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Outcome of Inhaler Withdrawal in Patients Receiving Triple Therapy for COPD

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Background: The purpose of this study was to document outcomes following withdrawal of a single inhaler (step-down) in chronic obstructive pulmonary disease (COPD) patients on triple therapy (long-acting muscarinic antagonist and a combination of long-acting β2-agonists and inhaled corticosteroid), which a common treatment strategy in clinical practice.

Methods: Through a retrospective observational study, COPD patients receiving triple therapy over 2 years (triple group; n=109) were compared with those who had undergone triple therapy for at least 1 year and subsequently, over 9 months, initiated inhaler withdrawal (step-down group, n=39). The index time was defined as the time of withdrawal in the step-down group and as 1 year after the start of triple therapy in the triple group.

Results: Lung function at the index time was superior and the previous exacerbation frequency was lower in the step-down group than in the triple group. Step-down resulted in aggravating disease symptoms, a reduced overall quality of life, decreasing exercise performance, and accelerated forced expiratory volume in 1 second (FEV_1) decline (54.7±15.7 mL/yr vs. 10.7±7.1 mL/yr, p=0.007), but there was no observed increase in the frequency of exacerbations.

Conclusion: Withdrawal of a single inhaler during triple therapy in COPD patients should be conducted with caution as it may impair the exercise capacity and quality of life while accelerating FEV_1 decline.

Keywords: Pulmonary Disease, Chronic Obstructive

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and progressive airflow limitation[1]. The principal therapeutic options aim to relieve symptoms and future risk[1]. In the current guidelines, inhalers are the mainstay for the pharmacological treatment of the disease[1-3]. Since long-acting β2-agonists (LABA) and long-acting muscarinic antagonists (LAMA) dilate airways by different mechanisms, the combination of LABA and LAMA results in greater bronchodilation than either inhaler alone[4-6]. Another pharmacological therapy for COPD is inhaled corticosteroid (ICS). While the recommendation for ICS in the management of stable COPD is limited to special conditions[1,2], in clinical practice, they are often prescribed in a combination inhaler with LABA, which provide greater symptom control, pulmonary function improvement, and exacerbation reduction than either individual component in patients with moderated to severe COPD[7-9]. Theoretically, therefore, adding LAMA to a LABA/ICS combination inhaler (i.e., triple therapy) could result in even greater treatment efficacy in COPD.

Given the progressive nature of COPD, most patients require triple therapy at some point during the course of the disease. Moreover, in most cases (unlike in asthma), once such treatment has been started, it is generally maintained. Nevertheless, there are triple therapy cases where one inhaler is withdrawn (step-down) because of a marked improvement in the symptoms or the development of side effects. However, no study has investigated the effects of step-down in COPD patients treated with triple therapy.

To investigate the effect of step-down (withdrawing one inhaler) in triple therapy, we retrospectively assessed the outcome of step-down in COPD patients who had been treated with LAMA and a LABA/ICS combination.

Materials and Methods

1. Patients

The data of all patients who were diagnosed with COPD in the Korean Obstructive Lung Disease (KOLD) Cohort were analyzed retrospectively. These patients were prospectively recruited from the 16 hospitals in South Korea in June 2005–October 2012 and inclusion criteria have been described elsewhere[10]. At the enrolment visit, all patients were evaluated with medical interviews, physical examinations, spirometry, and lung volume, diffusing capacity, and 6-minute walk distance (6MWD). The dyspnea degree was determined by using the modified Medical Research Council (MMRC) dyspnea scale. Health-related quality of life was evaluated by calculating the total score in the validated Korean version of the St. George's Respiratory Questionnaire (SGRQ). Comorbidity

scores were calculated by using the updated Charlson comorbidity index[11]. Chronic bronchitis was diagnosed if patients had a chronic cough and phlegm production for 3 months per year for at least 2 consecutive years. Volumetric computed tomography (CT) scans were performed by using a 16-multidetector CT scanner (Somatom Sensation; Siemens Medical System, Bonn, Germany), and the automatically calculated volume fraction of the lung below –950 Hounsfield units at full inspiration was termed as the emphysema index (EI).

