



Real-life effectiveness of fluticasone furoate/vilanterol after switching from fluticasone/salmeterol or budesonide/formoterol therapy in patients with symptomatic asthma: Relvar Ellipta for Real Asthma Control Study (RERACS study)

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Background: This study evaluated the efficacy of switching therapy from fluticasone propionate/salmeterol (FP/SM) or budesonide/formoterol (BD/FM) to fluticasone furoate and vilanterol (FF/VI) at the equivalent corticosteroid dose in a real-world setting.

Methods: A prospective, 3-month, open-label, parallel group, switching therapy trial was performed in symptomatic asthma patients under routine management. Patients using 1 puff of FP 250 µg/SM 50 µg b.i.d or 2 puffs of BD 160 µg/FM 4.5 µg b.i.d were switched to FF 100 µg/VI 25 µg once daily, while patients using 1 puff of FP 500 µg/SM 50 µg b.i.d or 4 puffs of BD 160/FM b.i.d was switched to FF 200 µg/VI 25 µg once daily. The primary outcome was improvement of the predicted forced expiratory volume in 1 second % (%FEV₁), while secondary outcomes were improvement of asthma symptoms evaluated by the asthma control test (ACT) and fractional exhaled nitric oxide (FeNO).

Results: The %FEV₁ was improved at 4 weeks after switching, and the improvement was maintained until 12 weeks. ACT also improved after switching. Patients with ACT <20 before switching showed greater improvement of symptoms at 4 weeks and 62% had an ACT score >20. FeNO decreased from 8 weeks.

Conclusions: In symptomatic asthma patients showing insufficient control, improvement of asthma was obtained by switching to FF/VI at the equivalent corticosteroid dose accompanied with the improvement of biomarkers. FF/VI can be a useful option for better control of asthma because of its high efficacy, long duration of action, and delivery via a single-action device.

Keywords: Asthma; fluticasone; furoate; vilanterol; real-world

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Introduction

The goals of asthma management are to achieve good control of symptoms and maintain normal activity. In spite of effective therapies being available, international surveys show that asthma control is suboptimal in many

countries (1). Although the situation varies between countries, it is problematic that from 50% to 90% of asthma patients show poor control of their disease (2-5). There are various reasons for poor control of asthma. Common causes related to medication are poor adherence, poor inhaler technique, and inadequate dosing. If possible, potential

risk factors should be eliminated and comorbidities managed (1,6,7).

New users of both single and fixed combined inhaled corticosteroids (ICS) have very low persistence rates with ICS treatment during the first year of follow-up and persistence with treatment is strongly influenced by patient factors, such as the severity of asthma and the daily dosing frequency (8). Good adherence is associated with fewer exacerbations, but the difference is only significant for patients whose adherence is greater than 75% of the prescribed dose compared with patients whose adherence is 25% or less (9). In a real-world study, not a clinical trial, adherence was higher among patients prescribed once-daily ICS compared with those prescribed ICS ≥ 2 times daily as, 61% vs. 41%, respectively (10). This trend was similar regardless of sex, ethnicity, age, and the severity of asthma. A study of step-down therapy also showed that adherence was higher among asthma patients prescribed once daily ICS compared with those prescribed ICS 2 times daily (76.0% vs. 58.7%, respectively), and clinical parameters also showed greater improvement in patients using once-daily ICS (11).

The Salford Lung Study evaluated the effectiveness and safety of switching to the once-daily inhaled combination of fluticasone furoate and vilanterol (FF/VI, Relvar[®]Elipta[®]) compared with continuation of maintenance therapy (usual care) in a large, real-world population of patients with chronic obstructive pulmonary disease (COPD) and asthma (12). In patients with a diagnosis of symptomatic asthma made by a general practitioner on maintenance inhaler therapy, including single ICS and ICS/long-acting beta-agonist (ICS/LABA), initiation of a once-daily FF/VI regimen improved asthma control without increasing the risk of serious adverse events compared with optimized usual care (13). Subgroup analysis also showed that initiating FF/VI was significantly better than continuing fluticasone propionate/salmeterol (FP/SM) for improving asthma control and quality of life (14). These reports suggest that once-daily treatment improves asthma control, but the efficacy of switching from FP/SM or budesonide/formoterol (BD/FM) to FF/VI at the equivalent corticosteroid dose and the changes of biomarkers has not been tested in a real-world study. Therefore, the objective of this study, the Relvar Ellipta Real Asthma Control Study (RERACS study), was to evaluate the efficacy of switching therapy from FP/SM or BD/FM to FF/VI at the equivalent corticosteroid dose with measuring biomarkers in the real-world setting.

