Original Article

Efficacy and safety of high-dose budesonide/formoterol in patients with bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplant

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Background: Bronchiolitis obliterans syndrome (BOS) is a rare, progressive and irreversible airway disease associated with significant mortality after allogeneic hematopoietic stem-cell transplantation (HSCT). In this study, we investigated the therapeutic effect of high-dose budesonide/formoterol (320/9 µg bid) in patients with BOS after HSCT already using low-dose budesonide/formoterol (160/4.5 µg bid).

Methods: After a retrospective chart review, patients who were initially treated with budesonide/formoterol 160/4.5 µg bid and increased their dose to 320/9 µg bid between March 2009 and February 2019 were enrolled. Pulmonary function test (PFT) and COPD assessment test (CAT) were performed before and after changing the drug dose. Efficacy was assessed within 3 months after increasing the drug dose; the primary variable was changes in forced expiratory volume in 1 second (FEV_1) and CAT score. Safety was assessed as the incidence of pneumonia within 3 months after increasing the drug dose.

Results: Seventy-seven patients were treated with budesonide 160 µg plus formoterol 4.5 µg twice a day for more than 3 months and the dose was increased to budesonide 320 µg plus 9.0 µg twice a day. After treatment with high-dose ICS/LABA (budesonide 320 µg plus formoterol 9.0 µg twice a day for 12 weeks), there were no significant differences in FEV_1 (before treatment 1.59 L *vs.* after treatment 1.65 L, P=0.182) or FVC (before treatment 2.93 L *vs.* after treatment 2.96 L, P=0.519) compared to before starting the high dose treatment. There were no significant differences in the total CAT score. Of all patients, 34.2% of patients had an increase in FEV_1 ≥100 mL and 35.3% of patients showed a decrease ≥2 points in CAT score. In safety assessment, there were no significant differences between the two periods.

Conclusions: Our study failed to show superior effect of high-dose budesonide/formoterol (320/9 µg) compared with low-dose. However, high-dose budesonide/formoterol was safe and there was no lung function deterioration.

Keywords: Budesonide/formoterol; bronchiolitis obliterans syndrome (BOS); allogeneic hematopoietic stem cell transplant (allogeneic HSCT); chronic graft-versus-host disease (chronic GVHD)

Introduction

Bronchiolitis obliterans syndrome (BOS) is a clinical diagnosis for the phenomenon of progressive airway obstruction after allogeneic hematopoietic stem cell transplant (HSCT) (1). BOS is characterized by progressive circumferential fibrosis and ultimate cicatrization of the small terminal airways that causes progressive dyspnea and a nonproductive cough and decreased pulmonary function characterized by an obstructive airflow pattern (2,3). Although BOS is a rare disease, probably due to challenges when making the diagnosis, its incidence is underestimated. In recent publications from Brazil (4) and Japan (5), the cumulative incidence of BOS in HSCT patients was reported to be 2.9% in 1 year, 3.7% in 3 years, and 3.43% in 5 years. The reported incidence of BOS varies among studies from 3% to 30% (6-10). In our experience, its incidence in patients who have undergone HSCT is 4.2% (11). BOS is very important to patients who have undergone HSCT because mortality and morbidity are extremely high. In a recent study of patients from 2002 to 2009, the overall survival of BOS patients was less than 55% (11). Furthermore, in another study, the 5-year survival rate of 47 HSCT recipients was 40% in those without BOS but 10% in those with it (8). Recent study has shown that the presence of BOS was associated with increased non-relapse mortality similar to patients with moderate-to-severe graft-versus-host disease (GVHD) but had no impact on overall survival (12). These studies show that the treatment and management of BOS in HSCT patients are important and that early detection and treatment result in better patient outcomes.

In a previous study, we found that budesonide/formoterol, montelukast, and N-acetylcysteine significantly improved lung function and respiratory symptoms in patients with BOS after HSCT (13). There are two types of budesonide/formoterol inhalers (160/4.5 and 320/9 µg), and the dose administered in the previous study was 160/4.5 µg. High-dose budesonide/formoterol (320/9 µg twice a day) significantly improves forced expiratory volume in 1 s (FEV1) in symptomatic asthma patients (14). Budesonide/formoterol decreases exacerbations in patients with moderate to very severe COPD (15). In 2004, a representative study of COPD showed that budesonide/formoterol 320/9.0 µg twice a day reduced the mean number of severe exacerbations by 24% and increased FEV1 by 15% *vs.* a placebo in patients with moderate to severe COPD (16). On the other hand, the side effects of inhaled corticosteroids (ICS) are proportional to the

steroid dose (17,18). Therefore, the efficacies and adverse events of high-dose and low-dose ICS/long-acting beta agonists (LABA) need to be compared. We investigated the impact of high-dose budesonide/formoterol (320/9 µg bid) in patients with BOS after HSCT already using low-dose budesonide/formoterol (160/4.5 µg bid).