Thereafter, the patients were followed every 3 months: at each visit, they were asked about the compliance regarding the prescribed medication, degree of dyspnea, and exacerbation history in the previous 3 months. Pre-bronchodilator spirometry was performed every 6 months. Post-bronchodilator spirometry after inhalation of 400 mg of albuterol, diffusing capacity, lung volume, 6MWD, and SGRQ were performed every 12 months. Spirometry (Vmax 22 instrument; SensorMedics, Yorba Linda, CA, USA and PFDX instrument; MedGraphics, St. Paul, MN, USA) was performed as recommended by the American Thoracic Society.

This study was approved by the Institutional Review Boards of all hospitals, and each patient provided written informed consent.

2. Study design

The KOLD Cohort patients who had been treated with LAMA and a LABA/ICS combination (i.e., triple therapy) for at least 1 year and had been followed for at least 2 years after the start of triple therapy were identified retrospectively. The patients who were treated continuously with triple therapy for more than 2 years were classified as the triple group. Patients who were treated with triple therapy at least for 1 year, after which LAMA or the LABA/ICS combination was withdrawn, and maintained only one inhaler without adding other long acting inhalers for at least 9 months was defined as the step-down group. The step-down group only included the patients who had not been prescribed discontinued inhaler for at least 9 months because it was considered that a period of at least 9 months was needed to evaluate the effect of step-down. Patients who replied that their compliance to the prescribed inhaler was <70% were excluded.

Some patients in the step-down group restarted the discontinued inhaler: they were defined as the step-up group. The remaining step-down patients who maintained the withdrawal were defined as the maintained step-down group.

Index time (IT) was defined as the time point of step-down in the step-down group. For the triple group, IT was arbitrarily defined as 12 months after the start of triple therapy. The variables that were obtained in the visit just preceding the IT were considered to be the IT baseline data.

We defined an exacerbation as a severe episode that required hospitalization or a visit to the emergency room[12]. The

numbers of exacerbation in the year before and after the IT were determined.

At first, the IT baseline data were compared between the triple and step-down group, and then changes in variables after the IT relative to the baseline values were compared between the two groups. The long-term effects of step-down (i.e., the effects over the entire follow-up period after the IT) on the decline of forced expiratory volume in 1 second (FEV_1) and on the time-to-first exacerbation were also determined.

Some patients in the step-down group restarted the discontinued inhaler (step-up group), and the data that were obtained after restarting the discontinued inhaler in the patients were not included in these analyses.

3. Statistical analysis

Descriptive statistics are presented as mean and standard deviation for normally distributed variables and as median (first and third quartiles) for non-normally distributed variables. To compare the triple and step-down groups in terms of baseline characteristics at the IT, Student's t test and chi-squared tests were used for the continuous variables and categorical variables, respectively. To compare the two groups in terms of variable changes after IT relative to baseline, analysis of covariance (ANCOVA) was used for continuous variables, and logistic regression analysis was used for categorical variables. To estimate the slopes of the long-term decline of FEV_1 in the various groups, a linear mixed effects model was fitted with fixed coefficients (fixed effects) for follow-up time, step-down group, follow-up time by step-down, baseline FEV_1, gender, age, smoking status, chronic bronchitis, and comorbidity score. Random intercepts and coefficients (random effects) of subject and group (each eye nested within subject) for the effect of time were used. Time by step-down interaction ef-

fect was included to explore whether the groups differed in terms of FEV_1 slopes. To investigate the long-term effect of step-down on exacerbations, Cox proportional hazard models were fitted with time-to-first exacerbation while adjusting for step-down group, gender, age, baseline FEV_1, smoking status, chronic bronchitis, comorbidity score, and previous exacerbation history. Statistical analyses were performed by using SAS version 9.3 (SAS Inc., Cary, NC, USA).