Methods

Study design

A prospective, 3-month, open-label, parallel group, switching therapy trial was performed in symptomatic asthma patients at Dokkyo University Hospital, Japan to assess the effectiveness of switching from FP/SM or BD/FM to FF/VI. Each patient's ICS was switched to the equivalent dose according to the previously described method (1). Patients using 1 puff of FP 250 μg /SM 50 μg (FP250/SM) b.i.d or 2 puffs of BD 160 μg /FM 4.5 μg (BD160/FM) b.i.d were switched to FF 100 μg /VI 25 μg (FF100/VI) once daily, while patients using 1 puff of FP 500 μg /SM 50 μg (FP500/SM) b.i.d or 4 puffs of BD160/FM b.i.d were switched to FF 200 μg /VI 25 μg (FF200VI) once daily (Figure 1). The primary outcome was improvement of the predicted percent forced expiratory volume in 1 second (%FEV1). The measurement was performed at the time in the morning to noon, and the regular use of ICS/LABA was not stopped. Secondary outcomes were improvement of asthma symptoms evaluated by the asthma control test (ACT) and the change of fractional exhaled nitric oxide (FeNO). The ACT score was used to classify patients as follows: ACT <20 was poor control, ACT ≥ 20 and ≤ 24 was good control, and ACT =25 was complete control. %FEV1 and FeNO (Sievers Instruments, Boulder, CO, USA) were determined as described previously (15-17). The screening visit was at 12 weeks prior to switching therapy and patients were switched to FF/VI at Visit 1 (week 0). Parameters were measured every 4 weeks from visit 1 (week 0) to visit 4 (week 12). This study was designed to have 90% power to detect a 1% (20 mL) difference of switching therapy effect during 3 months in %FEV1 with effective size 0.74 and two-sided alpha of 0.05 (13,18). A sample size of 32 patients was planned. For secondary outcome of ACT and FeNO, a sample size of 1 point with effective size 0.75, and a sample size 10 ppb with effective size 0.8 were sufficient to construct 90% power to detect in each parameter (18,19).

Patients

Eligibility criteria included asthma patients aged ≥ 20 years, use of FP/SM or BD/FM for at least 3 months (12 weeks) prior to enrollment this study, symptomatic asthma (ACT ≤ 24), and informed consent to participation in the study. Exclusion criteria were an age <20 years, ACT =25, intercurrent infection, and known or suspected allergy to FF/VI. Asthma was managed according to the 2014

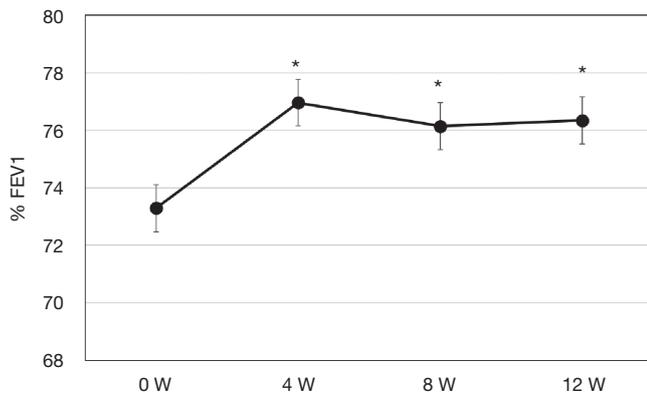


Figure 2 Changes of %FEV1 after switching from the previous ICS/LABA to FF/VI. *, $P < 0.05$ vs. week 0. ICS/LABA, inhaled corticosteroid/long-acting beta-agonist; FF/VI, fluticasone furoate/vilanterol; %FEV1, predicted percent forced expiratory volume in 1 second.

endpoint (%FEV1) showed improved at 4 weeks after switching therapy, and this improvement was maintained until 12 weeks ($P < 0.05$) (Figure 2). ACT also improved after switching therapy ($P < 0.05$). Patients with an ACT < 20 displayed marked improvement of their symptoms at 4 weeks and 62% of them had a score > 20 . Patients with an ACT ≥ 20 also demonstrated improvement of asthma symptoms at 12 weeks and 58% of them reached ACT = 25, indicating complete control (Figure 3A,B). FeNO was decreased at 8 weeks, with this level being maintained until 12 weeks ($P < 0.05$) (Figure 4).

