Differences in pulmonary function improvement after once-daily LABA/LAMA fixed-dose combinations in patients with COPD

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Research Article

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Abstract

**Objective:**

This real-world study evaluated the efficacy of once-daily long-acting β2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) for improving spirometry in patients with chronic obstructive pulmonary disease (COPD).

**Methods:**

We conducted this retrospective study at a single medical center in Taiwan from December 2014 to September 2020. Patients with COPD who were treated with once-daily LABA/LAMA FDCs for 12 months were enrolled. We evaluated their lung function improvement after 12 months treatment with different LABA/LAMA FDCs.

**Results:**

A total of 198 patients with COPD who were treated with once-daily LABA/LAMA FDCs were analyzed. A total of 114 patients were treated with umeclidinium/vilanterol (UMEC/VIL); 34 patients were treated with indacaterol/glycopyrronium (IND/GLY) and 50 patients were treated with tiotropium/olodaterol (TIO/OLO). The forced expiratory volume in 1 second (FEV1%) was significantly increased in the patients treated with all three once-daily FDCs (55.2% to 60.9%; Δ = 5.74%, p=0.012 for UMEC/VIL, 58.2% to 63.6%; Δ = 5.37%, p=0.023 for IND/GLY, and 54.1% to 57.7%; Δ = 3.61%, p=0.009 for TIO/OLO). Treatment of COPD patients with TIO/OLO resulted in a significant improvement in both forced vital capacity (FVC%) (71.7% to 77.9%; Δ = 6.16%, p=0.009) and residual volume (RV%) (180.1% to 152.5%; Δ = -27.55%, p<0.01) compared with those treated with UMEC/VIL (FVC%: 75.1% to 81.5%; Δ = 6.45%, p < 0.001; RV%:173.8% to 165.2%; Δ = -8.67%, p=0.231) or IND/GLY (FVC%: 73.9% to 79.3%; Δ = 5.42%, p = 0.08; RV%:176.8% to 168.3%; Δ = -8.47%, p=0.589).

**Conclusions:**

Patients with COPD who were treated with different once-daily LABA/LAMA FDCs all had pulmonary lung function improvement in FEV1. Patients treated with UMEC/VIL or TIO/OLO showed better improvement in FVC compared to those treated with IND/GLY. On the other hand, those receiving TIO/OLO had better improvement in RV compared to those who received UMEC/VIL or IND/GLY.

**Introduction**

Inhaled bronchodilators are the main pharmacological therapy for each stage of chronic obstructive pulmonary disease (COPD) (1). There is a lot of evidence to show that once-daily long-acting β2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) dual bronchodilators are superior for symptoms control and lung function improvement compared with monotherapy (2–5). Several studies also reported that the early use of LABA/LAMA dual bronchodilators may improve disease stability and prevent further
disease deterioration compared to monotherapy, including treatment-naive patients (6–8). As a result, LABA/LAMA dual bronchodilators are recommended as the initial therapy for COPD patients with more symptoms, high frequency of acute exacerbations (AEs) and poor lung function.

Nowadays, several different once-daily LABA/LAMA fixed-dose combination (FDCs) dual bronchodilator regimens are available, including (1) umeclidinium/vilanterol (UMEC/VIL) 55 µg/22 µg via an Anoro Ellipta™; (2) tiotropium/olodaterol (TIO/OLO) 2.5 µg/2.5 µg via a Spiolto Respimat™; and (3) indacaterol/glycopyrronium (IND/GLY) 110 µg/50 µg via an Ultibro Breezhaler™. The comparative efficacy of these different dual bronchodilator combinations has not been widely studied in symptomatic COPD patients. Several indirect comparison studies have tried to compare the efficacy of currently available LABA/LAMA FDC dual bronchodilators for COPD via network meta-analyses (9–11); they revealed that there was no significant difference in lung function improvement among the different medications. A few head to head studies revealed that UMEC/VIL regimens had larger increases in the forced expiratory volume in 1 second (FEV1) compared with TIO/OLO (12, 13). However, in another study, there was no significant change in FEV1 after inhaled UMEC/VIL compared with IND/GLY (14).