Results

1. Baseline characteristics at the IT

Of the 380 COPD patients in the KOLD Cohort, 181 patients were excluded because they were treated with either LAMA or a LABA/ICS combination inhaler alone (n=147) or oral medications and/or other types inhalers (n=34). The remaining 199 patients had been treated with triple therapy for >1 year. Of these, 29 and 20 were excluded due to insufficient follow-up and low compliance to the prescribed inhaler(s), respectively. Two patients who withdrew both inhalers were also excluded. Thus, there were 148 patients left. Of these, 109 were included in the triple group and 39 were in the step-down group (Figure 1). The median duration of triple therapy before IT in step-down groups was 18 months (12–81 months).

Table 1 shows the baseline characteristics at IT of the triple and step-down groups. The two groups did not differ significantly in terms of age, gender distribution, smoking history, chronic bronchitis, comorbidty score, MMRC, 6MWD, SGRQ score, or EI. However, the step-down group had significantly lower exacerbation/yr frequencies before IT than the triple group (0.36±0.58 vs. 0.78±0.99, p=0.002). Moreover, of the 109 triple group patients, 24 (22%) had more than two exacerba-
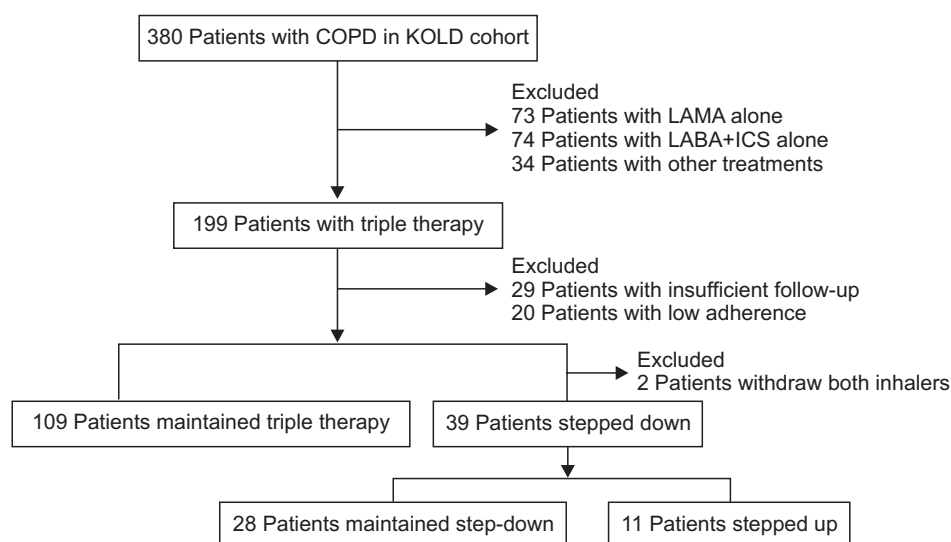

Figure 1. Flow chart illustrating the disposition of the patients who were enrolled and analyzed in the study. COPD: chronic obstructive pulmonary disease; KOLD: Korean Obstructive Lung Disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting β2-agonists; ICS: inhaled corticosteroid.

Table 1. Demographic and baseline clinical characteristics at the index time

| Clinical characteristic | Group | | p-value |
	Triple (n=109)	Step-down (n=39)	
Age, yr	68.4±7.4	70.7±6.8	0.089
Male, n (%)	105 (96.3)	38 (97.4)	>0.999
Current/Ex-smoker, n (%)	37/72 (33.9/66.1)	8/31 (20.5/79.5)	0.156
Smoking amount, pack-years	46.4±24.3	46.9±28.1	0.912
Chronic bronchitis symptoms, n (%)	32 (29.4)	8 (20.5)	0.401
Charlson comorbidity score	1.2±0.5	1.1±0.4	0.918
MMRC	1.86±1.14	1.87±1.11	0.965
6MWD, m	422.45±86.04	432.27±101.86	0.596
SGRQ total score	36.21±17.53	30.81±15.26	0.090
CT emphysema index, %	26.2±15.6	22.1±13.6	0.169
Exacerbation frequency/yr before the IT	0.78±0.99	0.36±0.58	0.002
<2/previous year, n (%)	85 (78.0)	37 (94.9)	
≥2/previous year, n (%)	24 (22.0)	2 (5.1)	0.015
Pre-bronchodilator FEV_1, L	1.31±0.44	1.49±0.38	0.021
Pre-bronchodilator FEV_1, % predicted	44.75±13.67	49.40±11.80	0.061
Post-bronchodilator FEV_1, L	1.42±0.49	1.63±0.39	0.016
Post-bronchodilator FEV_1, % predicted	48.39±14.58	54.30±11.93	0.015
Post-bronchodilator FEV_1/FVC, %	43.04±10.60	46.90±10.19	0.051
DLco, % predicted	65.72±24.10	68.93±19.42	0.615
IC, % predicted	77.51±22.15	76.56±21.33	0.348
RV/TLC, % predicted	48.66±11.51	42.23±11.89	0.300