Methods

Patients

Post-HSCT patients with respiratory symptoms or a decline in pulmonary function were referred to the Pulmonology Department of the BMT Center at Seoul St. Mary's Hospital, Seoul, South Korea. After a clinical diagnosis of BOS, one experienced pulmonologist (Rhee CK) treated all patients according to the same protocol and follow-up evaluation. There was a change in the protocol in March 2015, and the dose of budesonide/formoterol was increased from 160/4.5 to 320/9 µg twice a day in patients with BOS. After a retrospective chart review, patients who were initially treated with budesonide/formoterol 160/4.5 µg bid and increased their dose to 320/9 µg bid between March 2009 and February 2019 were enrolled.

The inclusion criteria were chronic GVHD in other organs and positive diagnostic pulmonary function tests (PFTs) using the modified NIH criteria (19) and treatment with budesonide/formoterol 160/4.5 µg bid and an increased dose to 320/9 µg bid for at least 3 months. The exclusion criteria were other pulmonary or infectious diseases, such as asthma, lung cancer, COPD, pneumonia, or tuberculosis-destroyed lungs, and a history of using other inhalers.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional ethic committee/review board of Seoul St. Mary's Hospital, which waived the requirement for informed consent due to the retrospective nature of the study (IRB No. KC19RESI0661).

Definition of BOS

We followed the modified NIH criteria for diagnosing BOS (19): FEV1/forced vital capacity (FVC) <0.7; FEV1 <75% of predicted with ≥10% decline over <2 years; absence of infection in the respiratory tract; one of the two supporting features of BOS (evidence of air trapping by expiratory computed tomography, or evidence of air trapping by

PFTs); and residual volume (RV) >120% of predicted or RV/total lung capacity elevated outside the 90% confidence interval.

Budesonide/formoterol therapy

After diagnosing BOS, all patients enrolled were treated with 160 µg budesonide plus 4.5 µg of formoterol fumarate in a dry powder inhaler (Symbicort Turbuhaler; AstraZeneca, Molndal, Sweden) twice a day for at least 3 months and then were switched to 320 µg budesonide plus 9.0 µg formoterol fumarate twice a day. All patients were educated about the inhaler treatment. Montelukast and acetylcysteine were administered together.

PFTs

PFTs were performed before HSCT for the baseline study and after HSCT for screening and diagnosing BOS and every 3–6 months. We compared pulmonary function before and after budesonide/formoterol 160/4.5 µg therapy and before and after increasing the dose of budesonide/formoterol. We compared the PFT data collected within the prior 12 weeks and that collected after 12 weeks from the day of raising the dose.

COPD assessment test (CAT) score

The CAT score was used to measure quality of life in patients with BOS. The CAT was performed before and at least 12 weeks after the budesonide/formoterol 160/4.5 µg treatment and budesonide/formoterol 320/9.0 µg treatment. The CAT considers eight symptoms: Q1 cough, Q2 phlegm, Q3 chest tightness, Q4 breathlessness going up hills/stairs, Q5 activity limitation at home, Q6 confidence leaving home, Q7 sleep, and Q8 energy.

Defining the group responding to high-dose ICS/LABA therapy

After 3 months of high-dose budesonide plus formoterol therapy and a clinical evaluation, the patients were categorized into two groups (responder or non-responder) according to therapeutic response: above or below the minimal clinically important difference (MCID) (20). The commonly accepted MCID for pulmonary function is an FEV1 of 100 mL and a CAT score of 2 points (21,22).

Safety assessment

Safety was assessed as the incidence of pneumonia within 3 months after increasing the drug dose. Oral candidiasis, pharyngitis, pneumonia, and other adverse events were checked in the safety assessment.