Few real-world studies have compared lung function efficacy in COPD patients administered one of the three once-daily LABA/LAMA FDCs. Cheng et al conducted a real-world study in Taiwan and reported that TIO/OLO resulted in superior lung function improvement (FEV1 and force vital capacity [FVC]) and reduced AEs, compared with the other regimens (IND/GLY and UMEC/VI) (15). Muraki et al reported that there were no significant differences in the COPD Assessment Test (CAT), the modified Medical Research Council (mMRC) dyspnea questionnaire, and spirometry items following the administration of the three FDCs (16). The efficacy of dual bronchodilators for lung function improvement are variable and there are many factors that can affect the efficiency of medication in real-world practice, such as adherence to medication, frequency of administration, the role of the device, the patients’ understanding and views of the disease and treatment (17–19); these factors cannot be seen or controlled for in randomized controlled trials (RCTs).

In addition, in most studies of COPD, only FEV1 has been focused on and used as an outcome measurement. However, the calculation of FEV1 alone has limitations due to the underlying heterogeneous nature of COPD and it is widely accepted that the FEV1 measurement alone does not effectively represent functional impairment (20). A comprehensive patient evaluation, including multiple parameters is required for efficient COPD phenotyping (21). As a result, more parameters of pulmonary function are needed to evaluate the efficacy of the different LAMA/LABA FDCs in COPD patients. This purpose of this real-world study was not only to evaluate the efficacy of the three different once-daily LAMA/LABA FDCs (UMEC/VIL, IND/GLY and TIO/OLO), but to also find out the potential differences among the three medications, with regards to objectively assessed pulmonary function parameters (FEV1, FVC and RV) in a heterogeneous COPD population.

**Materials And Methods**


Study patients

This study was conducted retroactively at the Division of Pulmonary and Critical Care Medicine, China Medical University Hospital, Taiwan between December 2014 and September 2020. The inclusion criteria of patients were as follows: (1) over 40 years old, (2) diagnosed with COPD based on clinical symptoms (such as breathing difficulty, cough, sputum production, and wheezing) and spirometry (post-bronchodilator FEV1/FVC < 0.7), and lifetime risk for the development of COPD; (3) patients who were being treated with once-daily LAMA/LABA FDCs for at least 52 weeks or 12 months. Patients were excluded if they were treated with triple therapy or mono therapy (LAMA or LAMA), or they had insufficient data available for further analysis. The study was approved by the China Medical University Hospital Institutional Review Board (CMUH110-REC1-245), and the need for informed consent was waived due to the observational and retrospective design of the study. The once-daily LABA/LAMA FDC included: (1) UMEC/VIL 55 µg/22 µg via an Anoro Ellipta™; (2) TIO/OLO 2.5 µg/2.5 µg via a Spiolto Respimat™; (3) IND/GLY 110 µg/50 µg via an Ultibro Breezhaler™. In order to improve their health outcomes and healthcare quality, all patients participated in healthcare case management.

Clinical data collection and treatment assessment

The clinical data of the patients, including age, sex, body height (BH), body weight (BW), body mass index (BMI), smoking status, history of asthma, comorbidities, pulmonary function tests (PFTs), CAT score, mMRC score, acute exacerbation in the previous year, and GOLD airflow limitation severity were collected. GOLD airflow limitation was divided into 4 stages based on the patient’s FEV1% predicted: stage 1/mild, FEV1 ≥ 80%; stage 2/moderate, 50–79%; stage 3/severe, 30–49%; stage 4/very severe FEV1 < 30% (22). After the primary treatment was started, patients underwent regular (every three to six months) follow-ups at our institute. The pulmonary function parameters (FEV1, FVC and RV) at 12 months of treatment were compared with the pre-LABA/LAMA FDC treatment values.