Values are presented as the mean±standard deviation unless otherwise indicated.
p-values were generated by Student's t tests for continuous variables and chi-squared tests for categorical variables.
MMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire; CT, computed tomography; IT: index time; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity.

tions in the previous year, which only two of the 39 step-down patients (5.1%) had (p=0.015). The step-down group also had significantly higher pre- and post-bronchodilator FEV_1 and percentage of predicted post-bronchodilator FEV_1 at IT than the triple group (p=0.021, p=0.016, and p=0.015, respectively).

2. Changes in COPD variables after the IT

Table 2 shows the changes relative to baseline in several COPD variables within 12 months after IT in the triple and step-down groups. Compared to the triple group, the step-down group exhibited a significant increase in the SGRQ total score and a significant decrease in 6MWD. Thus, the health status and exercise capacity of the patients aggravated after withdrawal. However, the triple and step-down groups did not differ in terms of changes in lung function variables, dyspnea degree, or exacerbation/year frequencies within 12 months

after IT.

3. Characteristics of the subgroups in the step-down group

Among the patients in the step-down group, 17 and 22 withdrew LAMA and a LABA/ICS combination, respectively. These two subgroups did not differ in terms of baseline characteristics except the patients who had withdrawn a LABA/ICS combination inhaler had a lower exacerbation/yr frequency than the patients withdrawn LAMA (0.18±0.40/yr vs. 0.59±0.71/yr, p=0.029).

Of the 39 patients in the step-down group, 28 maintained step-down (maintained step-down group) and 11 restarted the discontinued drug (step-up group) during the follow-up period (Figure 1). The patients in the step-up group restarted the discontinued drug 17±8 months (9–33 months) after IT. Six and five patients restarted LAMA and a LABA/ICS combi-

Table 2. Changes in COPD variables after the index time

Variable	Triple (n=109)		Step-down (n=39)		p-value for the change after the IT
	Just before the IT*	Just after the IT*	Just before the IT*	Just after the IT*	
Pre-bronchodilator FEV$_1$, L	1.31±0.44	1.28±0.46	1.49±0.38	1.48±0.36	0.752
Pre-bronchodilator FEV$_1$, % predicted	44.75±13.67	44.53±14.45	49.40±11.80	49.33±11.01	0.485
IC, % predicted	77.51±22.15	76.05±24.19	76.56±21.33	75.60±21.28	0.470
RV/TLC, % predicted	48.66±11.51	49.60±11.38	42.23±11.89	43.83±12.12	0.983
MMRC	1.86±1.14	1.94±1.09	1.87±1.11	1.72±1.05	0.146
6MWD, m	422.45±86.04	413.07±99.16	432.27±101.86	403.85±105.52	0.019
SGRQ total score	36.21±17.53	36.91±19.22	30.81±15.26	35.25±17.10	0.037
Exacerbation frequency/yr	0.78±0.99	0.72±1.00	0.36±0.58	0.28±0.65	0.266

Values are presented as the mean±standard deviation.

p-values were obtained by analysis of covariance (ANCOVA) for continuous variables and logistic regression analysis for categorical variables. All analyses were adjusted for baseline FEV$_1$, gender, age, smoking status, computed tomography emphysema index, and the time intervals when the variables were measured.

