/LABA prescription for at least 12 months before Day 0 and were treated with the same product during Part 2 without switching; this population was used for the comparison of medication adherence. As the severity and hospitalisation patterns for patients with chronic obstructive pulmonary disease (COPD) and asthma are different than for those with asthma alone (which may influence adherence), asthma patients with COPD (at least one claim with COPD ICD-10, items J42 or J43 or J44 or J47) were excluded from Part 2.

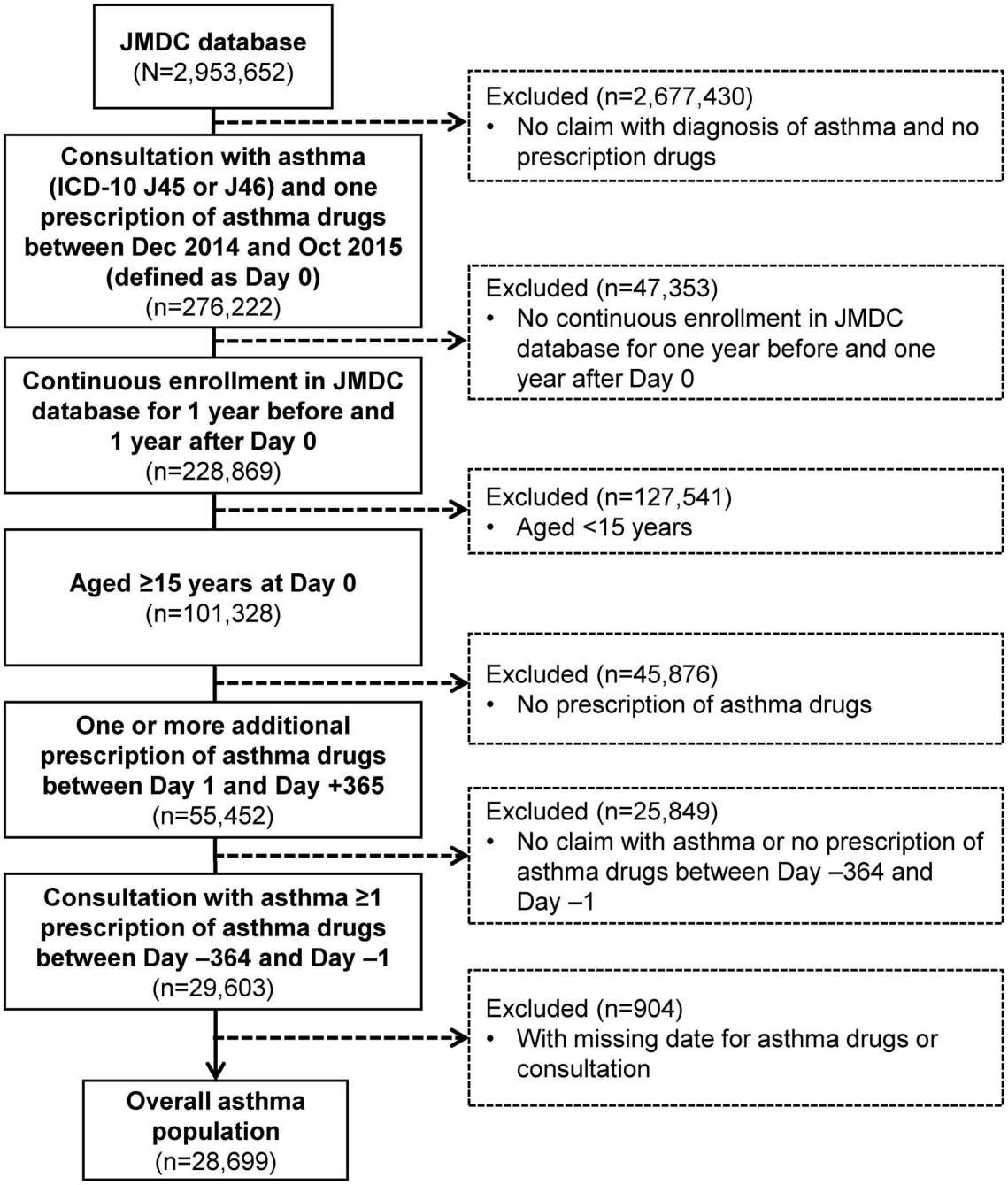

Fig. 1 Flow chart of inclusion criteria. *ICD* International Classification of Diseases, *JMDC* Japan Medical Data Center