Safety assessment revealed that no patient stopped medication or developed pneumonia during the study period. Hoarseness was noted in three patients as an adverse event.

Discussion

In the present study, switching symptomatic asthma patients from FP/SM or BD/FM to FF/VI improved their asthma symptoms evaluated by the ACT score, %FEV1, and FeNO. These results indicated that switching therapy from FP/SM or BD/FM to FF/VI improved symptoms and lung function in symptomatic asthma patients, and also reduced airway inflammation, despite changing inhalation from twice daily to once daily at the equivalent ICS dose. There are several reasons why once daily treatment may have led to improvement. The first is that adherence may have improved. It may also be important that the inhaled

steroid in FF/VI has a strong anti-inflammatory effect. A third factor is that the patients were switched to an easy-to-use device that makes erroneous operation unlikely. Accordingly, the effectiveness of switching to FF/VI may have been supported by all three factors. Adherence differs between clinical trials and the real-world setting. In a clinical study of asthma, patients must pass strict selection criteria to be registered. Thus, if there are initially 300 asthma patients and the %FEV1 criterion is set within 50–85%, the number of patients is reduced to 1/3. In addition, smokers are excluded, as well as patients with less than 12% airway reversibility in the past year, and so on. As a result, from the original 300 asthma patients, only 11 patients may be eligible for a clinical study (21). This is quite different from actually investigating the effect of a drug in routine clinical practice. In randomized controlled trials, adherence to inhaled drugs is more than 90% if patient diary cards used to assess drug use (22), while observational studies show very low adherence rates of less than 20% (8,23). Since there is a large gap between clinical trials and real-world medicine, there is a possibility that a large difference will arise when comparing twice daily inhalation and once daily inhalation (24). In a study performed during real-world clinical practice, it was clearly demonstrated that adherence was increased by once daily inhalation (11).

As for its anti-inflammatory effect, FF is a derivative of FP that has the highest affinity for glucocorticoid receptors among the existing inhaled steroids, followed by mometasone and budesonide (25). The LABA component of VI has a persistent adrenoceptor (β_2 -AR) agonist action comparable with that of indacaterol and longer than FM (26). Since FF100/VI provides an equivalent corticosteroid dose to FP250/SM, it is expected to achieve the same degree of asthma control from both its ICS and LABA components. In fact, once daily FF100/VI achieved similar improvement of %FEV1 compared with twice daily FP250/SM. However, FF100/VI was better for QOL, when comparing the proportion of patients with significant improvement of AQLQ by at least 0.5 (27). That study was a phase 3 randomized controlled trial, so it is considered that adherence was probably good, but a difference was still noted after switching therapy.

The difference in the duration of the anti-inflammatory effect might be important. It was reported that FeNO decreased 1 week after starting FF/VI, while FeNO increased to the level obtained with placebo at 18 days after discontinuation of FF/VI, indicating that the anti-inflammatory effect of FF/VI was sustained for 18 days (28).

