Efficacy of inhaled tiotropium add-on to budesonide/formoterol in patients with bronchiolitis obliterans developing after hematopoietic stem cell transplantation Running Title: Tiotropium in bronchiolitis obliterans after HSCT

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Article

Keywords: tiotropium, bronchiolitis obliterans syndrome, hematopoietic stem cell transplantation, lung, chronic graft-versus-host disease

Posted Date: June 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1678517/v1

Abstract

Background: Bronchiolitis obliterans syndrome (BOS) is the lung manifestation of chronic graft-versus-host disease, and a noninfectious pulmonary sequela of hematopoietic stem cell transplantation (HSCT). Despite the combination regimen including budesonide/formoterol that was previously shown as effective, a significant proportion of patients are unresponsive. We assessed whether inhaled tiotropium add-on to the combination regimen improve pulmonary function and the chronic obstructive pulmonary disease assessment test (CAT) scores in patients with BOS.

Methods: Post-HSCT patients with significant respiratory symptoms or poor pulmonary function referred to the pulmonology department of the HSCT Center of Seoul St. Mary's Hospital, were reviewed retrospectively. Patients defined as BOS and treated with budesonide/formoterol/tiotropium combination therapy after budesonide/formoterol therapy from January 2011 to June 2019 were enrolled.

Results: Total of 86 patients were evaluated. After tiotropium add-on, the absolute FEV1 increased significantly from 1.47 ± 0.49 to 1.53 ± 0.57 L ($p = 0.023$) and the % predicted FEV1 from 45.0 ± 12.8 to 46.8 ± 14.5% ($p = 0.031$). The % predicted DLCO increased significantly after tiotropium add-on (from 61.6 ± 16.7 to 64.3 ± 16.3%, $p = 0.028$). Among 56 patients with complete CAT scores, no significant change was present in total CAT scores. In all, 30 of the 72 patients (41.7%) evidenced FEV1 increases > 100 mL, and 20 of 56 patients (35.7%) had CAT score decreases of ≥ 2 points. When the FEV1 and CAT scores were combined, the overall response rate to tiotropium add-on was 56.2% (41/73). The response group evidenced a significantly greater FVC increase (both absolute ($p < 0.001$) and % predicted ($p < 0.001$)), and a significant decrease in the RV/TLC ratio compared to the no-response group ($p = 0.006$).

Conclusions: Inhaled tiotropium add-on to combination budesonide/formoterol significantly improved lung function, but not respiratory symptoms, in patients with post-HSCT BOS.

Introduction

Bronchiolitis obliterans syndrome (BOS) is the lung manifestation of chronic graft-versus-host disease (cGVHD)(1), a noninfectious pulmonary sequela of hematopoietic stem cell transplantation (HSCT) that features progressive fibrosis of the small terminal airways and *de novo* fixed airflow obstruction(2, 3). The National Institutes of Health consensus on cGVHD recommends diagnostic criteria for BOS(4). The prevalence of BOS in allogeneic HCT recipients is about 2–3%(5-7). BOS can be fatal; the overall survival rate is < 50% at 2 years(8). Current treatments for post-HSCT BOS include systemic or inhaled corticosteroids, long-acting beta-2 agonists, leukotriene receptor antagonists, and azithromycin(1, 9-11). However, systemic steroids were ineffective(12) and may also compromise the efficacy of immunomodulatory treatment. Inhalers act locally, and thus lack systemic side effects; more effort should be devoted to the development of inhaled bronchodilators. We previously found that a treatment regimen including budesonide/formoterol was effective(10, 13). A combination of budesonide/formoterol, montelukast, and n-acetylcysteine significantly improved lung function and

respiratory symptoms(10). However, a significant proportion of patients became unresponsive over time. A new treatment regimen is essential for such patients. We empirically added inhaled tiotropium to a combination including budesonide/formoterol when treating patients who did not respond to the tiotropium-free combination. We sought improvements in pulmonary function and the chronic obstructive pulmonary disease assessment test (CAT) scores.