Study Endpoints

Part 1: the primary endpoint of Part 1 was to describe the patient characteristics, medical facility and healthcare resource utilisation, SABA use, OCS use and asthma exacerbations of patients prescribed asthma drugs during the pre- and post-index periods. The secondary endpoint of Part 1 was to stratify the patient characteristics, and medical facility and healthcare resource utilisation during the pre-

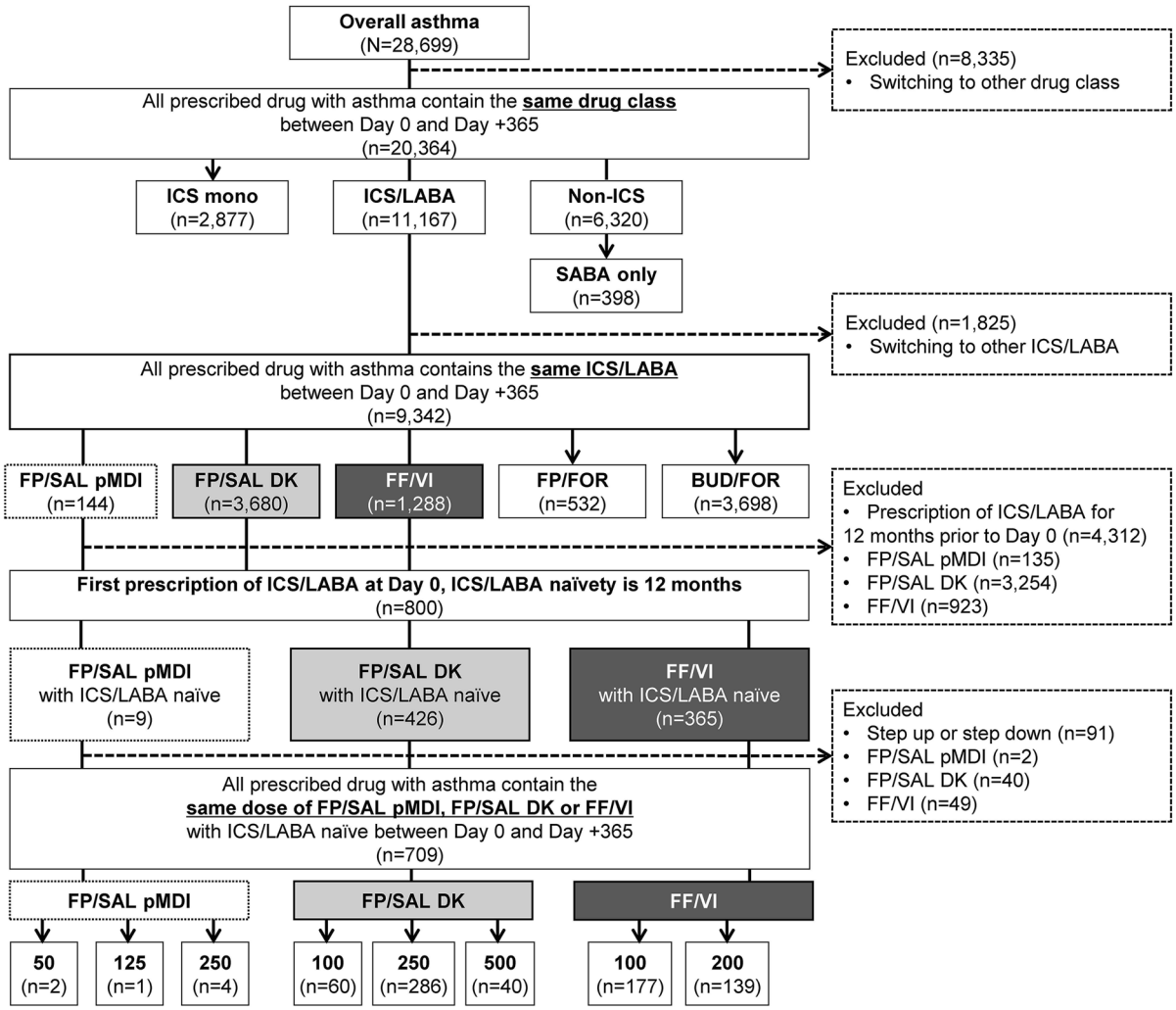

Fig. 2 Flow chart of comparison groups*. *Overall asthma: patients who met all inclusion criteria; ICS/LABA: patients who have used ICS/LABA, but not other drug classes (ICS monotherapy or non-ICS, including SABA) between Day 0 and Day + 365; ICS mono: patients who have used ICS monotherapy only between Day 0 and Day + 365; Non-ICS: patients who have only used non-ICS treatment (LTRA or theophillin or SABA) between Day 0 and Day + 365; SABA only: non-ICS patients who have only used SABA; FP/SAL DK or FF/VI with ICS/LABA-naïve: patients prescribed FP/SAL DK or FF/VI who have not used any ICS/LABA for 12 months prior to Day 0; FP/SAL DK 100/250/500: patients who are ICS/LABA-naïve and who have used FP/SAL DK at the same dose between Day 0 and Day + 365 (no step-up or step-down); FF/VI 100/200: patients prescribed FF/VI with ICS/LABA who are ICS/LABA-naïve and who have used FF/VI at the same dose between Day 0 and Day + 365 (no step-up or step-down). Patients who changed drug category or brand were not included. *DK* Diskus, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LTRA* leukotriene receptor antagonist, *pMDI* pressurised metered-dose inhaler, *SABA* short-acting β_2-agonist, *SAL* salmeterol, *VI* vilanterol

index period in the various subgroups according to asthma medication use/dose.

Part 2: the primary endpoint of Part 2 was to compare the number of prescribed days per year and PDC, as indicators of adherence, between patients treated with FF/VI and FP/SAL in the ICS/LABA-naïve cohort. Secondary endpoints were to compare SABA use, OCS use, persistence