Statistical analyses

Median and ranges are given for continuous variables. Categorical data are described as numbers and percentages (%). The *t*-test and paired *t*-test were performed to compare the PFT data and CAT scores. Categorical variables were compared using the chi-square or Fisher's exact test. All statistical tests were two-sided, with P values ≤0.05 denoting significance. The statistical analyses were performed using SPSS 24 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 290 patients were diagnosed with BOS at Seoul St. Mary's Hospital from March 2009 to February 2019, and 77 patients were treated with budesonide 160 µg plus formoterol 4.5 µg twice a day for more than 3 months and the dose was increased to budesonide 320 µg plus 9.0 µg twice a day. The baseline characteristics of the enrolled patients are shown in *Table 1*. Median age was 47.08 years (range, 22–70 years), and 67.5% of the participants were male. No current smokers were enrolled, and 28.6% were ex-smokers. Most of the patients had HSCT as treatment for acute leukemia (AML 42.9%, ALL 22.1%) or myelodysplastic syndrome (22.1%). It took a median of 654 days (40–2,973 days) to diagnose BOS. The rate of acute GVHD was 59.7%, and the rate of chronic GVHD was 100%. The eyes and oral cavity were the most frequent organs involved in chronic GVHD.

Treatment response–PFTs

After treatment with low-dose ICS/LABA (budesonide 160 µg plus formoterol 4.5 µg twice a day for 12 weeks), there were significant increases in FVC percent predicted (before 70.6% *vs.* after 73.8%, P=0.013) and DLCO percent predicted (before 47.9% *vs.* after 53.9, P=0.032). However, there were no significant differences in FEV1, FEV1 percent predicted, FEV1/FVC percent predicted and RV/TLC percent predicted. The statistical results

Table 1 Baseline characteristics of total patients with bronchiolitis obliterans syndrome (n=77)

Characteristics	Number or median	Range or %
Sex, male	52	67.5
Age	49.0	22–70
BMI	20.7	12.1–32.3
Smoking history		
Never	55	71.4
Former	22	28.6
Pack years	5.25	0–60
Hematologic malignancy		
AML	33	42.9
ALL	17	22.1
MDS	17	22.1
AA	2	2.6
CML	2	2.6
NHL	3	4.3
MPAL	2	2.9
HL	1	1.4
Donor type		
Unrelated	31	40.3
Sibling	31	40.3
FMT	15	19.5
HLA		
Full matched	52	67.5
Miss matched	25	32.5
Stem cell source		
PB	66	85.7
BM	8	10.4
Cord	3	3.9
Donor sex, male	44	57.1
Donor age	40	7–62
Time from HSCT to BOS diagnosis, days	434	40–2,973
Acute GVHD	46	59.7

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Number or median	Range or %
Chronic GVHD except lung	77	100
Oral	62	80.5
Eyes	53	68.8
Skin	26	33.8
GI	2	2.6
Liver	26	33.8
Joints	3	3.9
Genital tract	0	0
Systemic steroid use	48	62.3
Steroid dose, mg (equivalent dose of prednisolone)	5.0	0–25
Tacrolimus	21	27.3
Cyclosporin	15	19.5
MMF	30	39

BOS, bronchiolitis obliterans syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; AA, aplastic anemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; MPAL, mixed-phenotype acute leukemia; HL, Hodgkin lymphoma; FMT, familial-mismatched/haploidentical transplantation; HLA, human leukocyte antigen; PB, peripheral blood; BM, bone marrow; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease.

are given in *Table 2*. After treatment with high-dose ICS/LABA (budesonide 320 μg plus formoterol 9.0 μg twice a day for 12 weeks), there were no significant differences in FEV1 (before treatment 1.59 L *vs.* after treatment 1.65 L, P=0.182) or FVC (before treatment 2.93 L *vs.* after treatment 2.96 L, P=0.519) compared to before starting the high dose treatment. No significant differences were observed in FEV1/FVC with the high-dose combination treatment (56.3±18.2 before and 58.2±18.4 after the high dose treatment; P=0.150). No significant differences were observed in total lung capacity (TLC) (before 5.22 L *vs.* after 5.17 L, P=0.646), RV (before 2.14 L *vs.* after 2.10 L, P=0.595), or RV/TLC (before 41.0% *vs.* 41.0%, P=0.901) with the high-dose combination treatment. None of these