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR; 25th and 75th percentiles) or mean with standard deviation (SD). Analysis of variance (ANOVA) F-tests were conducted for each variable and treatment medication. Multiple comparisons with ANOVA analysis used Tukey’s honest significant difference test to analyze the clinical outcomes between users of different medications. Categorical variables were reported as the number of patients and percentages. Differences in categorical variables were examined using chi-squared test. The effectiveness of LABA/LAMA FDC therapy in patients with COPD was also analyzed using a paired t test. 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 198 patients with COPD who were treated with once-daily LABA/LAMA FDCs were enrolled in the current study (Fig. 1). Of the enrolled patients, 114 were treated with UMEC/VIL, 34 with IND/GLY, and 50 with TIO/OLO. Most of the enrolled patients were male (93.9%), with a mean age of 70.4 (SD 10.4) years, mean weight of 64.2 (SD 6.6) kg, and mean height of 163.1 (SD 11.6) cm. The mean packs/year of smoking in our cohort was 40.2 (SD 28.8). The most common comorbidity was congestive heart failure (CHF, n = 41, 20.7%), followed by coronary artery disease (CAD, n = 39, 19.7%). The mean FEV1/FVC ratio, FEV1%, FVC%, and RV% were 59.1 ± 9.9%, 55.7 ± 16.2%, 73.8 ± 16.5%, and 171.1 ± 63.1%, respectively. The GOLD III/IV group accounted for 36.2% (n = 71) of all study patients. The presence of comorbidities, the severity of GOLD stage, and the pulmonary function parameters (FEV1, FVC, and RV) before dual bronchodilator treatment showed no significant difference among the three examined LABA/LAMA FDCs (Table 1).
<table>
<thead>
<tr>
<th></th>
<th>Total (n = 198)</th>
<th>UMEC/VIL (n = 114)</th>
<th>GLY/IND (n = 34)</th>
<th>TIO/OLO (n = 50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (SD)</strong></td>
<td>70.4 (10.4)</td>
<td>70.6 (10.9)</td>
<td>72.4 (7.9)</td>
<td>68.5 (10.3)</td>
<td>0.229</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>186 (93.9)</td>
<td>109 (95.6)</td>
<td>32 (94.1)</td>
<td>45 (90.0)</td>
<td>0.381</td>
</tr>
<tr>
<td><strong>Body Height, cm (SD)</strong></td>
<td>163.1 (6.6)</td>
<td>163.1 (7.0)</td>
<td>162.3 (6.9)</td>
<td>163.6 (5.7)</td>
<td>0.651</td>
</tr>
<tr>
<td><strong>Body Weight, kg (SD)</strong></td>
<td>64.2 (11.6)</td>
<td>63.9 (11.3)</td>
<td>65.5 (11.7)</td>
<td>63.7 (12.2)</td>
<td>0.740</td>
</tr>
<tr>
<td><strong>BMI, kg/m² (SD)</strong></td>
<td>24.2 (4.1)</td>
<td>24.1 (4.1)</td>
<td>24.8 (3.8)</td>
<td>23.7 (4.3)</td>
<td>0.483</td>
</tr>
<tr>
<td><strong>Smoking, pack-years (SD)</strong></td>
<td>40.2 (28.8)</td>
<td>40.3 (29.2)</td>
<td>48.2 (31.5)</td>
<td>34.5 (25.1)</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>ACO (%)</strong></td>
<td>14 (7.1)</td>
<td>7 (6.1)</td>
<td>4 (11.8)</td>
<td>3 (6.0)</td>
<td>0.502</td>
</tr>
<tr>
<td><strong>CAD (%)</strong></td>
<td>39 (19.7)</td>
<td>22 (19.3)</td>
<td>7 (20.6)</td>
<td>10 (20.0)</td>
<td>0.984</td>
</tr>
<tr>
<td><strong>CHF (%)</strong></td>
<td>41 (20.7)</td>
<td>24 (21.1)</td>
<td>6 (17.6)</td>
<td>11 (22.0)</td>
<td>0.881</td>
</tr>
<tr>
<td><strong>Cancers (%)</strong></td>
<td>39 (19.7)</td>
<td>22 (19.3)</td>
<td>8 (23.5)</td>
<td>9 (18.0)</td>
<td>0.811</td>
</tr>
<tr>
<td><strong>Bronchiectasis (%)</strong></td>
<td>15 (7.6)</td>
<td>8 (7.0)</td>
<td>3 (8.8)</td>
<td>4 (8.0)</td>
<td>0.932</td>
</tr>
<tr>
<td><strong>FEV1/FVC, % (SD)</strong></td>
<td>59.1 (9.9)</td>
<td>59.4 (9.7)</td>
<td>59.3 (8.1)</td>
<td>58.1 (11.3)</td>
<td>0.740</td>
</tr>
<tr>
<td><strong>FEV1, L (SD)</strong></td>
<td>1.38 (0.45)</td>
<td>1.36 (0.43)</td>
<td>1.41 (0.46)</td>
<td>1.41 (0.48)</td>
<td>0.788</td>
</tr>
<tr>
<td><strong>FEV1, % (SD)</strong></td>
<td>55.7 (16.2)</td>
<td>55.3 (16.3)</td>
<td>58.2 (15.7)</td>
<td>54.8 (16.7)</td>
<td>0.610</td>
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<tr>
<td><strong>FVC, L (SD)</strong></td>
<td>2.35 (0.59)</td>
<td>2.29 (0.56)</td>
<td>2.38 (0.61)</td>
<td>2.46 (0.65)</td>
<td>0.214</td>
</tr>
<tr>
<td><strong>FVC, % (SD)</strong></td>
<td>73.8 (16.5)</td>
<td>74.8 (17.1)</td>
<td>73.9 (16.3)</td>
<td>72.3 (15.9)</td>
<td>0.713</td>
</tr>
<tr>
<td><strong>RV, % (SD)</strong></td>
<td>171.1 (63.1)</td>
<td>170.3 (57.5)</td>
<td>173.4 (68.5)</td>
<td>171.2 (74.1)</td>
<td>0.972</td>
</tr>
<tr>
<td><strong>MMEF25-75, % (SD)</strong></td>
<td>27.9 (12.1)</td>
<td>29.1 (11.2)</td>
<td>27.2 (9.7)</td>
<td>26.5 (14.8)</td>
<td>0.551</td>
</tr>
<tr>
<td><strong>GOLD stage, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.448</td>
</tr>
<tr>
<td>I</td>
<td>15 (7.7)</td>
<td>9 (8.0)</td>
<td>2 (5.9)</td>
<td>4 (8.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>110 (56.1)</td>
<td>65 (58.0)</td>
<td>23 (67.6)</td>
<td>22 (44.0)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>61 (31.1)</td>
<td>33 (29.5)</td>
<td>7 (20.6)</td>
<td>21 (42.0)</td>
<td></td>
</tr>
</tbody>
</table>