of ICS/LABA-naïve use and overall medication adherence of patients prescribed FF/VI or FP/SAL. Further details of the variables of interest and endpoints are provided in the Supplementary Information.

Variables and Outcomes Assessed

A list of variables collected using the JMDC Claims Database at baseline is included in Supplementary Table S1 (for further information please also see Appendices A–H). The number of prescribed days per year and PDC extracted from Day 0 to Day + 365 was examined as an indication of medication adherence as previously described [14, 15]. Briefly, the number of prescribed days per year was calculated by adding the prescribed day per product in the post-index period (please refer to Appendix C for prescribed days per product). PDC was calculated by dividing the number of prescribed days per year by 366 days (from Day 0 to Day + 365). For example, if twice-daily FP/SAL DK 500 μg 60 doses were prescribed six times in the post-index period, the number of prescribed days per year and PDC was calculated as follows: 30 days × 6 = 180 days, 180 days/366 days = 49.2%. Thresholds of 50% and 80% adherence were also analysed.

Statistical Analysis

Part 1: the analysis of Part 1 was descriptive, therefore, neither formal comparison between populations nor hypothesis testing were performed.

Feasibility Check: using data from the pre-index period, a feasibility check was performed at the time of analysis in Part 1 to determine whether to proceed to Part 2. Based on previous studies that reported on adherence [6, 8], the difference in PDC between FF/VI and FP/SAL was assumed to be in the range of 4–20%. Therefore, a sample size of 200 patients was deemed sufficient on the assumption that the change in PDC would be 10%, as shown in Supplementary Table S2. Hence, the study was progressed to Part 2 only if there were at least 200 ICS/LABA-naïve patients prescribed FF/VI or FP/SAL, and if the baseline characteristics between FF/VI- and FP/SAL-treated ICS/LABA-naïve patients were similar.