Table 2 Changes of pulmonary function after treatment of low-dose budesonide/formoterol treatment

Clinical variable, N=77	Before treatment	After treatment	Change of lung function	P value
FVC (L)	3.11 (1.10–4.96)	3.29 (1.12–4.85)	0.14 (0.47)	0.012
FVC (% predicted)	74.0 (29.0–97.0)	75.5 (35.0–107.0)	3.3 (11.1)	0.013
FEV1 (L)	1.70 (0.53–3.68)	1.80 (0.37–3.83)	0.06 (0.43)	0.205
FEV1 (% predicted)	50.5 (14.0–90.0)	54.0 (16.0–89.0)	1.1 (12.8)	0.467
FEV1/FVC (%)	57.0 (27.0–99.0)	56.0 (21.0–98.0)	−1.1 (13.7)	0.482
RV/TLC (%)	38.5 (18.0–70.0)	38.0 (14.0–61.0)	−1.1 (8.0)	0.359
DLCO (% predicted)	54.0 (14.0–86.0)	56.0 (35.0–94.0)	6.0 (7.5)	0.032

Data represent the median (range) or mean (SD). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, carbon monoxide diffusion in the lung.

Table 3 Changes of pulmonary function after treatment of high-dose budesonide/formoterol treatment

Clinical variable, n=77	Pre-HSCT	Before treatment	After treatment	Change of lung function	P value
FVC (L)	3.87 (0.96)	2.93 (1.04)	2.96 (1.14)	0.03 (0.42)	0.519
FVC (% predicted)	92.3 (12.4)	68.1 (17.7)	68.6 (20.5)	0.5 (9.8)	0.678
FEV1 (L)	3.10 (0.81)	1.59 (0.67)	1.65 (0.73)	0.04 (0.26)	0.182
FEV1 (% predicted)	92.8 (12.8)	45.3 (15.7)	47.2 (18.1)	1.5 (7.4)	0.098
FEV1/FVC (%)	79.8 (6.0)	56.3 (18.3)	58.2 (18.4)	1.2 (7.3)	0.150
TLC (L)	5.37 (1.12)	5.22 (1.38)	5.17 (1.38)	−0.02 (0.41)	0.646
TLC (% predicted)	91.4 (10.3)	86.8 (16.8)	86.9 (16.6)	−0.6 (22.0)	0.502
RV (L)	1.42 (0.46)	2.14 (0.80)	2.10 (0.77)	−0.03 (0.40)	0.595
RV (% predicted)	78.1 (23.2)	113.6 (42.5)	111.3 (41.0)	−2.0 (6.8)	0.466
RV/TLC (%)	26.7 (7.2)	41.0 (10.6)	41.0 (12.1)	−0.1 (6.2)	0.901
DLCO (% predicted)	63.9 (15.8)	61.4 (17.1)	60.7 (16.7)	0.2 (12.1)	0.896

Data represent the mean (SD). HSCT, hematopoietic stem cell transplantation; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, carbon monoxide diffusion in the lung.

changes and improvements were significant. The statistical results are given in *Table 3*.

Treatment response–CAT score

Of the 77 enrolled patients, 52 completed the CAT questionnaire before and after taking low-dose ICS/LABA (budesonide/formoterol 160/4.5 μg twice a day for 12 weeks). After treatment with low-dose ICS/LABA, there was significant decrease in total CAT score (P=0.001). Total CAT score decreased from 16.2 to 13.2 after low-dose

budesonide/formoterol therapy. When comparing each question, scores for question 1 (cough), question 3 (chest tightness) and question 4 (breastlessness going up hills/stairs) decreased significantly (*Table 4*). Sixty-seven patients completed the CAT questionnaire before and after raising their budesonide/formoterol dose to 320/9.0 μg. After raising the dose of combination therapy, there were no significant differences in the total CAT score (*Table 5*). The total CAT score before treatment was 16.51; it was 16.41 after treatment. When comparing each question, there was no significant decrease in the score for each question.

Table 4 Changes of COPD assessment test (CAT) score after low-dose budesonide/formoterol treatment

Clinical variable	Before treatment	After treatment	P value
Q1. Cough	1.71	1.19	0.005
Q2. Phlegm	1.37	1.37	1.000
Q3. Chest tightness	1.92	1.23	0.000
Q4. Breathlessness going up hills/stairs	3.46	2.90	0.002
Q5. Activity limitation at home	1.38	1.17	0.373
Q6. Confidence leaving home	1.83	1.52	0.179
Q7. Sleep	2.06	1.63	0.066
Q8. Energy	2.46	2.17	0.121
Total score	16.19	13.19	0.001

Data represent the mean CAT score.