Methods

Patients

Post-HSCT patients with significant respiratory symptoms or poor pulmonary function were referred to the pulmonology department of the HSCT Center of Seoul St. Mary's Hospital, Seoul, Korea. A single experienced pulmonologist (Rhee CK) treated and followed-up patients with BOS, using the same protocol. After retrospective chart review, patients treated with budesonide/formoterol/tiotropium combination therapy after budesonide/formoterol therapy from January 2011 to June 2019 were enrolled. The inclusion criteria were chronic GVHD in other organs and a positive diagnostic pulmonary function test (PFT) using the modified National Institute of Health criteria,(3, 14) and tiotropium use for at least 2 months (after addition to budesonide/formoterol. The exclusion criteria were any other pulmonary or infectious disease (asthma, chronic obstructive pulmonary disease, lung cancer, interstitial lung disease, pneumonia, or tubercular lungs), no history of previous budesonide/formoterol, and a history of other inhaler use. Approval was obtained from the institutional review board of Seoul St. Mary's Hospital, which waived the requirement for informed consent (KC22RIS10155). All methods were performed in accordance with the relevant guidelines and regulations.

Definition of BOS

The diagnostic criteria for BOS were fibrogenic deposits in the small airways or bronchioles of patients who underwent lung biopsies in patients who did not undergo biopsies or have chronic GVHD in other organs or air-trapping evident in high-resolution computed tomography (HRCT), and who had a positive PFT (the modified NIH criteria) [3, 12, 14]. In terms of PFT parameters, the modified NIH criteria are a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio < 0.7, an FEV1 < 75% of that predicted with ≥ 10% decline over < 2 years, absence of respiratory tract infection, air-trapping evident in expiratory CT or the PFT, and a residual volume (RV) > 120% that predicted or an RV/total lung capacity ratio outside the 90% confidence interval(13, 15). All HRCT scans were read by a single radiology specialist (Jung JI (10, 16-18)) who reviewed inspiratory before expiratory images. Air-trapping was considered present in expiratory images when certain lung regions failed to exhibit increases in attenuation and/or decreases in volume compared to those of the inspiratory images(7). Patients who satisfied the diagnostic criteria but lacked active infectious disease were diagnosed with BOS.

Tiotropium add-on

Prior to addition of tiotriopium, all patients had been treated with budesonide/formoterol, montelukast, and n-acetylcysteine; all received 160 μg budesonide and 4.5 μg formoterol fumarate via a dry powder inhaler (Symbicort Turbuhaler; AstraZeneca, Mölndal, Sweden) twice daily, 10 mg oral montelukast daily, and 200 mg oral n-acetylcysteine three times daily. After the clinician (Rhee CK) decided to add tiotropium, HandiHaler or Respimat inhalers were prescribed (one and two puffs daily, respectively).

Responders

After 3 months of add-on therapy, patients were grouped by their PFT results and CAT scores. A therapeutic response was defined by reference to the minimum clinically important difference (MCID); this distinguishes a small meaningless change from a small but meaningful change(19). The MCIDs for the FEV1 and CAT score are 100 mL(20) and 2 points respectively(21). The responsive group evidenced FEV1 increases > 100 mL or CAT score decreases ≧ 2.

Statistics

All statistical analyses were performed using the Statistical Package for the Social Sciences (ver. 20.0; SPSS Inc., Chicago, IL, USA). Continuous data are presented as means with ranges; the Student t-test was used to compare normally distributed continuous variables and the Mann-Whitney U-test to compare non-normally distributed continuous variables. The chi-square test was employed to compare categorical variables. The paired t-test was used to compare normally distributed parameters before and after tiotropium add-on. When parameters were non-normally distributed, the Wilcoxon rank test was performed. A p-value < 0.05 was considered significant.

Results

Baseline clinical characteristics

Table 1 lists the baseline clinical characteristics. Of the 86 patients, 45 (52.3%) were male. The mean age was 45.9 ± 12.7 years. Of underlying hematological diseases, acute myeloid leukemia (AML) was the most common (43.0%) followed by acute lymphoblastic leukemia (ALL) (27.9%). The mean duration between hematopoietic stem cell transplantation and BOS diagnosis was 20.0 ± 16.5 months. In terms of acute GVHD, 50 (62.5%) patients were so diagnosed. Chronic GVHD of the skin, oral cavity and eyes were most frequently noted.