Part 2: the null hypothesis was that the number of prescribed days per year and PDC between ICS/LABA-naïve FF/VI- and FP/SAL-treated patients was the same. The alternative hypothesis was that the number of days prescribed per year and PDC between ICS/LABA-naïve FF/VI- and FP/SAL-treated patients was different (two-sided test).

To control for potential confounding effects between the number of days prescribed per year and other variables of interest, baseline characteristics collected in the pre-index period were used as covariates for propensity score matching (PSM) if the number of patients exceeded 200 [16]. If the number of patients in each comparison group was < 200 after PSM, multivariate analysis would be conducted, with stratified propensity score as a covariate using the inverse probability of treatment weighting approach. All variables were summarised during Part 1 analysis and the study statistician selected the best candidate covariates in a blinded manner. Healthcare claims codes that could represent confounding factors between treatment and outcomes were identified (empirical covariates); the best empirical covariates were then combined with covariates a priori to estimate the propensity score using unconditional logistic regression. Variables included in the PSM included age, gender, pre-index concomitant disease, number of prescribed drugs, presence/absence of SABA and OCS, night-time visits to clinic/hospital and hospitalisations. Pre-ICS dose was also factored into the model but the reference model fitting index, i.e., C-statistics, was lower; therefore, the model without pre-ICS dose was selected. The default comparison was FF/VI (once-daily) versus FP/SAL DK (twice-daily). In addition, as a sensitivity analysis, dose comparisons of FF/VI 100 μg versus FP/SAL DK 250 μg, FF/VI 100 μg versus FP/SAL DK (100 + 250 μg) and FF/VI 200 μg versus FP/SAL DK 500 μg were conducted.

RESULTS

Part 1—Patient Characteristics and Medical Facility and Healthcare Resource Utilisation

In total, Day 0 data were available for 28,699 patients (overall asthma population). The mean age was 42.7 years (standard deviation [SD] 13.0) and 48.7% were male. Baseline demographics and disease characteristics during the pre-index period according to prescribed asthma medication at Day 0 are presented in Supplementary Table S3. ICS/LABA was the main asthma treatment; 11,167 (38.9%) patients were continuous ICS/LABA users (i.e., prescribed ICS/LABA at all visits for asthma treatment from Day 0 to Day +365). Overall, 2877 (10.0%) patients were treated with ICS monotherapy, 6320 (22.0%) patients were treated with non-ICS medications, 8335 (29.0%) patients were switched to other drug class and 398 (1.4%) patients were treated with SABA only (Fig. 2).

Healthcare resource utilisation during the post-index period based on prescribed asthma medication at Day 0 is presented in Supplementary Table S4. The mean number of asthma-related visits was 4–5.3 in the overall population, with no differences observed according to season; the proportion of asthma-related emergency room visits and hospitalisations was < 1% of patients. The proportion of patients who experienced at least one asthma exacerbation with systemic corticosteroid (SCS) was approximately 10%; exacerbations where the definition included antibiotic use occurred in 45–50% of patients.

The total cost of treatment was approximately 100,000 yen per patient per year overall, including 60,000–70,000 yen for the drug cost alone. Mean (SD) total costs were higher in ICS/LABA-treated patients [96,460 yen (164,624)] compared with patients treated with ICS-monotherapy [72,758 yen (132,753)], non-ICS therapy [62,461 yen (124,453)] and SABA only [38,018 yen (49,650)].

The proportion of patients who had at least one pulmonary function test in a larger facility (LF, ≥ 100 beds) and in a smaller facility (SF, < 100 beds) during Part 1 was 21.2% (n = 769/3622) and 13.6% (n = 3398/25,077), respectively. Overall, 11.2% of patients had at least one flow volume test (LF 18.2%; SF 10.2%); and 10.4% (LF 16.8%; SF 9.5%) had their vital capacity tested.