Table 5 Changes of COPD assessment test (CAT) score after high-dose budesonide/formoterol treatment

Clinical variable	Before treatment	After treatment	P value
Q1. Cough	1.88	1.78	0.525
Q2. Phlegm	2.06	2.09	0.848
Q3. Chest tightness	1.79	1.50	0.065
Q4. Breathlessness going up hills/stairs	3.56	3.40	0.267
Q5. Activity limitation at home	1.56	1.66	0.551
Q6. Confidence leaving home	1.85	1.85	1.000
Q7. Sleep	1.60	1.66	0.742
Q8. Energy	2.21	2.47	0.129
Total score	16.51	16.41	0.896

Data represent the mean CAT score.

Change in pulmonary function in the therapeutic response group

Statistical analyses were performed for therapeutic responsiveness. Of the 77 patients, 73 completed PFTs before and after the high-dose budesonide/formoterol treatment. Of these, 25 (34.2%) had an increase in FEV1 ≥100 mL. On the other hand, 68 of the 77 patients completed the CAT before and after high-dose budesonide/formoterol combination therapy. Of these, 24 (35.3%) showed a decrease ≥2 points. Among the 25 patients with increase in FEV1 ≥100 mL, 10 patients had decreased in CAT score ≥2 points, 8 patients had decreased in CAT score by 1 to –1 point and 6 patients had increased in CAT score ≥2 points. One patient did not completed CAT. Among the 24 patients with decrease in CAT score ≥2 points, 10 patients had increase in FEV1 ≥100 mL, 8 patients had increased in FEV1 by 100 to –100 mL and 6 patients had decreased in FEV1 ≥100 mL. Twenty-six (38.2%) patients were included in the therapeutic response group (*Figure 1*). *Table 6* shows baseline characteristics of the response group and the non-response group. When compared with non-responder group, those who had response with high-dose budesonide/formoterol were significantly older (54.7 *vs.* 43.2, P<0.001), had a significantly longer pack-year history of smoking (10.8 *vs.* 2.2, P=0.034), had higher proportion of former smokers (46.2% *vs.* 19%, P=0.017). There were significant differences in baseline pulmonary function before HSCT when BOS did not occur. The responder group showed significantly lower FEV1 (2.76 *vs.* 3.28 L, P=0.010),

Table 6 Comparison of baseline characteristics between therapeutic responder group and non-responder group

Characteristics	Non-responder, N=42	Responder, N=26	P value
Age (years)	43.5 [22–66]	58.5 [31–66]	<0.001
Male sex, n (%)	29 (69.0)	16 (64.5)	0.525
Height (cm)	170.5 [149–186]	164.5 [144–180]	0.052
Weight (kg)	58.0 [35–93]	57.0 [38–82]	0.449
Body-mass index (kg/m²)	20.7 (12.1–32.3)	20.8 (16.2–25.6)	0.657
Smoking status	0.0 [0–20]	0.0 [0–60]	0.017
Former smoker, n	8 (19.0)	12 (46.2)	
Never smoker, n	34 (81.0)	14 (53.8)	
Cigarette pack-years	2.2 [0–20]	10.8 [0–60]	0.034
Donor age	39.8 [7–57]	37.2 [23–62]	0.407
Time from HSCT to BOS diagnosis, days	668.6 [40–2,973]	584.5 [80–1,894]	0.540
Maximal score of chronic GVHD (except lung)	2.4 [1–5]	2.5 [1–6]	0.899
Systemic steroid	27 (64.4)	16 (61.5)	0.819
Steroid dose, mg (equivalent dose of prednisolone)	5.9 [0–20]	5.5 [0–20]	0.786
Tacrolimus	10 (23.8)	9 (34.6)	0.335
Cyclosporin	10 (23.8)	5 (19.2)	0.658
Mycophenolate mofetil	19 (45.2)	6 (23.1)	0.065
Side effect more than one	5 (11.9)	2 (7.7)	0.579
Pre-HSCT PFT results			
FVC	4.10 (2.33–6.72)	3.52 (2.04–5.05)	0.188
FVC (% predicted)	93.0 (59.0–118.0)	59.0 (118.0–91.0)	0.951
FEV1	3.35 (1.89–5.37)	1.89 (5.37–2.73)	0.010
FEV (% predicted)	92.5 (64.0–120.0)	64.0 (120.0–91.5)	0.273
FEV1/FVC (%)	81.5 (71.0–97.0)	71.0 (97.0–76.0)	0.002
TLC	5.58 (3.22–8.04)	3.22 (8.04–5.34)	0.375
TLC (% predicted)	92.0 (62.0–116.0	62.0 (116.0–92.5)	0.259
VC	4.22 (2.38–6.72)	2.38 (6.72–3.59)	0.089
VC (% predicted)	95.0 (59.0–122.0)	59.0 (122.0–97.5)	0.361
RV	1.25 (0.67–2.95)	0.67 (2.95–1.42)	0.170
RV (% predicted)	67.0 (34.0–144.5)	34.0 (144.5–83.0)	0.234
RV/TLC (%)	24.0 (11.0–44.3)	11.0 (44.3–30.2)	0.008
DLCO	14.90 (8.30–25.20)	8.30 (25.20–12.95)	0.116
DLCO (% predicted)	61.5 (31.0–94.0)	31.0 (94.0–61.0)	0.678
DLCO/VA	3.19 (2.07–17.30)	2.07 (17.30–2.80)	0.242
DLCO/VA (% predicted)	70.0 (45.0–104.0)	45.0 (104.0–67.0)	0.747

