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Comparison of Budesonide/formoterol versus Fluticasone furoate/vilanterol as maintenance and reliever therapy for asthma control: a real-world observational study

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Abstract

Background Previous studies have reported reduced acute exacerbation rates and improved symptom control in asthma patients treated using inhaled corticosteroids plus formoterol maintenance and reliever therapy (MART). Fluticasone furoate (FF) and vilanterol (VIL) also provide rapid bronchodilation and sustained anti-inflammatory effects, however no studies have investigated FF/VIL as MART for asthma control.

Methods From October 1, 2021 to September 30, 2023, this retrospective study included asthma patients classified as step 3 or 4 according to the Global Initiative for Asthma guidelines, who were then divided into two groups. One group received BUD/FOR as MART, while the other received FF/VIL as MART. Pulmonary function tests, exacerbation rates, Asthma Control Test (ACT), fractional exhaled nitric oxide (FeNO) levels, and blood eosinophil counts were measured before and after 12 months of treatment.

Results A total of 161 patients were included, of whom 36 received BUD/FOR twice daily as MART, and 125 received FF/VIL once daily as MART. After 12 months of treatment, the FF/VIL group showed a significant increase in ACT scores by 1.57 ($p < 0.001$), while the BUD/FOR group had an increase of 0.88 ($p = 0.11$). In terms of FeNO levels, the BUD/FOR group experienced a decline of -0.2 ppb ($p = 0.98$), whereas the FF/VIL group had a mild increase of + 0.8 ppb ($p = 0.7$). Notably, there was a significant difference in the change of FeNO between the two groups (Δ FeNO: -0.2 ppb in BUD/FOR; + 0.8 ppb in FF/VIL, $p < 0.001$). There were no significant alterations observed in FEV1, blood eosinophil count, or acute exacerbation decline in either group.

Conclusions In the current study, patients treated with FF/VIL as MART showed improvements in ACT scores, while those treated with BUD/FOR as MART exhibited a reduction in FeNO levels. However, the difference between the two treatment groups did not reach clinical significance. Thus, FF/VIL as MART showed similar effectiveness to BUD/FOR as MART.

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Introduction

Asthma presents with variable symptoms and airflow limitation due to airway inflammation. This inflammation causes airway hyperresponsiveness and exacerbations, making it a crucial target for asthma treatment [1]. Inhaled corticosteroids (ICSs) are the primary treatment for managing asthma symptoms and minimizing future risks due to inflammation. Long-acting B2 agonists (LABAs) are added to ICSs when asthma symptoms are not fully controlled by ICSs alone [2]. Budesonide/formoterol (BUD/FOR) can serve as both a controller and a rescue medication thanks to the rapid and long-acting bronchodilator properties of formoterol. This treatment is termed Single maintenance and reliever therapy (SMART). Previous studies have shown that asthma patients treated with SMART had reduced acute exacerbation rates, improved symptom control, and required a lower dosage of ICSs [3–7].

According to the Global Initiative for Asthma (GINA) guidelines, [2] there are two treatment options for asthma patients based on different relievers. In Track 1, the reliever is an as-needed low-dose ICS plus formoterol, while in Track 2, the reliever is an as-needed short-acting B2 agonist (SABA). Previous studies have reported that Track 1 is the preferred approach for adults [2–7]. However, most of these studies were traditional randomized controlled trials with close monitoring of compliance and inhalation techniques. Consequently, they may not fully represent real-world clinical settings where medication adherence is lower and technique errors are common, impacting treatment effectiveness [8, 9].

A recently approved asthma treatment combines fluticasone furoate (FF) and vilanterol (VIL) in a new ICS/LABA combination. FF demonstrates superior affinity for the glucocorticoid receptor and longer retention in respiratory tissues compared to other glucocorticoids such as fluticasone propionate (FP) and BUD [10]. VIL exhibits superior affinity and selectivity for the β2-adrenoceptor than FOR, providing faster onset and longer duration of action than salmeterol (SM) in human airways [9]. It also delivers effective 24-h bronchodilation in asthma patients receiving ICS treatment [11, 12]. In the UK's Sanford Lung Study, asthma patients on FF/VIL (once daily) were twice as likely to achieve or improve asthma control compared to those on usual care (other ICS/LABA twice daily) [13, 14]. In a real-world study, patients using once-daily ICSs had higher adherence (61%) than those using ICSs ≥ 2 times daily (41%), with better adherence correlating to fewer exacerbations [15, 16]. Based on these data, FF/VIL shows promise in providing stronger anti-inflammatory and faster bronchodilation effects with longer duration than current ICS/LABA treatments.