Pulmonary function changes after tiotropium add-on

Table 2 and Figure 1 show the pulmonary function parameters when tiotropium was added and 3 months later. After add-on, no significant change was observed in the percentage predicted or absolute FEV value. The absolute FEV_1 increased significantly from 1.47 ± 0.49 to 1.53 ± 0.57 L (p = 0.023) and the % predicted FEV_1 from 45.0 ± 12.8 to 46.8 ± 14.5% (p = 0.031). The FEV_1/FVC ratio increased from 56.4 ± 18.7 to 57.2 ± 17.8% (p = 0.041). No significant change in the RV/TLC ratio was observed. The %

predicted diffusing capacity for carbon monoxide (DLCO) increased significantly after tiotropium add-on (from 61.6 ± 16.7 to 64.3 ± 16.3%, p = 0.028).

CAT score changes after tiotropium add-on

Fifty-six patients completed the CAT questionnaires at both the time of tiotropium add-on and 3 months later (Table 3). The CAT score did not change significantly over time (p = 0.833). The median score at the time of tiotropium add-on was 16 (10.25–22) but 15 (10.25–21.75) 3 months later. Only the answers to question 4 (breathlessness increasing) and 8 (energy) differed significantly over time. The CAT 4 score fell from 4 (3–4) to 3 (2.25–4) (p = 0.038) and the CAT 8 score increased from 2 (1–3) to 3 (2–3) (p = 0.006).

Therapeutic responses and associations with pulmonary function change

The therapeutic response was an improvement in the FEV1 or CAT score. In all, 30 of the 72 patients (41.7%) evidenced FEV1 increases > 100 mL (Fig. 2A); 20 of 56 patients (35.7%) had CAT score decreases ≥ 2 points (Fig.2B). When the FEV1 and CAT scores were combined, the overall response rate to tiotropium add-on was 56.2% (41/73) (Fig.2C). We found no significant difference in baseline characteristics between the no-response and response groups, with the exceptions of underlying hematological disease and chronic GVHD status (Table 4). The PFT and CAT scores at the time of tiotropium add-on did not affect the therapeutic response (Table 5). However, changes in the FVC and FEV1, and the FEV1/FVC and RV/TLC ratios, between the time of tiotropium add-on and 3 months later differed significantly. The response group evidenced a significantly greater FVC increase (both absolute [−0.21 ± 0.34 vs. 0.25 ± 0.31 mL, p < 0.001] and % predicted [−5.0 ± 9.8% vs. 6.2 ± 6.9%, p < 0.001]) and a significant decrease in the RV/TLC ratio compared to the no-response group (−2.3 ± 5.7 vs. 2.6 ± 6.0, p = 0.006).

Discussion

We evaluated the utility of tiotropium add-on in BOS patients previously treated with budesonide/formoterol; we assessed the responses of both respiratory symptoms and pulmonary function. Tiotropium add-on significantly improved the FEV1. We earlier showed that the rapid lung function loss in patients with post-HSCT BOS was associated with poorer pulmonary function and overall survival than those of a group evidencing gradual declines.(22) It is essential to prevent lung function decline, thus to stabilize disease. The current treatment regimens include systemic or inhaled corticosteroids, long-acting beta-2 agonists, leukotriene receptor antagonists, and azithromycin(1, 9-11). Compared to our previous study of patients receiving budesonide/formoterol, the proportion who exhibited an overall response was smaller (56 vs. 82%) although we used the same MCID criteria (10). This was also evident when the CAT scores and FEV1 values were compared. The study groups differed; our present patients had previously received combination budesonide/formoterol and none evidenced no or reduced therapeutic response. Thus, addition of inhaled tiotropium was valuable.