ICS usage (with or without LABA) was as follows: ICS-monotherapy, LF 17.1% (n = 620/3622) versus SF 9% (n = 2257/25,077); ICS/LABA, LF 44.1% (n = 1598/3622) versus SF 38.2% (n = 9569/25,077), while OCS usage was 17.7% in LF compared with 11.0% in SF. The exacerbation rate in LF versus SF (exacerbation with SCS use) was 13.6% versus 8.6%, but the exacerbation rate including antibiotic use (exacerbation with SCS and/or antibiotic use) was 33.2 versus 47.9%, respectively. The frequency of all-cause and asthma-related night-time visits in LF versus SF was 19.9% versus 33.9% and 3.6% versus 16.9%, respectively.

The proportion of male patients was higher in patients treated with FF/VI (54.1%), FP/SAL pressurised metered-dose inhaler (63.2%), and FP/SAL DK (58.5%) compared with those treated with FP/formoterol (FOR) (45.9%) and budesonide (BUD)/FOR (48.5%). More general practitioners tended to use FP/FOR compared with FF/VI or FP/SAL DK (data not shown).

Feasibility Check: the criteria were met to proceed to Part 2; 365 ICS/LABA-naïve patients were prescribed FF/VI and 426 ICS/LABA-naïve patients were prescribed FP/SAL (Supplementary Table S5). For the pre-index ICS data, which excludes Day 0, the mean (SD) dose (μg/day) (FP equivalent) was 25.3 ± 64.1 and 38.4 ± 102.5 in the FP/SAL DK and FF/VI groups, respectively. The proportion of patients who received at least one prescription was 29.2 and 27.9% in the FP/SAL DK and FF/VI groups, respectively.

Part 2—Medication Adherence

After PSM, the sample size was 602; ICS/LABA-naïve FF/VI, n = 301; ICS/LABA-naïve FP/SAL, n = 301. Baseline demographics and disease characteristics of ICS/LABA-naïve patients treated with FP/SAL and FF/VI before and after PSM are shown in Supplementary Table S6.

Treatment groups were comparable for these characteristics with one exception: before PSM, a significantly higher proportion of ICS/LABA-naïve patients treated with FP/SAL had been hospitalised at least once pre-index compared with ICS/LABA-naïve patients treated with FF/VI [365/379 patients (96.3%) versus 306/330 patients (92.7%); $p = 0.04$]. After PSM, the difference between these proportions [289/301 (96.0%) vs 288/301 (95.7%), respectively] was not statistically significant.

A univariate analysis of medication adherence, SABA use, OCS use and use of OCS burst in FP/SAL- and FF/VI-treated ICS/LABA-naïve patients is shown in Table 1 (where a burst was defined as $\geq$ 140 mg of OCS within 14 days). Patients had more prescribed days per year with FF/VI versus FP/SAL [mean (SD), 97.8 (115.9) vs 80.5 (92.7), $p = 0.04$] and a higher PDC [mean (SD), 26.7 (31.5) vs 21.9 (24.8); $p = 0.04$]. Significantly more patients had a $\geq$ 80% adherence (13.3% vs 6.0%; $p = 0.003$) in terms of PDC with FF/VI versus FP/SAL, and there was a trend towards more patients having a $\geq$ 50% (19.6% vs 13.6%; $p = 0.062$) rate of adherence.

SABA, OCS, and OCS burst use were similar between patients prescribed FP/SAL or FF/VI; the mean (SD) number of SABA canisters per year was 0.2 (0.9) versus 0.2 (0.6), respectively ($p = 0.4964$), mean (SD) OCS dose was 0.1 (1.1) versus 0.1 (0.4) mg/day, respectively ($p = 0.508$), and mean (SD) frequency of OCS burst use was 0.0 (0.1) versus 0.0 (0.1), respectively ($p = 0.738$). Regarding the dose comparison, FF/VI 100 μg was associated with higher adherence compared with FP/SAL (100 + 250 μg). No difference was found between FP/SAL DK 500 μg versus FF/VI 200 μg although the number of FP/SAL patients ($n = 40$) was probably insufficient to enable a valid comparison.