In Track 2 of asthma management, the reliever is an as-needed SABA. Even though SABAs can provide quick relief for asthma symptoms, over-users are less likely to perceive their health and asthma control as excellent, often unaware that frequent usage can worsen control [17]. We were curious whether FF/VIL could be used for both maintenance and reliever therapy, an approach that could help to prevent the overuse of SABAs. Therefore, we conducted this real-world study to evaluate lung function improvements, exacerbation rates, quality of life, and biomarkers (fractional exhaled nitric oxide [FeNO], blood eosinophil count) in asthma patients treated with BUD/FOR as SMART versus FF/VIL as MART.

Materials and methods

Study patients

This retrospective study was conducted at the Division of Pulmonary and Critical Care Medicine, China Medical University Hospital, Taiwan, from October 1, 2021 to September 30, 2023. The inclusion criteria were patients: (1) aged 20 years or older; (2) diagnosed with asthma based on clinical symptoms and spirometry characteristics, including diurnal peak expiratory flow (PEF) variability of over 20%, forced expiratory volume in one second (FEV1) improvement of over 12% and 200 ml after 400 ug inhaled salbutamol, clinical symptoms (e.g., difficulty breathing, cough, sputum production, wheezing), and lifetime asthma risk; (3) with data on FeNO, serum eosinophil count; (4) who received combination therapy with an ICS + LABA (e.g., BUD/FOR or FF/VIL) as MART; and (5) classified as steps 3 and 4 according to the GINA guidelines [2].

The exclusion criteria were patients: (1) diagnosed with cancer; (2) who had previously received biological agents such as omalizumab, mepolizumab, benralizumab, or dupilumab; (3) treated with triple therapy (ICS + LABA + LAMA); (4) who had used short-acting bronchodilators as rescue inhalers in the past 6 months, including monotherapy such as SABAs or combination therapy: SABA + short-acting muscarinic antagonist; and (5) with insufficient available data for further analysis or those lost to follow-up. The enrolled patients were divided into two groups. One group received BUD/FOR as MART, while the other received FF/VIL as MART for asthma control. Patients being treated with FF/VIL as MART were administered either FF/VIL 92/22 ug or FF/VIL 184/22 ug as 1 puff once daily (QD), with the option to take more puffs when they experienced discomfort. All patients participated in healthcare case management to enhance their health outcomes and healthcare quality. The study received approval from the China Medical University Hospital Institutional Review Board (CMUH112-REC1-175). The requirement for informed consent was

waived because of the observational and retrospective nature of the study design.

Clinical data collection and treatment assessment

Clinical data including age, sex, body height, body weight, body mass index (BMI), smoking status, serum eosinophil count, FeNO, history of other comorbidities, pulmonary function tests (PFTs), Asthma Control Test (ACT) score, and acute exacerbations (AEs) in the previous year were collected. Following the initiation of primary treatment, the patients were regularly followed up at our institute every 1 to 3 months. The pulmonary function parameters (FEV1, forced vital capacity [FVC], and FEV1/FVC), ACT score, AEs, eosinophil count, and FeNO were compared at the 6th month of treatment with the values before initiating ICS + LABA-based treatment.

Asthma Control Test (ACT)

The ACT questionnaire is used to assess symptom control. It consists of 5 items evaluating the frequency of shortness of breath, general asthma symptoms, rescue medication usage, asthma impact on daily functioning, and overall self-assessment of control. Scores range from 5 to 25, with higher scores indicating better control. The patients completed the questionnaire every 1 to 3 months during outpatient visits. We reviewed medical charts to identify inclusion timing, with subsequent assessments of pulmonary function, and number of AE occurring 12 months later.

Acute Exacerbations (AEs)

AEs are episodes marked by a progressive increase in symptoms such as shortness of breath, cough, wheezing, or chest tightness, coupled with a decline in lung function. We reviewed medical charts to identify exacerbation episodes. Mild exacerbation was defined as a deterioration in symptoms requiring a brief course of oral systemic corticosteroids for asthma control. Moderate to severe exacerbation was defined as a deterioration in symptoms or lung function, increased bronchodilator usage, emergency room visits, or hospitalization due to the need for systemic corticosteroids, or asthma exacerbations necessitating systemic corticosteroids for at least 3 days [18].

Spirometry and FeNO

After initiating primary treatment, the patients were regularly followed up at our institute every 1 to 3 months. Spirometry was conducted before administering the daily dose of ICS + LABA, and FEV1% and FVC% values were calculated by dividing the measured FEV1 and FVC values by predicted FEV1 and FVC values in a similar age, sex, and body composition population. FeNO was measured in a single breath, exhaled directly into an analyzer, at an exhalation flow rate of 0.05 L/s for more than 6 s, and values were expressed as parts per billion (ppb) [19]. The pulmonary function parameters (FEV1, FVC, and FEV1/FVC) and FeNO levels were compared with the initial treatment values after 12 months of treatment.