Data represent the median (range) or n (%). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; VC, vital capacity; RV, residual volume; DLCO, carbon monoxide diffusion in the lung; VA, alveolar volume.

FEV1/FVC percent predicted (76.9% *vs.* 81.8%, P=0.002) and significantly higher RV/TLC percent predicted (30.0 *vs.* 25.0, P=0.008). The pulmonary functions before high-dose budesonide/formoterol therapy, non-responder showed significantly lower FEV1 percent predicted (42.6% *vs.* 52.8%, P=0.006), lower VC percent predicted (70.4% *vs.* 82.0%, P=0.008) and significantly higher RV percent predicted (123.2% *vs.* 99.7%, P=0.036, *Table* 7). In terms of pulmonary function decline, when comparing lung function of pre-HSCT study and just before increasing the dose of budesonide/formoterol, FVC (1.10 *vs.* 0.64 L, P=0.035), FEV1 (1.80 *vs.* 1.07 L, P<0.001) and FEV1 percent predicted (49.5% *vs.* 37.0%, P=0.010) in the non-responder group decreased more than in the responder group. The non-responder group had more increase in RV percent predicted (44.4% *vs.* 17.9%, P=0.045) and RV/TLC percent predicted (16.8% *vs.* 9.6%, P=0.026). *Table 8* shows the results.

Safety assessment

In the safety assessment, 9 of the 77 patients (11.7%) developed pneumonia during the 3 months before the budesonide/formoterol 320/9 µg treatment and 8 of 77 patients (10.4%) developed pneumonia during the 3 months after the budesonide/formoterol 320/9 µg treatment, and there were no significant differences between the two periods (P=1.000). Fourteen patients (18.2%) developed bronchitis symptoms requiring antibiotics during the 3 months before the budesonide/formoterol 320/9 µg treatment and seven (9.1%) had bronchitis symptoms with antibiotics during the 3 months after the budesonide/formoterol 320/9 µg treatment and there were no significant differences between the two periods (P=0.167). Twenty-nine patients (37.7%) received antibiotic therapy for any cause during the 3 months before the budesonide/formoterol 320/9 µg treatment and twenty (26.0%) received antibiotic therapy for any cause during the 3 months after the budesonide/formoterol 320/9 µg treatment, and there were no significant differences between the two periods (P=0.078). No other complications or adverse events were reported.