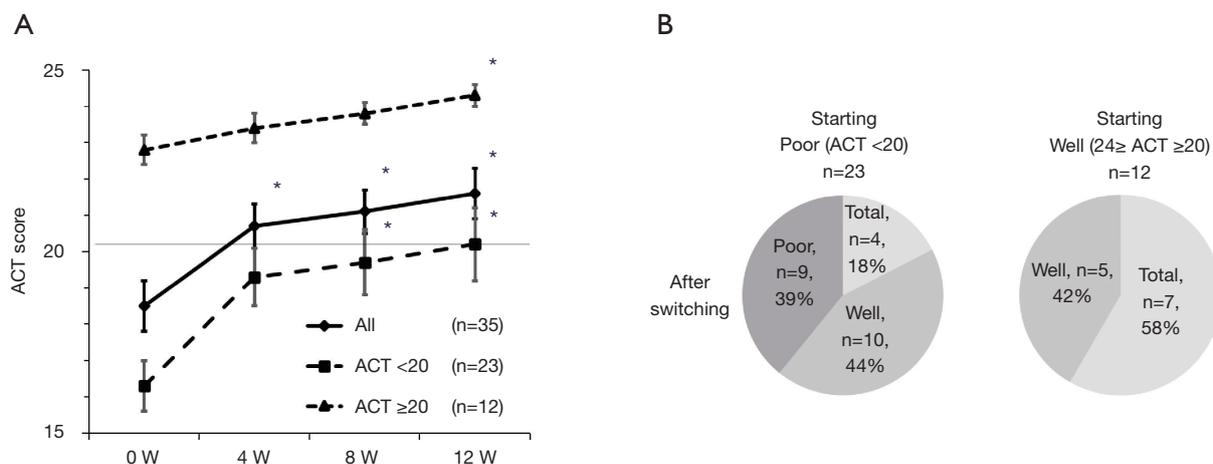


Figure 3 Changes of the ACT score after switching from ICS/LABA to FF/VI. *, $P < 0.05$ vs. week 0 (A). ACT scores and ratios of the patients after switching to FF/VI. Patients with ACT <20 before starting FF/VI ($n=23$) were defined as the poor control group. Patients with ACT ≥ 20 and ≤ 24 before starting FF/VI ($n=12$) were defined as the good control group (B). ACT, asthma control test; ICS/LABA, inhaled corticosteroid/long-acting beta-agonist; FF/VI, fluticasone furoate/vilanterol.

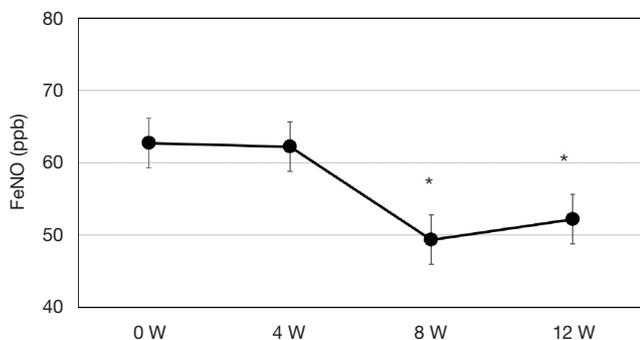


Figure 4 Changes of FeNO after switching from ICS/LABA to FF/VI. *, $P < 0.05$ vs. week 0. FeNO, fractional exhaled nitric oxide; ICS/LABA, inhaled corticosteroid/long-acting beta-agonist; FF/VI, fluticasone furoate/vilanterol.

The duration of the anti-inflammatory effect of BD, FP, and beclomethasone estimated from FeNO was 7, 14, and 7–14 days, respectively (29–31). The bronchodilatory effect evaluated by FEV1 and peak expiratory flow was also sustained for 4 days longer after cessation of FF/VI (28). In present study, mean FeNO values were decreased by switching therapy, but still above 50 ppb, nevertheless improving ACT and %FEV1. Response to ICS could be different from high-FeNO >100 ppb patients and low-FeNO >60 to 100 (30). The high-FeNO patients showed progressive fall in FeNO according to ICS dosing up, but low-FeNO patients showed modest fall. The levels of

FeNO seemed to be affected the discordance of between ACT score and objective measures such as %FEV1 and FeNO. Another reason to discordance might be poor adherence rates. The study for real-world revealed the poor adherence rate as low as 20–40% by examining electric monitoring device (13).

Finally, as already mentioned, FF/VI is inhaled once a day, and 95% of patients can handle it successfully from the first use (32), which is also a very important point for an inhaled medication.

Limitations of this study are that monocentric, without blinding or control group and small population. Precise background of patients, such as blood eosinophil count, airway reversibility and chest computed tomography were also not examined. The purpose of this study was to reveal asthma control in real world. Therefore, to avoid the controlled adherence based on clinical study, adherence was also not examined by questionnaires or automatic recorders. It might be possible to track adherence by examining Elipta® device turned in at the end of the study. A recent report referencing the Salford Lung Study suggested the key learnings for the design of future pragmatic effectiveness randomized control trials, such as importance of infrastructure, recruiting broad population, local healthcare professionals and careful study design (33).

In conclusion, improvement was obtained after symptomatic asthma patients with insufficient control by ICS/LABA were switched to FF/VI at the equivalent

corticosteroid dose. FF/VI may be a useful option for better treatment of asthma in the real-world setting because of its high clinical efficacy, long duration of activity, and delivery via a single-action device.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki. The Human Research Committee of Dokkyo University approved this study and it was registered as clinical trial number C-274-03. All patients gave written informed consent before enrollment.

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