DISCUSSION

In this retrospective analysis of prescribing patterns for asthma medication, ICS/LABA was found to be the major asthma treatment in Japan. Compared with twice-daily FP/SAL, once-daily FF/VI was associated with a higher rate of medication adherence, as measured by prescription days and PDC), a lower rate of treatment discontinuation and no difference in SABA and OCS use.

The use of ICS/LABA has increased in Japan, with previous reports estimating a change from 9.2% of patients in 2008 to 18.2% in 2010 and 30.9% in 2013 [3, 4]. In this current study in Japan, we found that 38.9% of patients were continuous ICS/LABA users, and ICS/LABA was the major asthma treatment drug (continuous ICS monotherapy: 10%, continuous non-ICS medications: 22.0%, switched to other drug class: 29.0%). During the pre- and post-index period, medical facility uses (including nighttime visits and hospitalisations) and receipt of pre-index SABA and OCS were generally similar between patients treated with ICS/LABA, ICS-monotherapy and non-ICS. In total, 1.4% of patients were identified as using SABA only. These patients received a mean of 5.8 canisters per year, despite the fact that patients are only recommended to receive SABA as reliever therapy and should be prescribed ICS(/LABA) for maintenance [1]; however, SABA use overall was low compared with global data [17]. SABA use may be lower in Japan than in other regions as all patients with asthma can receive ICS/LABA if they consider it appropriate. The proportion of patients with well-controlled asthma in Japan is higher than in the EU [4]. In addition, the JMDC database mainly covers office workers and this population may have milder asthma compared with the total asthma population in Japan. Finally, inclusion of patients aged 15 years on Day 0 means that patients aged 14 years may have been included in the pre-index period analysis. However, all the relevant drug categories (ICS/LABA, ICS, LTRA and theophylline) can be used in patients aged 14 years, therefore, any potential bias of pre-treatment by age is limited.

The level of asthma control has been demonstrated previously to be directly proportional to adherence rate [18]. Better adherence to ICS/LABA combination therapy has been shown to be associated with reduced asthma-related emergency room visits and hospitalisations. Consequently, the SABA and individual corticosteroid use is lower [19]. Non-adherence to asthma medication is associated with

Table 1 Univariate analysis of medication adherence, SABA use, OCS use and OCS burst of FP/SAL and FF/VI with ICS/LABA-naïve

Variable	COPD-negative asthma		*p* value Fisher's exact test	*p* value *t* test
	FP/SAL DK with ICS/LABA-naïve (*n* = 301)	FF/VI with ICS/LABA-naïve (*n* = 301)		
Prescribed days per year (mean ± SD)	80.5 ± 92.7	97.8 ± 115.9	0.0431	
Proportion of days covered [PDC (%)] (mean ± SD)	21.9 ± 24.8	26.7 ± 31.5	0.037	
Adherence, *n* (%)				
≥ 50%	41 (13.6)	59 (19.6)	0.0623	–
≥ 80%	18 (6.0)	40 (13.3)	0.0034	–
Frequency of visit (mean ± SD)				
Total	2.8 ± 2.8	3.4 ± 3.7	–	0.0365
January	0.2 ± 0.4	0.3 ± 0.5	–	0.1891
February	0.2 ± 0.5	0.3 ± 0.5	–	0.1319
March	0.2 ± 0.4	0.3 ± 0.5	–	0.0543
April	0.2 ± 0.4	0.3 ± 0.6	–	0.0048
May	0.2 ± 0.4	0.3 ± 0.6	–	0.0090
June	0.2 ± 0.5	0.3 ± 0.5	–	0.3795
July	0.2 ± 0.4	0.3 ± 0.5	–	0.2230
August	0.2 ± 0.5	0.3 ± 0.5	–	0.1238
September	0.2 ± 0.4	0.3 ± 0.5	–	0.3913
October	0.3 ± 0.5	0.3 ± 0.5	–	0.2753
November	0.3 ± 0.5	0.3 ± 0.5	–	0.5644
December	0.3 ± 0.5	0.3 ± 0.5	–	0.8681
SABA				
Canisters per year (mean ± SD)	0.2 ± 0.9	0.2 ± 0.6	–	0.4964
Proportion of patients who were prescribed at least 4 canisters, n (%)	2 (0.7)	3 (1.0)	1.0000	–
Canisters per year (Mean ± SD)	8.5 ± 6.4	4.7 ± 0.6	–	0.3394
OCS				
Mean ± SD dose (mg/day)	0.1 ± 1.1	0.1 ± 0.4	–	0.5076
Proportion of patients who were prescribed at least once, n (%)	26 (8.6%)	28 (9.3%)	0.8867	–
Mean ± SD dose (mg/day)	1.2 ± 3.6	0.6 ± 1.0	–	0.4375