The principal BOS pathophysiology post-HSCT is irreversible small airway narrowing attributable to fibrotic changes (23); inhaled bronchodilators would thus be expected to be less efficacious than in patients with other airway diseases(24-26) in whom airway reversibility is (at least somewhat) preserved. However, to reduce BOS progression and preserve the remaining lung function, we thought it important to assess the efficacies of inhaled bronchodilators in BOS patients. We previously showed that the combination of budesonide/formoterol, montelukast, and n-acetylcysteine significantly improved the lung function and respiratory symptoms of BOS patients(10). However, many patients did not respond; a new treatment was essential. We found that add-on tiotropium aided the subgroup non-responsive to budesonide/formoterol.

Why did tiotropium improve the mean FEV1 and the DLCO? Importantly, the improvements were not attributable to tiotropium alone, rather to the synergistic effects of tiotropium and budesonide/formoterol. Efficacy of the combination bronchodilator therapies were shown in studies on COPD patients (27, 28). As tiotropium efficacy in post-HSCT BOS patients has received little attention, it was appropriate to review the COPD works. Combinations of a long-acting beta-agonist and a long-acting muscarinic antagonist improve bronchodilation more so than either drug alone (29). In an animal model, tiotropium inhibited airway modeling including extracellular matrix deposition (ECM) (30). Tiotropium triggered airway smooth muscle cell relaxation and prevented ECM deposition(30). However, the effects of tiotropium on the small airways of post-HSCT BOS patients require further evaluation.

Our work had certain limitations. The therapeutic responses were assessed using PFT and CAT scores obtained 3 months after tiotropium add-on; we lack data on long-term effects and further studies are needed. We did not evaluate the effect of inhaled tiotropium alone; the observed therapeutic response may be attributable to only tiotropium or the combination treatment. However, the CAT and PFT scores were measured before and after tiotropium initiation. Finally, this was not a randomized controlled study, rather a retrospective cohort work. However, all patients were treated by the same expert pulmonologist who adhered to a defined protocol.

Conclusions

Inhaled tiotropium add-on to combination budesonide/formoterol significantly improved lung function, but not respiratory symptoms, in patients with post-HSCT BOS.

Abbreviations

BOS: bronchiolitis obliterans syndrome; HSCT: hematopoietic stem cell transplantation; CAT: chronic obstructive pulmonary disease assessment test; cGVHD: chronic graft-versus-host disease; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; HRCT: high-resolution computed tomography; RV: residual volume; MCID: minimum clinically important difference; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; DLCO: diffusing capacity for carbon monoxide

Declarations

Declarations

Approval was obtained from the institutional review board of Seoul St. Mary’s Hospital, which waived the requirement for informed consent (KC22RIS10155).

Competing interests

CK Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. All other authors also do not have competing interest.

Declarations

Abbreviations

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL, non-hodgkin lymphoma; MDS, myelodysplastic syndrome; AA, aplastic anemia; FMT, familial mismatched transplantation; HLA, human leukocyte antigens; PB, peripheral blood; BM, bone marrow; HSCT, hematopoietic stem cell transplantation; BOS, bronchiolitis obliterans syndrome; GVHD, graft versus host disease

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CAT, COPD assessment test; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV/TLC, residual volume to total lung capacity ratio

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Authors’ contributions

RCK was responsible for study concept and design. PS, YJ, LS, CB, KY, LS, KH, and RCK contributed to patient recruitment and follow-up. All authors contributed to data acquisition.

Acknowledgements

Not applicable.

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RCK was responsible for study concept and design. PS, YJ, LS, CB, KY, LS, KH, and RCK contributed to patient recruitment and follow-up. All authors contributed to data acquisition.

LJU and RCK performed data analysis. LJU and RCK contributed to the drafting of this manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

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

Declarations

Approval was obtained from the institutional review board of Seoul St. Mary's Hospital, which waived the requirement for informed consent (KC22RIS10155).