Comparing pulmonary function and safety profile in control group

As a control group for the patient who raised the dose of the budesonide/formoterol from 160/4.5 to 320/9 µg,

we investigated the patient group that had treatment with budesonide/formoterol 160/4.5 µg twice a day for more than 6 months. Of the 290 patients diagnosed with BOS, 77 patients who increased the dose of budesonide/formoterol from low to high were enrolled in our study. Of the remaining 213 patients, 93 patients received low-dose budesonide/formoterol inhaler treatment, 95 patients received high-dose budesonide/formoterol inhaler treatment, 16 patients received fluticasone/salmeterol inhaler treatment, and 9 received other inhaler treatments. Of 93 patients who received low-dose budesonide/formoterol treatment, 75 patients continued low-dose budesonide/formoterol treatment for more than 6 months and performed the PFTs.

We compared the differences between PFTs, CAT score, and adverse events at 3 months after 160 treatments and 6 months after these 75 patients. There were no significant differences between 3 and 6 months after low-dose budesonide/formoterol treatment in lung function, CAT score and adverse events (*Tables 9-11*).

Discussion

The therapeutic effect and safety of high-dose budesonide/formoterol were investigated in patients with BOS after allogeneic HSCT. We found no significant differences in FEV1 or CAT scores between the two periods of before and after increasing the dose of budesonide/formoterol. However, some patients (34.2% in FEV1 and 35.3% in CAT score) had significant improvements that met the MICD.

The main basis of BOS therapy remains as corticosteroids (23). However, if there is no response to steroid treatment and lung function continues to deteriorate, death will ensue. In a recent study, up to a 76% 2-year survival was reported (24), but more than 60% of patients with BOS after allogeneic HSCT progress to death (8).

Bergeron *et al.* reported the results of ICS and bronchodilator use for BOS after allogeneic HSCT in a retrospective study (25), which sparked a randomized control trial for budesonide/formoterol performed in 32 patients that showed that budesonide/formoterol 800/24 µg twice daily significantly increased FEV1 in patients with mild/severe BOS after allogeneic HSCT but had some limitations (26). A few studies have investigated the optimal dose of budesonide/formoterol in patients with BOS after allogeneic HSCT. However, this study is the first to compare efficacies and adverse events between budesonide/

Table 7 Comparison of pulmonary function between therapeutic responder group and non-responder group

Clinical variable	No-response	Response	P value
Before high-dose combination therapy			
FVC	2.97 (1.07)	3.00 (0.95)	0.914
FVC (%)	66.7 (18.2)	74.3 (13.9)	0.073
FEV1	1.58 (0.68)	1.69 (0.60)	0.501
FEV1 (%)	42.6 (15.0)	52.8 (13.6)	0.006
FEV1/FVC (%)	55.7 (19.1)	57.9 (15.4)	0.624
VC	5.32 (1.41)	5.03 (1.37)	0.438
VC (%)	86.8 (16.9)	88.3 (15.7)	0.716
TLC	3.08 (1.02)	3.08 (0.97)	0.978
TLC (%)	70.4 (16.5)	82.0 (15.2)	0.008
RV	2.23 (0.86)	1.96 (0.63)	0.183
RV (%)	123.2 (47.1)	99.7 (30.1)	0.036
RV/TLC (%)	42.0 (11.8)	39.3 (8.2)	0.333
DLCO	15.70 (5.03)	14.51 (5.06)	0.367
DLCO (%)	59.3 (14.6)	65.0 (16.2)	0.157
DLCO/VA	4.19 (0.79)	3.77 (0.84)	0.054
DLCO/VA (%)	94.6 (17.6)	89.3 (19.9)	0.281
(Pre-HSCT) – (before high-dose combination therapy)			
ΔFVC	1.10 (0.97)	0.64 (0.62)	0.035
ΔFVC (%)	23.7 (18.3)	17.5 (17.9)	0.172
ΔFEV1	1.80 (0.84)	1.07 (0.64)	0.000
ΔFEV1 (%)	49.5 (18.5)	37.0 (19.4)	0.010
ΔFEV1/FVC (%)	26.2 (19.7)	19.0 (15.9)	0.120
ΔVC	1.31 (1.16)	0.89 (0.97)	0.160
ΔVC (%)	22.1 (16.7)	14.4 (17.1)	0.090
ΔRV	−0.56 (1.09)	−0.33 (0.88)	0.404
ΔRV (%)	−44.4 (55.5)	−17.9 (35.9)	0.045
ΔTLC	0.74 (1.80)	0.56 (1.66)	0.701
ΔTLC (%)	3.3 (15.9)	4.0 (17.5)	0.889
ΔRV/TLC (%)	−16.8 (13.7)	−9.6 (8.4)	0.026
ΔDLCO	0.93 (5.53)	−0.88 (3.44)	0.158

Data represent the mean (SD). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; VC, vital capacity; RV, residual volume; DLCO, carbon monoxide diffusion in the lung; VA, alveolar volume.