Table 1 continued

Variable	COPD-negative asthma		*p* value Fisher's exact test	*p* value *t* test
	FP/SAL DK with ICS/LABA-naïve (*n* = 301)	FF/VI with ICS/LABA-naïve (*n* = 301)		
OCS burst				
Frequency of burst (≥ 140 mg within 14 days) (mean ± SD)	0.0 ± 0.1	0.0 ± 0.1	–	0.7383
Proportion of patients who used OCS burst at least once, *n* (%)	3 (1.0%)	3 (1.0%)	1.0000	–
Frequency of burst (≥ 140 mg within 14 days) (mean ± SD)	1.3 ± 0.6	1.0 ± 0.0	–	0.3739

Data generated by propensity score matching that controlled for age, gender, pre-index concomitant disease, number of prescribed drugs, presence/absence of SABA (> 4 puffs) and OCS, night-time visits to clinic/hospital and hospitalisations *COPD* chronic obstructive pulmonary disease, *DK* Diskus, *FF* fluticasone furoate, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *OCS* oral corticosteroid, *PDC* proportion of days covered, *SABA* short-acting β_2-agonist, *SAL* salmeterol, *SD* standard deviation, *VI* vilanterol

increased emergency department visits and hospital utilisation, which increases asthma-related resource use and adds to the financial burden [19, 20]. Overall, medication adherence in the current study was lower than expected; however, adherence was better with once-daily FF/VI (prescribed days per year: 97.8 days, PDC: 27%) compared with FP/SAL (prescribed days per year: 80.5 days, PDC: 22%). The findings on asthma medication adherence in Japan from the current study are in line with previous reports from international studies. In a recent similar, retrospective, observational study, using pharmacy and medical claims from a large US health plan database from 2013 to 2016, once-daily FF/VI was associated with greater adherence (PDC 43% vs 36%, $p < 0.0001$), less treatment discontinuation [adjusted hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.69–0.79], and similar risk of asthma exacerbation (adjusted HR 0.99; 95% CI 0.85–1.15) compared with twice-daily, fixed dose BUD/FOR metered-dose inhaler (MDI) [21]. It should be noted that this US cohort had a higher rate of asthma-related hospitalisations in the prior year (5–6%) than the Japanese cohort in our study (0.6%), which is suggestive of more severe asthma and may explain the increased adherence reported with FF/VI in that study (PDC of 43% [21] versus 27% reported here). Another US-based study has reported an adjusted PDC (that accounts for the difference in days between a prescription being issued and filled) value of 25% for ICS/LABA users, which is similar to our findings [22]. In the recent Salford Lung Study (SLS)-Asthma, initiation of a once-daily treatment regimen of combined FF/VI improved asthma control without increasing the risk of serious adverse events, when compared with continuation of optimised usual care [achievement of asthma control test (ACT) score ≥ 20 or improvement of ≥ 3; 71% vs 56%; odds ratio 2.00, 95% CI 1.70–2.34; $p < 0.0001$] [17].