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Tables

Table 1

Clinical characteristics of patients with bronchiolitis obliterans syndrome (n=86)

	Number (%)
Recipient sex, male	45 (52.3%)
Recipient age	45.9±12.7
Hematologic diseases	
AML	37 (43.0%)
ALL	24 (27.9%)
CML	3 (3.5%)
NHL	3 (3.5%)
MDS	16 (18.6%)
AA	3 (3.5%)
Donor type (n=80)	
Unrelated	34 (42.5%)
Sibling	29 (36.3%)
FMT	17 (21.3%)
HLA (n=74)	
full-match	49 (66.2%)
mismatch	25 (33.8%)
Stem cell source (n=81)	
PB	68 (84%)
BM	13 (16%)
Time from HSCT to BOS diagnosis, months	20.0±16.5
Acute GVHD (n=82)	50 (62.5%)
Chronic GVHD (except lung) (n=85)	
Skin	31 (36.5%)
Oral	47 (55.3%)
Eyes	23 (27.1%)
Liver	20 (23.5%)
GI tract	5 (5.9%)

Joint	3 (3.5%)
Sicca	17 (20.0%)
Systemic steroid use	80 (93.0%)
Tacrolimus	35 (40.7%)
Cyclosporin	22 (25.6%)
Mycophenolate mofetil	37 (43.0%)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL, non-hodgkin lymphoma; MDS, myelodysplastic syndrome; AA, aplastic anemia; FMT, familial mismatched transplantation; HLA, human leukocyte antigens; PB, peripheral blood; BM, bone marrow; HSCT, hematopoietic stem cell transplantation; BOS, bronchiolitis obliterans syndrome; GVHD, graft versus host disease

Table 2

Changes of pulmonary function test and CAT score (before and after tiotropium add on)

Clinical variable	At time of tiotropium add on	After tiotropium add on	Changes in lung function or symptom score	P-value
FVC (absolute)	2.77±0.95	2.82±1.02	0.05±0.40	0.268
FVC (% predicted)	69.0±16.9	70.4±18.3	1.4±10.0	0.074
FEV1 (absolute)	1.47±0.49	1.53±0.57	0.06±0.23	0.023
FEV1 (% predicted)	45.0±12.8	46.8±14.5	1.8±7.0	0.031
FEV1/FVC (%)	56.4±18.7	57.2±17.8	1.2±4.3	0.041
RV/TLC (%)	40.9±9.3	40.5±8.4	-0.4±6.2	0.601
DLCO (% predicted)	61.6±16.7	64.3±16.3	2.7±10.7	0.028

Abbreviations: CAT, COPD assessment test; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV/TLC, residual volume to total lung capacity ratio

Table 3

Changes of COPD assessment test (CAT) score after tiotropium add-on (n=56)

Clinical variable	Tiotropium add on	After tiotropium add-on	P-value
Q1. Cough	1 (0-3)	1 (0.25-3)	0.833
Q2. Phlegm	2 (0.25-3)	2 (1-3)	0.151
Q3. Chest tightness	2 (0.25-3)	1 (0-3)	0.186
Q4. Breathlessness going up	4 (3-4)	3 (2.25-4)	0.038
Q5. Activity limitation at home	1 (0-3)	1 (0-3)	0.156
Q6. Confidence leaving home	2 (0.25-3)	1 (0-3)	0.335
Q7. Sleep	1 (0-2.75)	2 (1-3)	0.242
Q8. Energy	2 (1-3)	3 (2-3)	0.006
Total sum of the eight items	16 (10.25-22.0)	15 (10.25-21.75)	0.725

Data represent the median (IQR). P-values shown in bold are significant at the 0.05 level

Table 4

Comparison of clinical characteristics between therapeutic response group and no-response group