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR; 25th and 75th percentiles) or mean with standard deviation (SD). Group differences were evaluated using the t-test for normally distributed continuous data and the Kruskal–Wallis test for non-normally distributed and ordinal data. Categorical variables were presented as counts and percentages and analyzed using the chi-square test or Fisher's exact test. A paired t-test was used to compare mean FEV1%, ACT score, AE, serum eosinophil count, and FeNO before and after the initial primary treatment. All tests of significance were two sided, and a p-value ≤ 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using MedCalc for Windows, version 18.10 (MedCalc Software, Ostend, Belgium).

Results

Baseline characteristics

A total of 161 asthma patients treated with ICS/LABA were enrolled in this study. Among them, 36 patients received BUD/FOR twice daily as MART, while 125 patients received FF/VIL once daily as MART (Fig. 1). The baseline clinical characteristics of the patients are presented in Table 1. Most patients were female (54.6%), with an average age of 53.4 years, and mean weight and height of 66.9 kg and 161.7 cm, respectively. The most common comorbidity was gastroesophageal reflux disease (32.3%), followed by rhinitis (20.4%). The patients in the FF/VIL group had higher body weight (68.5 vs 61.4 kg, $p = 0.024$), body height (162.6 vs 158.8 cm, $p = 0.019$), and BMI (25.7 vs 24.2 kg/m^2, $p = 0.039$) compared to those in the BUD/FOR group. In terms of T2 biomarkers, there were no significant differences between these two groups. The baseline blood eosinophil count was 145/μl (96.1–215.2) in the BUD/FOR group, and 169.5/μl (140.6–203.9) in the FF/VIL group. The level of FeNO in the two groups was similar, at 27.8 ppb (20.7–34.7) in the BUD/FOR group and 28.7 ppb (24.1–33.3) in the FF/VIL group. Overall, 65% ($n = 106$) of the patients were categorized as step 3, while 35% ($n = 55$) were categorized as step 4. There were no significant differences in the presence of comorbidities, asthma severity stage, and pulmonary function parameters (FEV1, FVC) between the two groups. However, the MMEF 25/75 in the BUD/

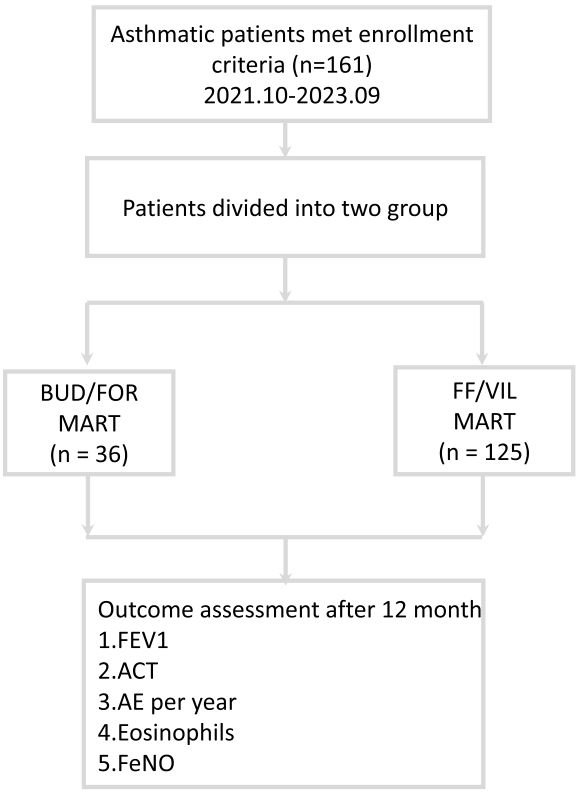

Fig. 1 Flowchart of patient enrollment. ACT, Asthma Control Test; AE, acute exacerbation; BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol; FEV1, forced expiratory volume exhaled in the first second; FeNO, fractional exhaled nitric oxide; MART, maintenance and reliever therapy

Table 1 Patient characteristics between BUD/FOR and FF/VIL

	BUD/FOR ($n=36$)	FF/VIL ($n=125$)	p-value
Age, years	55.8(50.7–60.9)	52.8(50.1–60.5)	0.305
Male (%)	13 (36.1)	60 (48.0)	0.208
Body Height, cm	158.8 (156.3–161.4)	162.6 (161.1–164.2)	0.019
Body Weight, kg	61.4 (55.7–66.9)	68.5 (65.5–71.4)	0.024
BMI	24.2(22.1–26.3)	25.7 (24.8–26.5)	0.039
Smoking, pack-years	10 (27.8)	37 (29.6)	0.833
Eosinophil, /ul	145.0 (96.1–215.2)	169.5 (140.6–203.9)	0.187
FeNO, ppb	27.8 (20.7–34.7)	28.7(24.1–33.3)	0.839
Total IgE, IU/mL	152(94.7–171.5)	115 (85.4–172.9)	0.588
CAD	1(2.8)	8(6.4)	0.406
Bronchiectasis	3 (8.4)	8(6.4)	0.585
GERD	13(36.1)	39(31.2)	0.579
Rhinitis	7(19.4)	26(20.8)	0.859
FEV1/FVC, %	77.1 (74.3–80.1)	80.9 (79.2–82.6)	0.345
FEV1, %	88.8(81.9–95.7)	91.6(88.5–94.9)	0.382
FVC, %	95.5(89.2–101.8)	92.6(90.1–95.2)	0.331
MMEF25-75, %	64.9(55.3–74.5)	85.1(78.5–91.5)	0.003
ACT	23(22–24)	22(21–23)	0.025
Acute exacerbation	0.27(0.11–0.45)	0.22(0.13–0.31)	0.576
OCS	9(25.0)	21(16.8)	0.267
Treatment step			0.233
Step 3	27(75.0)	79(63.2)	
Step 4	9(25.0)	46(36.8)	