*"Just before the IT" refers to the most recent results before the IT and "Just after the IT" refers to the first results collected after the IT. MMRC was measured every 3 months, pre-bronchodilator FEV$_1$ was measured every 6 months, and IC, RV/TLC, 6MWD, SGRQ total score, and exacerbation/year were measured every 12 months.

COPD: chronic obstructive pulmonary disease; IT: index time; FEV$_1$: forced expiratory volume in 1 second; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity; MMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire.

Table 3. Changes in variables after the index time in the maintained step-down and step-up groups

Variable	Maintained step-down (n=28)		Step-up (n=11)		p-value for the change after the IT
	Just before the IT*	Just after the IT*	Just before the IT*	Just after the IT*	
Pre-bronchodilator FEV$_1$, L	1.50±0.37	1.53±0.35	1.45±0.40	1.37±0.39	0.557
Pre-bronchodilator FEV$_1$, % predicted	49.45±12.12	50.62±11.45	49.29±11.51	45.90±9.50	0.611
IC, % predicted	77.27±21.00	76.64±21.19	74.70±23.21	72.75±22.70	0.861
RV/TLC, % predicted	40.75±10.87	41.96±10.90	46.00±14.01	48.50±14.29	0.996
MMRC	1.75±1.04	1.54±1.00	2.18±1.25	2.18±1.08	0.110
6MWD, m	451.6±81.8	406.8±100.7	383.6±125.6	398.5±116.9	0.069
SGRQ total score	28.46±12.90	33.77±16.89	36.81±19.51	39.68±17.97	0.780
Exacerbation frequency/yr	0.25±0.44	0.18±0.61	0.64±0.81	0.55±0.69	0.117

Values are presented as the mean±standard deviation.

p-values were obtained by analysis of covariance (ANCOVA) for continuous variables and logistic regression analysis for categorical variables. All analyses were adjusted for baseline FEV$_1$, gender, age, smoking status, emphysema index, and the time intervals when the variables were checked.

*"Just before the IT" refers to the most recent results before the IT, and "Just after the IT" refers to the most recent results after the IT. MMRC was measured every 3 months, pre-bronchodilator FEV$_1$ was measured every 6 months, and IC, RV/TLC, 6MWD, SGRQ total score, and exacerbation/yr were measured every 12 months.

IT: index time; FEV$_1$: forced expiratory volume in 1 second; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity; MMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire.

nation inhaler, respectively. The maintained step-down and step-up groups did not differ significantly in terms of baseline variables at IT, although the patients in the step-up group tended to have worse lung function, poorer exercise performances, a lower quality of life, and more frequent exacerba-