ACO: Asthma and COPD overlap; AE: Acute Exacerbation; BMI: Body Mass Index; CAD: Coronary heart disease; CAT: COPD Assessment Test; CHF: Congestive heart failure; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GOLD: the Global Initiative for Chronic Obstructive Lung Disease; GLY/IND: Glycopyrronium/Indacaterol; MMEF: Maximal Mid-Expiratory Flow; IQR: interquartile range; RV: Residual volume; SD: Standard deviation; TIO/OLO: Tiotropium/Olodaterol; UMEC/VIL: Umeclidinium/Vilanterol
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</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>10 (5.1)</td>
<td>5 (4.5)</td>
<td>2 (5.9)</td>
<td>3 (6.0)</td>
<td></td>
</tr>
<tr>
<td>CAT (IQR)</td>
<td>6.5 (6.5-7)</td>
<td>6.0 (4-8.75)</td>
<td>6.5 (4-10.0)</td>
<td>7.5 (5.0-13.0)</td>
<td>0.058</td>
</tr>
<tr>
<td>AE in last year (IQR)</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0.270</td>
</tr>
</tbody>
</table>

ACO: Asthma and COPD overlap; AE: Acute Exacerbation; BMI: Body Mass Index; CAD: Coronary heart disease; CAT: COPD Assessment Test; CHF: Congestive heart failure; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GOLD: the Global Initiative for Chronic Obstructive Lung Disease; GLY/IND: Glycopyrronium/Indacaterol; MMEF: Maximal Mid-Expiratory Flow; IQR: interquartile range; RV: Residual volume; SD: Standard deviation; TIO/OLO: Tiotropium/Olodaterol; UMEC/VIL: Umeclidinium/Vilanterol

**Pulmonary function changes following treatment**

We evaluated whether there were any significant differences in the pulmonary function parameters before and after 12 months treatment with the different medications (UMEC/VIL, IND/GLY and TIO/OLO). Patients treated with UMEC/VIL had significantly better improvements in absolute FEV1 values ($\Delta = 0.099$ L, $p = 0.012$) compared to those treated with IND/GLY and TIO/OLO ($\Delta = 0.116$ L, $p = 0.057$; $\Delta = 0.056$ L, $p = 0.107$) (Fig. 2). Those treated with UMEC/VIL also had significantly better improvements in absolute FVC values than those treated with IND/GLY and TIO/OLO ($\Delta = 0.115$ L, $p = 0.031$ vs. $\Delta = 0.052$ L, $p = 0.532$ vs. $\Delta = 0.118$ L, $p = 0.093$) (Fig. 3).