Strengths of the study include: the large size of the JMDC Claims Database, which uses unique identifiers allocated to individual subscribers so that patients can be followed up despite hospital changes or visits; provision of real-world evidence on ICS/LABA use and

adherence, which is difficult to study prospectively in a real-world setting; and the use of PSM to compare FF/VI with FP/SAL. The real-world data provided herein, including the trends in LF compared with SF, may help Japanese physicians to better tailor treatment for their patients with asthma.

Limitations of a study such as this are that it evaluated prescription rates, and not whether the medication had been taken as prescribed. Although PDC is a commonly used metric to assess adherence [22], this is an indirect measure and may be confounded by inaccurate reporting, different analysis calculations [23], and the lack of disease severity data [24]. In spite of these limitations, using such a widely available measure does permit interrogation of a large data set, providing broad population insights. In myocardial infarction patients, PDC adherence metrics were similar to those measured using an electronic pill bottle [25]. The correlation between PDC and other adherence measures in asthma, however, is complicated by several factors including unclear inhaler dosage instructions (such as '1–2 puffs daily') and adherence bias in different methods of analysis. For example, one study in the Netherlands found self-reported adherence levels were approximately half of those indicated by pharmacy data (24.4% versus 57.7% adherence, respectively), which may have been biased by the defined treatment episodes assessed by the pharmacy data as this was not required for the self-reporting [26]. Nonetheless, our findings of PDC adherence $\geq$ 80% 26.7% FF/VI and 21.9% FP/SAL are similar to those reported for an adjusted PDC (based on the time taken to fill a prescription in the US from dispense date) $\geq$ 75% of 25% for ICS/LABA [22]. Further analyses may benefit from the application of another adherence measure, the proportion of prescribed days covered (PPDC), which may indicate instances of nonadherence resulting from ICS not being prescribed for chronic daily use, rather than a failure to collect prescribed medication [23].

Additional limitations of this study design mean it is difficult to eliminate any influence from unknown factors such as disease severity, disease duration, or clinical symptoms; however, the current study used asthma exacerbation, SABA and OCS use, together with a requirement for asthma duration of at least one year, to try to standardise asthma disease severity in the cohort via propensity score matching. Finally, the population in this study is a cohort population from a prescription database of the National Federation of Health Insurance Societies and, therefore, contains fewer elderly patients as compared with the general asthma population in Japan.

CONCLUSIONS

In this retrospective analysis of prescribing patterns for asthma medication in Japan, ICS/LABA was found to be the major asthma treatment. The use of once-daily FF/VI was associated with higher medication adherence (as measured by number of prescribed days and PDC), a lower rate of treatment discontinuation, and similar SABA and OCS use, compared with twice-daily FP/SAL.

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Compliance with Ethics Guidelines. The study used anonymised data, therefore, no patient consent was requested, as this is not required for such studies in Japan. Ethical approval was obtained from the Ethics Review Committee at the Kitamachi Clinic (1-1-3 Kichijojikitamachi, Musashino city, Tokyo 180-0001).

Disclosures. Jun Takai was an employee of GSK as the study accountable person until August 2017, and contracted for the business consignment with GSK from September 2017 to March 2018 to contribute to the development of the study report. Jun Takai's current affiliation is Division of Medical Biochemistry, Tohoku Medical and Pharmaceutical University, Miyagi, Japan. Henrik Svedsater is an employee of GSK. Isao Mukai is an employee of GSK. Akihiro Kobayashi is an employee of GSK. Henrik Svedsater owns stock options in GSK. Ryo Atsuta received consultancy fees from GSK and his current affiliation is Akihabara Atsuta Allergy and Respiratory Medicine Clinic.

Data Availability. The GSK-sponsored datasets generated during and/or analysed during the current study can be requested by making an enquiry via http://www.clinicalstudydatarequest.com.

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