Clinical parameters	No-response group	Response group	p-value
Number	32	41	
Recipient sex, male	13 (40.6%)	24 (58.5%)	0.129
Recipient age	43.6±13.1	47.2±12.5	0.221
Hematologic diseases			
AML	15 (46.9%)	16 (39.0%)	0.501
ALL	6 (18.8%)	12 (29.3%)	0.301
CML	3 (9.4%)	0 (0.0%)	0.045
NHL	3 (9.4%)	0 (0.0%)	0.045
MDS	5 (15.6%)	11 (26.8%)	0.251
AA	0 (0.0%)	2 (4.9%)	0.205
Donor type (n=68)	(n=28)	(n=40)	0.680
Unrelated	9 (32.1%)	17 (42.5%)	
Sibling	12 (42.9%)	14 (35.0%)	
FMT	7 (25.0%)	9 (22.5%)	
HLA (n=63)	(n=26)	(n=37)	0.794
full-match	17 (65.4%)	23 (62.2%)	
mismatch	9 (34.6%)	14 (37.8%)	
Stem cell source (n=69)	(n=28)	(n=41)	0.574
PB	24 (85.7%)	33 (80.5%)	
BM	4 (14.3%)	8 (19.5%)	
Time from HSCT to BOS diagnosis, months	16.4±11.1	19.7±15.3	0.298
	(n=29)	(n=40)	
Acute GVHD (n=69)	17 (58.6%)	30 (75.0%)	0.150
Chronic GVHD (except lung) (n=72)			
Skin	14 (45.2%)	14 (34.1%)	0.342
Oral	14 (45.2%)	25 (61.0%)	0.182
Eyes	9 (29.0%)	10 (24.4%)	0.658
Liver	9 (29.0%)	8 (19.5%)	0.346

GI tract	2 (6.5%)	3 (7.3%)	0.886
Joint	3 (9.7%)	0 (0.0%)	0.042
Sicca	6 (19.4%)	9 (22.0%)	0.788
Systemic steroid use	31 (96.9%)	36 (87.8%)	0.162
Tacrolimus	13 (40.6%)	16 (39.0%)	0.890
Cyclosporin	11 (34.4%0	11 (26.8%)	0.486
Mycophenolate mofetil	16 (50.0%)	15 (36.6%)	0.250

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL, non-hodgkin lymphoma; MDS, myelodysplastic syndrome; AA, aplastic anemia; FMT, familial mismatched transplantation; HLA, human leukocyte antigens; PB, peripheral blood; BM, bone marrow; HSCT, hematopoietic stem cell transplantation; BOS, bronchiolitis obliterans syndrome; GVHD, graft versus host disease

Table 5

Comparison of baseline pulmonary function and CAT score between response and no-response group.

	No-response group	Response group	p-value
Tiotropium add on			
FVC (absolute)	2.62±0.93	2.88±0.97	0.119
FVC (% predicted)	67.6±16.8	70.0±17.1	0.785
FEV1 (absolute)	1.36±0.42	1.55±0.53	0.122
FEV1 (% predicted)	42.8±11.3	46.7±13.7	0.295
FEV1/FVC (%)	55.6±20.2	56.4±17.3	0.513
RV/TLC (%)	41.2±11.6	41.0±7.8	0.834
DLCO (% predicted)	60.6±17.4	62.8±15.6	0.438
CAT score	14.5±7.8	18.0±7.4	0.077
Δ FVC (absolute)	-0.21±0.34*	0.25±0.31*	<0.001
Δ FVC (% predicted)	-5.0±9.8*	6.2±6.9*	<0.001
Δ FEV1 (absolute)	-0.12±0.14*	0.20±0.20*	<0.001
Δ FEV1 (% predicted)	-3.3±5.7*	5.7±5.3*	<0.001
Δ FEV1/FVC (%)	0.2±4.8	1.9±3.8*	0.048
Δ RV/TLC (%)	2.6±6.0	-2.3±5.7*	0.006
Δ DLCO (% predicted)	-0.65±11.3	4.83±9.91*	0.069
Δ CAT score	4.4±4.5*	-3.1±6.0*	<0.001

* Indicates significant with-in group change according to Wilcoxon-rank test or Paired T test.

Abbreviations: CAT, COPD assessment test; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV/TLC, residual volume to total lung capacity ratio