In addition, the percentage changes of pulmonary function parameters after 12 months of treatment were as follows. Patients treated with UMEC/VIL had a significant increase in the percentage changes in FEV1 (55.2–60.9%; $\Delta = 5.74\%$, $p = 0.012$) and FVC values (75.1–81.1%; $\Delta = 6.45\%$, $p < 0.001$) (Fig. 2; Fig. 3). However, the patients treated with IND/GLY only had a significant increase in FEV1 values (58.2–63.6%; $\Delta = 5.37\%$, $p = 0.023$) (Fig. 2). In the TIO/OLO users, all pulmonary function parameters significantly improved, including FEV1 (54.1–57.7%; $\Delta = 3.61\%$, $p = 0.009$), FVC (71.7–77.9%; $\Delta = 6.16\%$, $p = 0.009$), and RV (180.1–152.5%; $\Delta = -27.55\%$, $p = 0.007$) (Fig. 2; Fig. 3; Fig. 4). We found that TIO/OLO treatment might have more effects on lung hyperinflation due to the significant reduction in RV.

**Minimal clinically important differences in FEV1, FVC, and CAT score following treatment**

We also assessed lung function improvements and quality of life according to minimal clinically important differences (MCIDs) in FEV1, FVC, and CAT score among the three groups. Around 40% of the patients in the three groups reached a MCID in FEV1 (43.5% in UMEC/VIL, 41.2% in IND/GLY, 38.3% TIO/OLO). Patients treated with UMEC/VIL and TIO/OLO had a higher MCID in FVC (48.1%, 46.8%) than those treated with IND/GLY (33.3%). There was no significant difference in CAT score improvement among the three groups (Table 2).
Table 2
The MCID of FEV1, FVC, and CAT after these three medicines treatment

<table>
<thead>
<tr>
<th></th>
<th>UMEC/VIL (n = 114)</th>
<th>GLY/IND (n = 34)</th>
<th>TIO/OLO (n = 50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, MCID (%)</td>
<td>49(43.5)</td>
<td>14(41.2)</td>
<td>19(38.3)</td>
<td>0.868</td>
</tr>
<tr>
<td>FVC, MCID (%)</td>
<td>55(48.1)</td>
<td>11(33.3)</td>
<td>27(46.8)</td>
<td>0.316</td>
</tr>
<tr>
<td>CAT, MCID (%)</td>
<td>30(28.0)</td>
<td>10(30.3)</td>
<td>14(28.5)</td>
<td>0.873</td>
</tr>
</tbody>
</table>

CAT: CAT : The COPD Assessment Test; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; GLY/IND: Glycopyrronium/Indacaterol; MCID: minimal clinically important difference; TIO/OLO: Tiotropium/Olodaterol; UMEC/VIL: Umeclidinium/Vilanterol

Discussion

To the best of our knowledge, this is the first study to directly compare patients with COPD who were treated with different once-daily LABA/LAMA FDCs (UMEC/VIL, GLY/IND, and TIO/OLO), including an assessment of multiple pulmonary function parameters. The current study reported that pulmonary function improvement was significantly affected by the different types of medication. There was a statistically significant increase in FEV1 and FVC for patients treated with UMEC/VIL for 12 months. Patients treated with GLY/IND for 12 months only had a significant improvement in FEV1. However, all pulmonary function parameters (FEV1, FVC, and RV) were significantly improved in patients who received 12 months of TIO/OLO treatment; there was a particularly notable reduction in RV.

A meta-analysis of dual bronchodilation with LAMA/LABA in COPD patients, which enrolled 14 papers and one congress abstract, and included 23,168 patients, found that all dual bronchodilation therapies elicited a greater increase in FEV1 than monotherapy alone. The IND/GLY combination increased FEV1 by 89.44 mL (95% CI, 76.04-102.85); FEV1 was increased by 54.75 mL following TIO/OLO combination treatment (95% CI, 45.70–63.80); UMEC/VIL combination treatment increased FEV1 by 83.66 mL (95% CI, 65.65-101.67) (9). Another network meta-analysis of data extracted from 22 studies was performed by linking the efficacy and safety outcomes, and it reported that TIO/OLO > UMEC/VIL > GLY/IND following an indirect comparison (23). However, published data regarding a direct comparison of TIO/OLO, UMEC/VIL, and GLY/IND is limited.