tions (Table 3). Also, the two groups did not differ significantly in terms of change in the variables within 12 months after IT (Table 3).
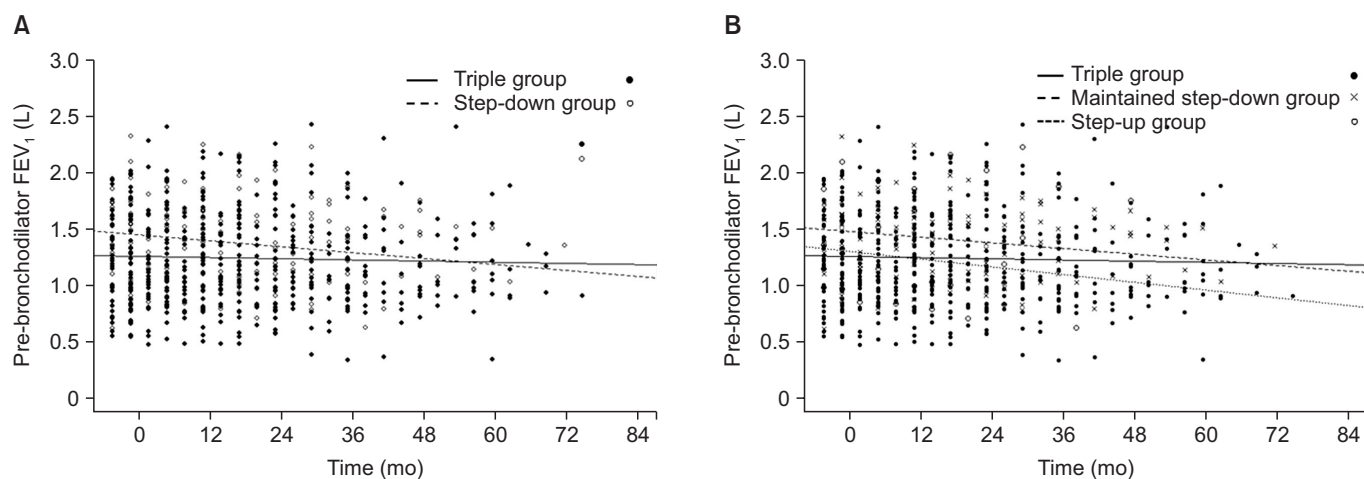
Figure 2. Mean rate of change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1) during follow-up. (A) The decline in lung function in the step-down group after the index time was significantly accelerated compared to that in the triple group. (B) The maintained step-down and step-up groups had a significantly accelerated decline in lung function after the index time compared to the triple group.
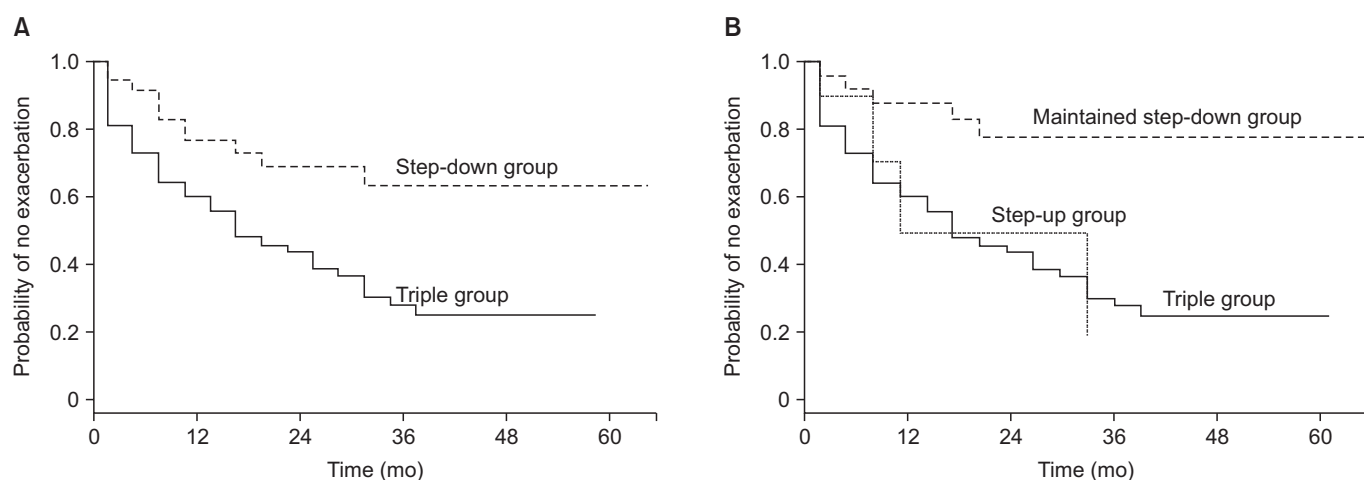

Figure 3. Kaplan-Meier curves for the estimated probability of chronic obstructive pulmonary disease exacerbations. (A) The step-down group had a significantly longer time to the first exacerbation than the triple group. (B) The maintained step-down group had a significantly longer time to the first exacerbation than the triple group and also than the step-up group.

4. Effect of step-down on FEV_1 decline and exacerbations

Although the short-term FEV_1 did not deteriorate after step-down, the step-down group exhibited more pronounced long-term annual declines in FEV_1 after IT than the triple group (54.7±15.7 mL/yr vs. 10.7±7.1 mL/yr, p=0.007) (Figure 2A).