Figures

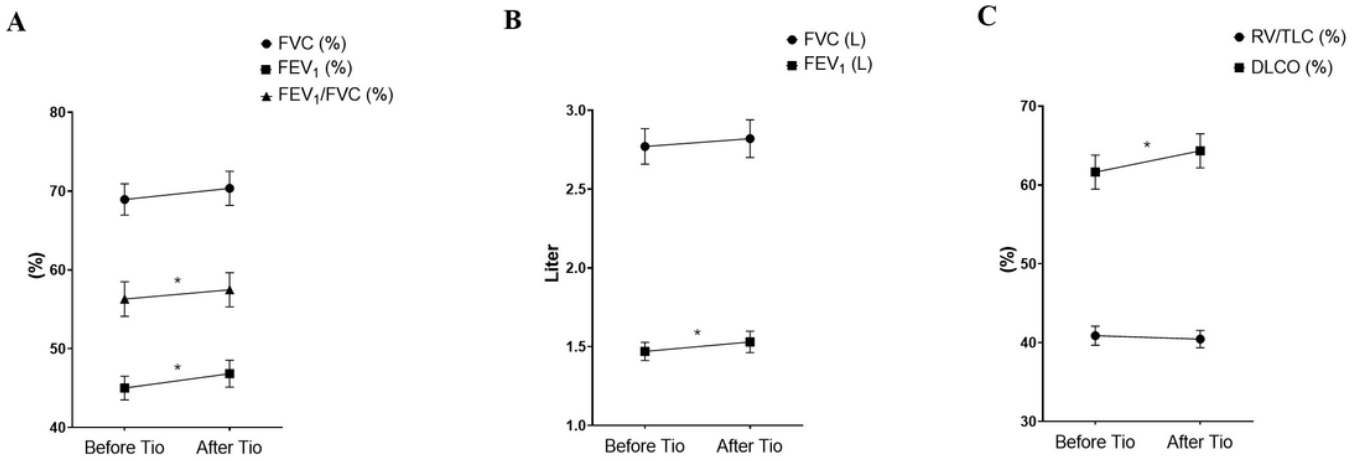

Figure 1

Comparison of pulmonary function parameters when tiotropium was added and 3 months later; (A) FVC (%), FEV_1 (%), and FEV_1/FVC (%), (B) FVC (L) and FEV_1 (L), (C) RV/TLC (%) and DLCO (%),

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV/TLC, residual volume to total lung capacity ratio

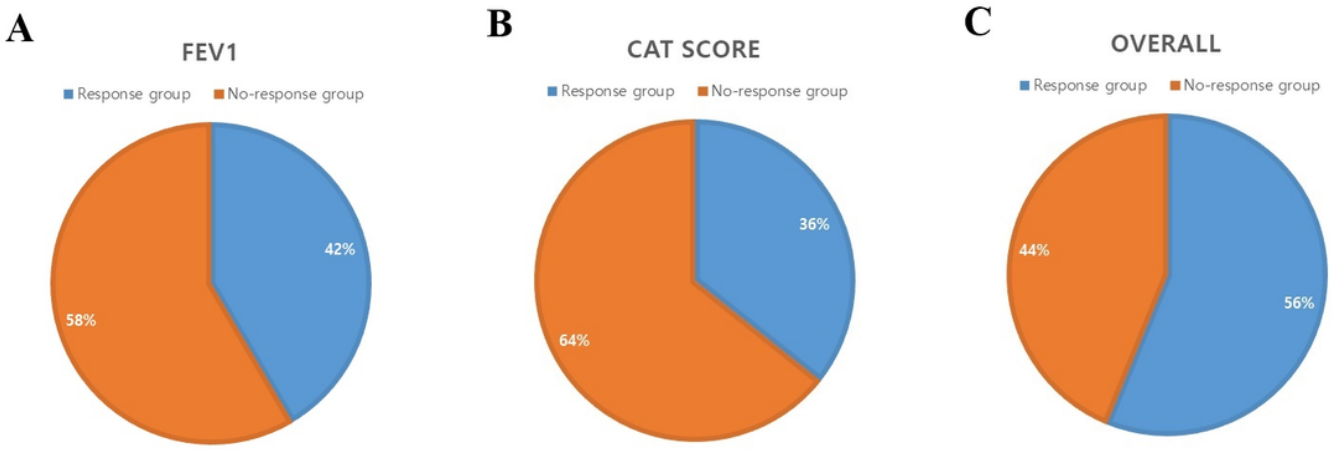

Figure 2

Comparison of response and no-response groups by (A) FEV_1 increases > 100 mL, (B) by CAT score decreases ≥ 2 points, (C) when FEV_1 and CAT scores were combined

Abbreviations: CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV/TLC, residual volume to total lung capacity ratio