A direct comparison study indicated that at 8 weeks UMEC/VIL was superior to TIO/OLO for the primary endpoint of through FEV1 (167 ml in UMEC/VIL and 110 ml in TIO/OLO, p = 0.001.) (12). Another 12-week direct comparison study demonstrated that IND/GLY and UMEC/VIL provided clinically meaningful and comparable bronchodilation (14). In the current study, medication delivered via a DPI (IND/GLY and UMEC/VIL) resulted in a no significantly greater improvement in FEV1 compared with SMI (TIO/OLO) after 52 weeks treatment, which was consistent with previous reports. However, a real-world study from Taiwan reported that TIO/OLO was superior to IND/GLY and UMEC/VIL in relation to FEV1 (98.7 vs 65.2 vs 64.4 ml, respectively; p < 0.001), and FVC (127.3 vs 58.2 vs 79.1 ml; p < 0.001) after 12 months treatment (15). A prospective direct comparison study (open-labeled) in Japan of the three once-daily
LABA/LAMA FDCs, reported no significant differences in spirometry parameters after 12 weeks treatment (16). These few studies appear to be contradictory in their findings, however, this could be explained by the different study designs, the different patient cohorts, and the differences between retrospective real-world studies and RCTs. A more direct comparison of these three medications using RCTs might be needed in the future.

Poor inhaler adherence and technique error can lead to poor COPD control. Lower adherence to medication in COPD was shown to be associated with a lower FEV1, a higher risk of admission to hospital and death (24). It is common that patients do not use their devices properly in real-world practice (25) and this can be affected by several factors, including frequency of administration, device preference, and the patients’ understanding of COPD and the necessary treatment (19, 25). One study reported that fewer COPD patients made critical errors with ELLIPTA compared with other commonly used devices, and that most patients (57–70%) made no errors using ELLIPTA (26). Our study reported that UMEC/VIL (delivered via ELLIPTA DPI) showed the greatest improvement in FEV1 and FVC among the three different medications, however, this could be associated with the increased convenience of using the ELLIPTA DPI.

Small airway disease (SAD) is a key pathological feature of COPD. Patients with COPD accompanied by SAD have worse respiratory reactance, worse spirometry results, more severe lung hyperinflation, and a poorer health status (27). Most inhaled therapies cannot deliver to small airways sufficiently (28). An in vitro study tried to compare drug delivery to the lung among four different inhalers (Respimat, Breezhaler, Genuair, and ELLIPTA). The modeled dose to the lung was found to be highest in Respimat (59% for moderate COPD; 67% for severe COPD). Respimat showed the lowest number of particles depositing in the mouth–throat model and the highest number reaching all regions of the simulation lung model (29). The measurement of FEV1 by spirometry is not specific for SAD, with larger airways contributing substantially to the expired volume (30). COPD patients with small airway involvement usually have more gas trapping with a higher RV (31, 32). SAD was also associated with bronchodilator responsiveness in terms of FVC, but not in terms of FEV1 (27). Our study reported that TIO/OLO (delivered via Respimat SMI) tended to show an increased improvement in FVC and RV among the three different medications, indicating an improvement in SAD because the lung deposition would be better with Respimat compared with the DPI therapies (29). Cheng et al also reported that patients treated with TIO/OLO had significantly better improvements in FEV1 and FVC compared to those treated with UMEC/VIL or IND/GLY in COPD patients with low FEV1 or FVC, which means more hyperinflation (15). We need more real-world study rather than rather than in-vitro study to confirm the concept.