FOR group was significantly lower than that in the FF/VIL group (64.9% vs 85.1%, $p=0.003$).

ACT

Both treatment groups demonstrated a positive response in terms of the quality of life, as evidenced by improvements in ACT scores. The ACT scores significantly increased by 1.57 in the FF/VIL group ($p<0.001$), and by 0.88 in BUD/FOR group ($p=0.11$) (Fig. 2). The improvement in ACT score was higher in the patients treated with FP/VIL was than those treated with BUD/FOR. (Δ ACT:+1.57 (1.23–1.92) in the FP/VIL group;+0.88 (-0.22–2.01) in the BUD/FOR group, $p<0.001$) (Table 2). However, the difference in improvement between the two groups did not reach the Minimal Clinically Important Difference (MCID) threshold of 3 points.

Spirometry

The mean FEV1/FVC ratio, FEV1%, and FVC% were 77.1%, 88.8%, and 95.5% in the BUD/FOR group, and 80.9%, 91.6%, and 92.6% in the FF/VIL group. After 12 months of treatment, there was an improvement in FEV1 in patient treated with FF/VIL though it was not significant (Fig. 3). There was no significant difference in the improvement of FEV1 between groups (Δ FEV1%: -0.06% in BUD/FOR vs. 1.26% in FF/VIL; $p=0.186$) (Table 2).

AEs

After 12 months of follow-up, the AE rate decreased by 0.14% ($p=0.134$) in the patients treated with BUD/FOR, and by 0.04% in FF/VIL ($p=0.458$) (Fig. 4) The difference did not reach significance in both groups. The reduction in the annualized rate of exacerbations was similar between the two groups after 12 months of treatment (-0.14% in the BUD/FOR group; -0.04% in the FF/VIL group, $p=0.492$) (Table 2).

Laboratory data (FeNO and Eosinophils)

After 12 months of treatment, patients treated with BUD/FOR showed a decline in FeNO (-0.2 ppb, $p=0.98$), while there was a mild increase in FF/VIL (+0.8 ppb, $p=0.7$). Although there is a statistically significant difference in FeNO changes between the two groups, the clinical difference is not evident. (Δ FeNO: -0.2 ppb in the BUD/FOR group;+0.8 ppb in the FF/VIL group, $p<0.001$)

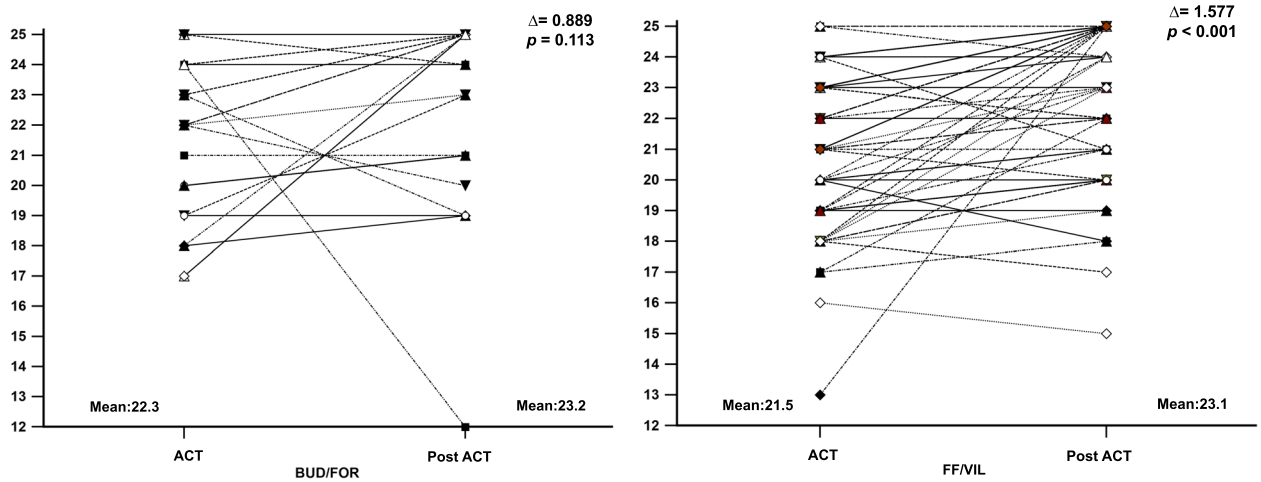

Fig. 2 Differences in ACT scores in the asthma patients before and after 6 months of treatment with (**A**) BUD/FOR, (**B**) FF/VIL. Data are presented as mean and standard deviation. ACT, Asthma Control Test; BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol

Table 2 The clinical parameters improvement between BUD/FOR and FF/VIL

	BUD/FOR ($n=36$)	FF/VIL ($n=125$)	p-value
Δ FEV1%	-0.06(-4.35–4.23)	1.26(-1.58–4.11)	0.186
Δ ACT	0.88 (-0.22–2.01)	1.57 (1.23–1.92)	< 0.001
Δ AE	-0.14 (-0.32–0.04)	-0.04 (-0.14–0.06)	0.492
Δ FeNO	-0.201(-19.1–18.7)	0.804 (-3.37–4.98)	< 0.001
Δ Eosinophil	-44(-121.1–32.3)	-38(-86.5–10.49)	0.345

ACT Asthma control test, *AE* Acute exacerbation, *BUD/FOR* budesonide/formoterol, *FF/VIL* Fluticasone furoate and vilanterol, *FEV1* Forced expiratory volume exhaled in the first second, *FeNO* Fractional exhaled nitric oxide

(Fig. 5 and Table 2). Patients treated with BUD/FOR or FF/VIL both showed a decline in blood eosinophil count. The decrease was -44.4/μl in the BUD/FOR group ($p=0.242$) and -38.1/μl in the FF/VIL group ($p=0.123$) (Fig. 6) There was no significant difference between these two groups (Δ Eosinophil: -44/μl in the BUD/FOR group; -38/μl in the FF/VIL group, $p=0.345$) (Table 2).

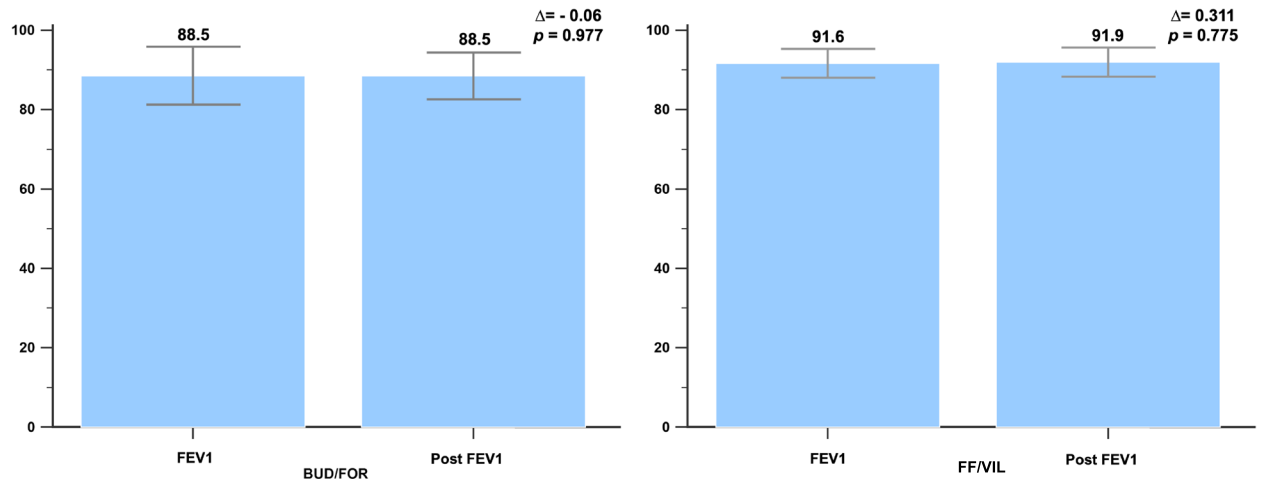

Fig. 3 Differences in FEV1 in the asthma patients before and after 6 months of treatment with (**A**) BUD/FOR, (**B**) FF/VIL. Data are presented as mean and standard deviation. FEV1, forced expiratory volume exhaled in the first second; BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol

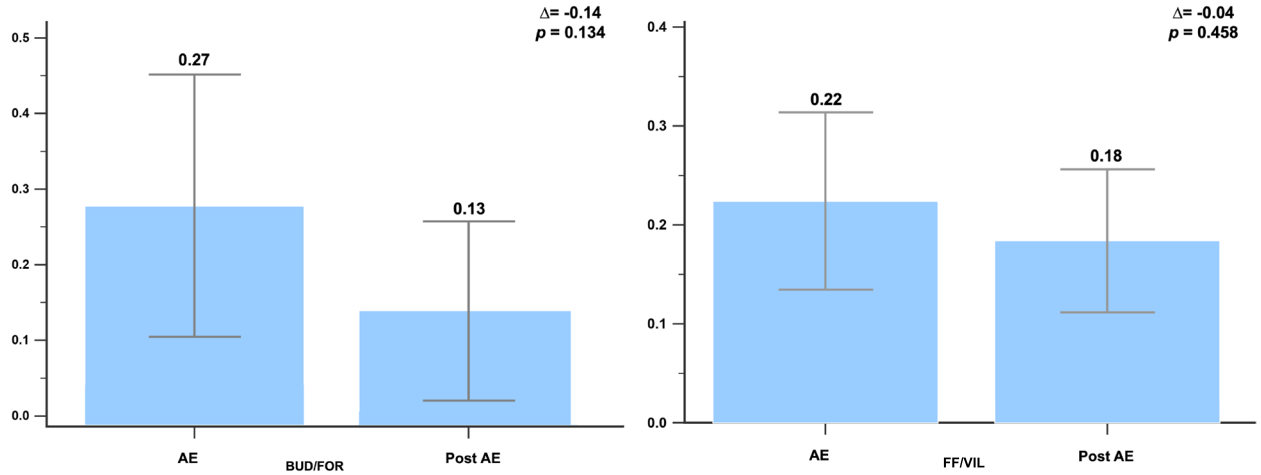

Fig. 4 Differences in AE rates in the asthma patients before and after 6 months of treatment with (**A**) BUD/FOR, (**B**) FF/VIL. Data are presented as mean and standard deviation. AE, acute exacerbation; BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol

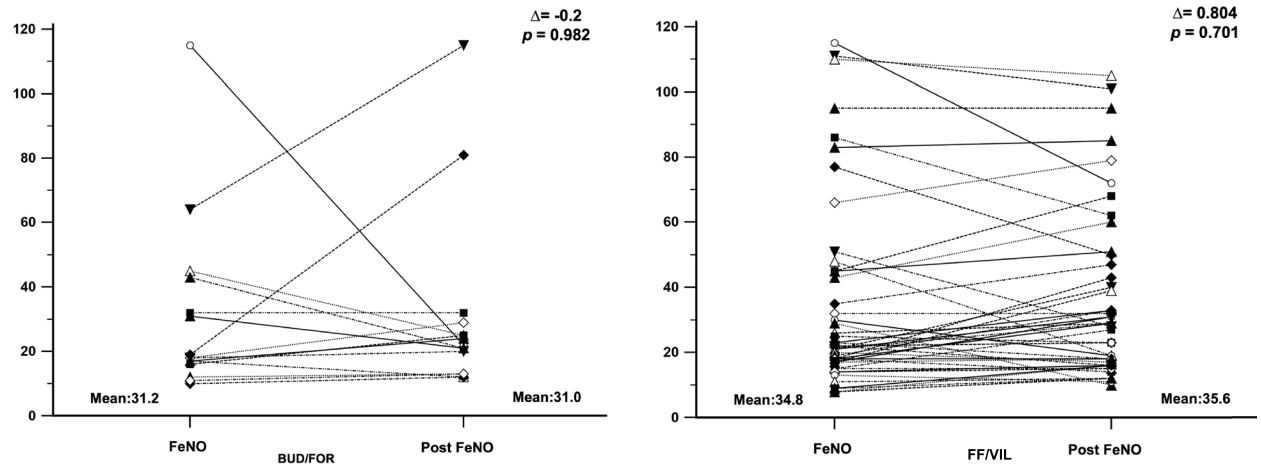

Fig. 5 Differences in FeNO in the asthma patients before and after 6 months of treatment with (**A**) BUD/FOR, (**B**) FF/VIL. Data are presented as mean and standard deviation. FeNO, fractional exhaled nitric oxide; BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol

Discussion

To the best of our knowledge, this study represents the first attempt to compare the effectiveness of BUD/FOR as MART with FF/VIL as MART. In the present study, all patients in this study exhibited a decrease in adverse events (AEs) and blood eosinophil counts, although these reductions were not statistically significant. Patients treated with FF/VIL experienced significant improvements in ACT scores. Furthermore, FeNO levels significantly decreased in patients treated with BUD/FOR. These findings suggest that FF/VIL as a maintenance and reliever therapy (MART) may provide comparable effectiveness to BUD/FOR as MART and may even offer better symptom control.

The primary goals of asthma treatment include symptom control, risk reduction, decreased AE rates, and improved quality of life. The GINA guidelines recommend the regular use of ICS + LABA for patients at steps 3 and 4. There are two treatment approaches for these patients, differing primarily in the choice of reliever medication. In Track 1, the reliever is as-needed low-dose ICS-formoterol, which is the preferred approach for adults according to GINA. In Track 2, an as-needed SABA or ICS-SABA is an alternative when Track 1 is not feasible [2, 20]. Single use of SABA as a reliever for asthma patients is no longer recommended due to concerns of overuse of SABA and underuse of controller medications such as ICS.