With regard to the maintained step-down and step-up subgroups in the step-down group, their annual rates of FEV_1 decline were 52.9±14.6 mL/yr and 72.3±48.3 mL/yr, respectively (p=0.92) (Figure 2B). Comparison of the step-down patients who discontinued LAMA or a LABA/ICS combination revealed that their annual rates of FEV_1 decline did not differ significantly (53.0±18.6 mL/yr vs. 52.5±17.4 mL/yr, p=0.98).

Figure 3 shows Kaplan-Meier curves for the estimated probability of COPD exacerbations. The step-down patients had longer time-to-the first exacerbation than the triple patients (Figure 3A): the hazard ratio of the probability of exacerbation in step-down group was 0.400 (95% confidence interval [CI], 0.202–0.791; p=0.008) compared to the triple group. The maintained step-down group also had a significantly longer time-to-first exacerbation than the triple group and step-up group, the hazard ratio was 0.221 (95% CI, 0.086–0.571; p=0.002) and 0.201(95% CI, 0.058–0.699; p=0.012) (Figure 3B), respectively.

Discussion

In this retrospective observational study, we found that over 50% (199/380) of the KOLD cohort patients had been treated with triple therapy. Among them, about one-third of the patients tried to withdraw one of the two inhalers, and about one-third of those restarted their discontinued inhaler. The patients in the step-down group showed relatively better lung function and fewer exacerbations before the step-down than the triple group patients, which suggests that the patients who underwent step-down may have had less severe COPD than the triple group patients. However, we also observed that when one of the two inhalers was withdrawn, the quality of life and exercise performance of the patients declined significantly. Moreover, even though the two groups did not differ significantly in terms of FEV_1 within 6 months after IT, the step-down group exhibited a faster long-term FEV_1 decline than the triple group, although this did not associate with an increased frequency of exacerbations.

Although the guidelines recommend that triple therapy should only be used in stable COPD for a narrow range of indications[1,2], triple therapy is widely used in clinical practice. The high prevalence of triple therapy prescription in our cohort may be due in part to the fact that LABA-alone inhalers disappeared in 2007 in our country and were replaced by the LABA/ICS combination inhalers. Only in 2012 did indacaterol, a new ultra-long-acting LABA-alone inhaler, become available in our country. Therefore, despite the guidelines regarding ICS use in stable COPD, patients were inevitably treated with a LABA/ICS combination inhaler if a LABA was needed in this period.

While several studies suggested that triple therapy improves lung function and quality of life in COPD[13-15], the benefit appears to be rather small, and its clinical relevance remains uncertain[16,17]. There is also concern about ICS overuse in COPD[18] because of the elevated risk of side effects[19-21]. Two randomized controlled trials evaluated the effect of withdrawing ICS in COPD patients who are treated with a combination of LABA/ICS; both showed that withdrawing ICS led to an acute and persistent deterioration in lung function and dyspnea, even when LABA treatment was continued[22,23]. Nevertheless, recent systematic reviews did not find evidence supporting the notion that withdrawing ICS causes the outcomes of COPD patients to deteriorate significantly[24,25].

In the present study, we hypothesized that the FEV_1 firstly measured after IT would drop after step-down because the withdrawal of LAMA or LABA/ICS would eliminate the bronchodilatory effects of these drugs that are usually seen in the initial phase of the treatment[8,26]. We also hypothesized that drug discontinuation would not affect the long-term FEV_1 decline because at present, a drug that can modify the long-term decline of FEV_1 in COPD does not exist. However we found that step-down group exhibited a faster long-term

FEV_1 decline without short-term FEV_1 drop after IT. One of the possible explanations for the lack of acute deterioration of FEV_1 after step-down in the present study is that some of the patients who underwent step-down might still have had and used the remnants of previous prescriptions for the same kind of inhaler at home.