Airflow limitation, as diagnosed by spirometry, remains the standard diagnosis for COPD. Most previous studies have relied on FEV1 or FVC only for an assessment of disease severity or reversibility of bronchodilators (33–36). However, a measurement of FEV1 alone is not sufficient to determine the complexity of COPD, especially in those with SAD. Lung volume, including inspiratory capacity (IC) or RV are potentially useful parameters for detecting the response to bronchodilator therapy (37, 38). The additional measurement of FVC in the present study could help detect more bronchodilator responders compared with FEV1 alone (36, 39). The current study aimed to provide a comprehensive overview of the
common parameters (FEV1, FVC, and RV) of spirometry in our clinical practice, to help distinguish the different effects of these three medications. COPD patients treated with TIO/OLO showed improvement in all measured pulmonary function parameters, especially in RV. After 52 weeks treatment IND/GLY and UMEC/VIL showed more improvement in FEV1 and FVC as opposed to RV in COPD patients. We conducted this study to provide additional data to primary care clinical physicians, to help enhance the efficacy of COPD management.

There were several limitations in the current study. First, this was a retrospective observational study, which was performed at a single medical center with a relatively small number of patients and some degree of selection bias. Following the inclusion criteria, people who did not use the same once-daily LABA/LAMA dual bronchodilator FDC continuously for 12 months were excluded. The decision regarding which type of medication to treat patients with was made by their primary care physician. The treatment strategy is based on the clinical physician's judgement, the patients’ preference and adherence, and the medication available. UMEC/VIL was the first available once-daily LABA/LAMA FDC in our hospital; therefore, the number of patients in each group was imbalanced. Third, we might need more parameters of spirometry for a full SAD evaluation, including IC, total lung capacity (TLC), and RV/TLC. We chose the three most commonly used parameters of spirometry, and RV can be used to replace IC in our clinical practice. Newton et al reported a significant reduction in RV and increases in FVC and IC following the administration of a bronchodilator in moderate to severe hyperinflated COPD patients (37). Finally, all baseline data were available, but some follow-up data were missing. There were few differences in baseline lung function data before and after performing the paired t test. The baseline pulmonary function parameters (FEV1, FVC, and RV) still showed no significant difference among the three LABA/LAMA FDCs after performing the paired t test (Supplement Table). Despite these limitations, the current study provides the first real-world comparison of the efficacy of the three most commonly used once-daily LABA/LAMA FDCs, and it was conducted via comprehensive measurements of spirometry parameters.

**Conclusion**

Patients with COPD treated with either of the three once-daily LABA/LAMA FDCs for 12 months, showed improvement in pulmonary lung function, including FEV1, FVC and RV. All of the patients treated with once-daily FDCs had improvements in FEV1. Those treated with UMEC/VIL or TIO/OLO had better improvements in FVC compared to those treated with IND/GLY. TIO/OLO (agents delivered by SMI) treatment was superior for the reduction of RV and an improvement in FVC, which may indicate that it is beneficial for improving small airway obstruction.

**Abbreviations**

COPD, chronic obstructive pulmonary disease; ICS, inhaled glucocorticoid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ACO, asthma and COPD overlap; AE, acute exacerbation; mMRC, Modified Medical Research Council; CAT,
Declarations

Acknowledgements

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Author contributions

WCC and WCH participated in the study conception and design. WCC, BRW, WCH, WCL, CHC, WCC, CYT, and CYC participated in data acquisition. WCC and WCH participated in data analysis and interpretation. WCC and WCH drafted the manuscript, with all authors revising it critically for intellectual content. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The Investigational Review Board [China Medical University & Hospital Research Ethics Center (CMUHREC)] approved this retrospective study at China Medical University Hospital [CMUH110-REC1-245] and complied with the ethical standards of the Declaration of Helsinki. The requirement for individual patient consent was waived by the Ethics Review Boards because of the retrospective study design.

Consent for publication

Not applicable.

Competing interests

No conflicts of interest exist for the specified authors.
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References


Figures

Figure 1

Patient enrollment flowchart.
Figure 2

The significant difference in FEV1(L) and FEV1(%) in COPD patients before and after 12 months of treatment with (A) UMEC/VIL, (B) IND/GLY, and (C) TIO/OLO.
Figure 3

The significant difference in FVC(L) and FVC (%) in COPD patients before and after 12 months of treatment with (A) UMEC/VIL, (B) IND/GLY, and (C) TIO/OLO.

Figure 4

The significant difference in RV (%) in COPD patients before and after 12 months of treatment with (A) UMEC/VIL, (B) IND/GLY, and (C) TIO/OLO.

Supplementary Files

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