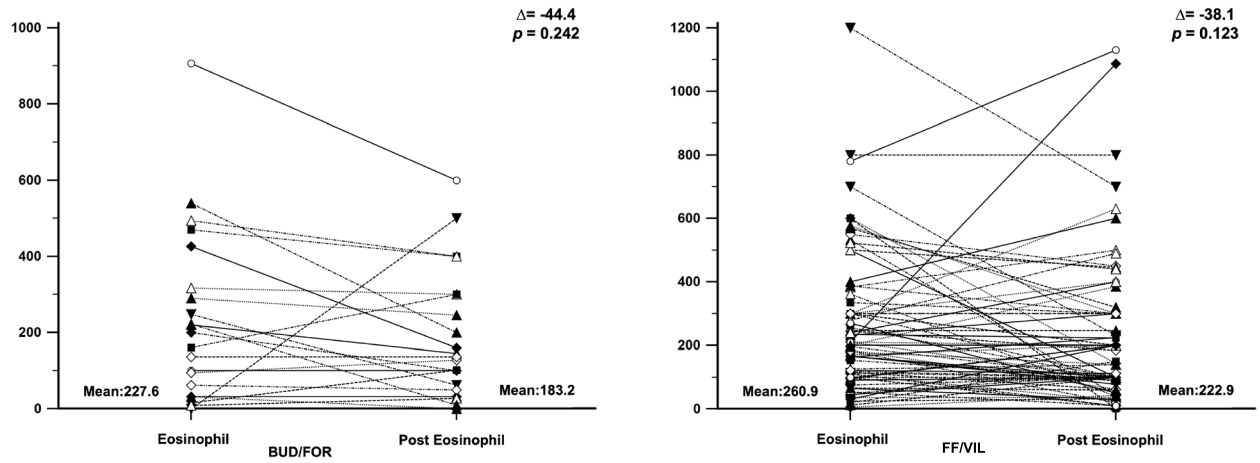

Fig. 6 Differences in eosinophil count in the asthma patients before and after 6 months of treatment with (**A**) BUD/FOR, (**B**) FF/VIL. Data are presented as mean and standard deviation. BUD/FOR, budesonide/formoterol; FF/VIL, fluticasone furoate/vilanterol

Anti-inflammatory reliever (AIR) therapy is now recommended, which combines both controller and reliever medications in the same inhaler [21]. ICS-formoterol has been proven as an AIR for mild asthma, providing better symptom control, reduced exacerbations, and anti-inflammatory effects compared to SABA alone. In cases of worsening asthma, ICS-formoterol can also be used as MART [22]. The rationale behind using ICS-formoterol as MART lies in the rapid onset of action with formoterol, providing quick symptomatic relief. Patients treated with ICS-formoterol as MART have been reported to have similar symptom relief and lower AE rates compared to those treated with other ICS + LABA using SABA as a reliever [3, 4, 23, 24]. In these studies, the matched patients were treated with SM/FP [4, 23]. There was limited evidence available regarding the efficacy of MART compared to FF/VIL.

The newly approved asthma treatment FF/VIL is an innovative ICS/LABA combination. FF has a higher glucocorticoid receptor affinity than FP and BUD, which may enhance its anti-inflammatory effects [25, 26]. VIL is highly selective for the beta-2 adrenoceptor and has a longer duration of action compared to other LABAs such as indacaterol or FOR [11, 27]. VIL also exhibits similar functional potency to FOR, but is more potent than SM. In addition, a rapid onset of action has been observed with VIL, with a time to therapeutic effect as early as 6 min. This onset of action is similar between VIL and FOR, and it is faster than SM. These characteristics can lead to rapid symptom relief and long-lasting effects [11, 25]. Our findings showed that the patients treated with FF/VIL as MART had improved symptom control and reduced risk of AEs, and these effects were comparable to those receiving BUD/FOR as MART.

The Salford Lung Study examined the effectiveness and safety of initiating once-daily inhaled FF/VIL versus continuing usual care in asthma patients in the UK [13]. The results of the study showed that the patients initiating treatment with FF/VIL experienced improved asthma control compared to those continuing usual care (other ICS with short-acting reliever or ICS + LABA twice daily), regardless of their initial asthma control status [14]. In the RERACS study, symptomatic asthma patients, regardless of prior treatment with FP/SM or BUD/FOR, transitioning to FF/VIL were found to have improved symptom control compared to previous therapies [28]. In a randomized crossover trial with stable asthma patients on ICS/LABA control, the patients received either FF/VIL or BUD/FOR for 8 weeks before switching treatments. The results showed that FF/VIL was comparable to BUD/FOR in improving pulmonary function, ACT scores, Asthma Control Questionnaire—5 (ACQ5) scores, and FeNO levels at baseline and after 8 weeks [29]. The current study is the first to report that FF/VIL as MART provides comparable effectiveness to BUD/FOR as MART. It appears that patients experienced better symptom control with FP/VIL compared to BUD/FOR, as indicated by the improvement in ACT scores. Ease of use, compliance, and FF/VIL components likely contribute to its asthma management effectiveness [30]. We suggest that once-daily FF/VIL may be an effective alternative treatment for asthma control even without a SABA.