Our study showed that the pre-bronchodilator FEV_1 decline of the triple group was 10.7 mL/yr. This is smaller than the mean annual decline of pre-bronchodilator FEV_1 of 26 mL in the patients in the UPLIFT study who were treated with triple therapy (50% of the patients in the tiotropium-treated arm were also being treated with a combination LABA/ICS inhaler)[26]. In contrast, our patients in the step-down group had a greater annual decline of FEV_1 than other groups of patients treated with LAMA alone (mean pre-bronchodilator FEV_1, 31–35 mL/yr; post-bronchodilator FEV_1, 40–42 mL/yr) or a combination of LABA/ICS (mean post-bronchodilator FEV_1, 39 mL) in other studies[8,26].

The rate of FEV_1 decline in this study should be interpreted cautiously, because, the faster FEV_1 decline in the step-down group could also be explained by the additive loss of the bronchodilatory effect of one inhaler after real withdrawal during the follow-up period. Also, the step-down group had a relatively higher baseline FEV_1 than the triple group, which is known to be one of the risk factors for a rapid decline in FEV_1[27]. In addition, several studies found that patients who discontinue treatment have a more rapid decline in lung function than those who continue treatment, although the reason for this is not clear[26,28]. All of these could explain, at least in part, why there was a relatively large difference between the step-down and triple groups in terms of annual FEV_1 decline.

Withdrawing one inhaler (step-down) did not affect the exacerbation frequency and step-down group had a significantly longer time-to-first exacerbation than triple group. However, it does not mean that step-down is always safe in terms of exacerbation, because step-down group showed better FEV_1 and less exacerbation frequency before the IT. It is well known that the best predictors of future exacerbation in COPD are a history of exacerbations and low FEV_1[29]. However, it is important to know that step-down did not lead to increase the exacerbation frequency.

Interestingly, the results of our study are similar to those of a recent study done by Magnussen et al.[30], where stepwise withdrawal of ICS in severe stable COPD patients treated with triple therapy resulted in a significant decline in lung function without increasing the frequency of moderate or severe exacerbations. Therefore, we speculated that the accelerated decline of lung function in our step-down group was due specifically to the withdrawal of an ICS. However, the step-down patients who withdrew LABA/ICS did not differ from those who withdrew LAMA in terms of rate of FEV_1 decline.

Since this study was a retrospective observational study, it has several limitations. First, the reason for discontinuing the

inhalers in the middle of treatment could not be determined. It could have been because the patient exhibited marked improvement in symptoms and/or lung function, or developed unbearable complications. It could also have reflected economic issues. Secondly, although we only included patients who replied that their inhaler compliance exceeded 70%, and we meticulously examined the medical records, this did not guarantee that individual patients actually took all of the prescribed medication. Also, patients who underwent step-down may not have withdrawn the inhaler at the IT, and may still have had and used medication remaining from previous prescriptions for some time. This could explain why the step-down group exhibited a significant deterioration in 6MWD and SGRQ (measured every 12 months) but not in MMRC (checked every 3 months) or pre-bronchodilator FEV_1 (measured every 6 months), and may also explain the discrepancy between short-term FEV_1 change and long-term FEV_1 decline.

Lastly, we used the pre-bronchodilator FEV_1 for measuring FEV_1 decline rather than the more widely used post-bronchodilator FEV_1. This reflects the fact that in our cohort, each patient underwent pre-bronchodilator FEV_1 testing every 6 months while post-bronchodilator FEV_1 was tested every 12 months. Therefore, we considered pre-bronchodilator FEV_1 to be better for monitoring the change in FEV_1 soon after IT and the long-term decline of FEV_1.

In conclusion, withdrawing one of the two inhalers during treatment with triple therapy in COPD patients aggravated the exercise capacity and quality of life. Additive loss of the bronchodilatory effect of one inhaler after the real withdrawal seemed to affect the rate of FEV_1 decline. However, step-down did not associate with an increased frequency of exacerbations. Tailoring or modification of the treatment regimen should always be considered to reduce the economic burden and unnecessary side effects of the treatment. Therefore, a well-designed randomized controlled study that precisely evaluates the effect of the step-down is needed. It is also important to identify the patients in whom step-down would be safe or disadvantageous in terms of patient outcome.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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