FeNO serves as a biomarker for airway inflammation, with higher levels often indicating poorer asthma control and increased exacerbations [31]. In a crossover randomized controlled trial conducted in New Zealand, patients administered FF/VIL for 2 weeks showed

decreased airway inflammation, as indicated by reduced FeNO levels. Remarkably, the suppression of FeNO endured for about 18 days after stopping treatment, highlighting the sustained anti-inflammatory impact of FF/VIL on the airways [32]. However, the FeNO level decreased by 0.2 ppb in the BUD/FOR group and increased by 0.8 ppb in the FF/VIL group. The reason for the difference may be because FeNO levels can be influenced by several factors, including age, sex, height, obesity, prior diagnosis, and smoking status [33]. The patients in the FF/VIL group had higher weight, height, and BMI compared to those in the BUD/FOR group in the present study. Besides, the increased use of ICS in the BUD/FOR group, particularly as the frequency of medication administration increased. This heightened exposure to ICS may have contributed to the more pronounced reduction in FeNO observed during the study period.

A higher blood eosinophil count may be associated with increased AEs and more asthma-related hospitalizations [34]. Previous studies have indicated that asthma patients treated with SMART had lower rates of AEs compared to those treated with other combinations of ICS/LABA plus SABA [5, 20]. However, the reduction in the incidence of AEs was not significant in the BUD/FOR group, which may be due to the small number of patients. Certainly, various factors can influence blood eosinophilic counts, including medications, stress, exposure to pollutants, and allergic reactions. Lower baseline eosinophilic counts can exhibit more significant variations [35]. We may repeat measurements of peripheral blood eosinophil counts at multiple time points to have comprehensively assess the eosinophilic nature of a patient's asthma [36].

There are several limitations in the current study. First, it is a retrospective observational study conducted in a single medical center, resulting in a relatively small sample size and potential selection bias. Second, the treatment strategy was based on clinical physician judgment, patient preference, and adherence, introducing variability. Notably, the frequency of medication administration differed between the two treatment strategies. Shared decision-making with patients was practiced, with many opting for FF/VIL as their controller due to its dosing frequency. Consequently, patients treated with BUD/FOR as controller plus SABA as reliever were excluded from the study, leading to an imbalance in the number of patients between the two groups. Third, the relatively high ACT scores observed in this study could be attributed to the fact that they were obtained from medical charts at the onset of treatment for patients who had been continuously receiving MART or FF/VIL as controller therapy without a SABA for 12 months. Some patients may have been previously treated with alternative therapies, for example other ICS/LABA combinations such as beclometasone/FOR or FP/SM, or monotherapy. This could potentially result in the difference in improvement between the two groups not reaching the MCID threshold of 3 points. Fourth, the forced mid-expiratory flow (FEF25-75%) is lower in BUD/FOR. Maximal Mid Expiratory Flow (MMEF) is a pulmonary function test that report small airway disease and airway hyperresponsiveness [37]. FEF25-75% values were lower than those in controlled asthma groups and were associated with lower ACT scores [38].

In our study, the lower FEF25-75% in the BUD/FOR group compared to the FF/VIL group suggests a potential difference in small airway involvement between the two groups. This difference may be reflected in the change in ACT scores. However, this is a retrospective study and patient number was relatively small, further study may be needed for clarification. Despite these limitations, this study represents the first real-world comparison of the efficacy between BUD/FOR as MART and FF/VIL as MART in patients with step 3 and 4 asthma, with comprehensive measurements including, FEV1, AE rate, serum IgE, and blood eosinophil count.

Conclusions

In summary, patients treated with FF/VIL as MART showed improvements in ACT scores, while those treated with BUD/FOR as MART exhibited a reduction in FeNO levels. However, the difference between the two treatment groups did not reach clinical significance. Our results indicate that FF/VIL as MART has comparable clinical effectiveness to BUD/FOR as MART. Nevertheless, larger prospective randomized controlled studies are necessary to validate these findings.

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Authors' contributions
WCH, CHC, and WCC designed the study. All authors contributed to patient enrolment and data collection. WCH and WCC analyzed the data. WCH and WCC drafted the manuscript.

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Availability of data and materials
The corresponding author is willing to provide the datasets used and/or analyzed in the current study upon reasonable request.

Declarations

Ethics approval and consent to participate
The retrospective study was approved by the Institutional Review Board of China Medical University Hospital (CMUH112-REC1-175). The need for individual patient consent was waived by the Institutional Review Board (IRB) of China Medical University Hospital (CMUH) due to the retrospective design. All

methods in the study adhered to relevant guidelines and regulations, including the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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