Table 8 Adverse events

Events	Period during 3 months before increase	Period during 3 months after increase	P value
Pneumonia	9	8	1.000
Bronchitis	14	7	0.167
Antibiotics therapy	29	20	0.078

Table 9 Comparison of changes of pulmonary function after 3 months and 6 months treatment of low-dose budesonide/formoterol

Clinical variable	After 3 months treatment	SD	After 6 months treatment	SD	Change of lung function	SD	P value
FVC (L)	3.08	0.94	2.94	1.05	−0.13	0.77	0.140
FVC (% predicted)	79.3	13.5	77.8	15.6	−1.5	8.5	0.144
FEV1 (L)	2.20	0.75	2.15	0.77	−0.05	0.29	0.190
FEV1 (% predicted)	66.8	17.6	65.8	18.7	−1.0	8.8	0.335
FEV1/FVC (%)	69.9	15.5	69.6	16.2	−0.3	5.4	0.694
TLC (L)	4.85	0.87	4.82	1.06	−0.03	0.60	0.690
TLC (% predicted)	87.5	12.8	87.2	14.1	−0.3	9.1	0.809
VC (L)	3.24	0.75	3.19	0.83	−0.05	0.39	0.362
VC (% predicted)	84.6	13.0	83.0	15.5	−1.5	10.2	0.255
RV (L)	1.59	0.51	1.66	0.54	0.07	0.40	0.186
RV (% predicted)	89.9	27.5	93.6	31.5	3.7	22.7	0.210
RV/TLC (%)	33.0	8.9	34.2	9.4	1.2	6.84	0.176
DLCO	16.48	4.54	16.64	4.67	0.16	2.85	0.658
DLCO (% predicted)	70.1	17.8	76.0	40.0	6.0	41.7	0.267
DLCO/VA	4.04	0.85	4.09	0.87	0.05	0.60	0.547
DLCO/VA (% predicted)	91.1	18.3	92.5	18.4	1.4	14.3	0.462

Data represent the mean (SD). HSCT, hematopoietic stem cell transplantation; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, carbon monoxide diffusion in the lung.

formoterol 160/4.5 and 320/9.0 μg in patients with BOS after allogeneic HSCT. In a previous study, we administered a combined treatment of budesonide/formoterol 160/4.5 μg twice daily, N-acetylcysteine, and montelukast, which significantly increased FEV1 in patients with BOS after allogeneic HSCT (13). The present study has the strength of using real world data and serves as a follow-up to our previous study.

BOS is a disease in which pulmonary function continues to decrease (2,24). After the treatment of high-dose budesonide/formoterol, the CAT score and the lung function did not deteriorate in our study. It is encouraging that some patients improved over the MCID. Future

research is needed to identify the predictors of the response in patients with BOS. It will be important to distinguish the phenotypes of BOS that are responsive to treatment.

The greatest concern regarding high-dose ICS was the adverse events after the increase. In this study, there were no significant differences in adverse events before and after the dose increase.

Our study had some limitations. It was not a randomized controlled study. We investigated the adverse events by retrospective chart review and there may have been under-detection of adverse events. Also, observation period for adverse events was relatively short. Finally, the responder may have had underlying reactive airway disease or early

Table 10 Comparison of changes of COPD assessment test (CAT) score after 3 and 6 months treatment of low-dose budesonide/formoterol

Clinical variable	After 3 months treatment	After 6 months treatment	P value
Q1. Cough	0.85	0.93	0.505
Q2. Phelgm	1.17	1.28	0.473
Q3. Chest tightness	1.13	1.23	0.471
Q4. Breathlessness going up hills/stairs	2.32	2.17	0.228
Q5. Activity limitation at home	0.73	0.88	0.333
Q6. Confidence leaving home	1.07	0.97	0.626
Q7. Sleep	1.72	1.72	1.000
Q8. Energy	2.05	1.92	0.424
Total score	11.03	11.10	0.920

Data represent the mean CAT score.

Table 11 Comparison of adverse events after 3 and 6 months treatment of low-dose budesonide/formoterol

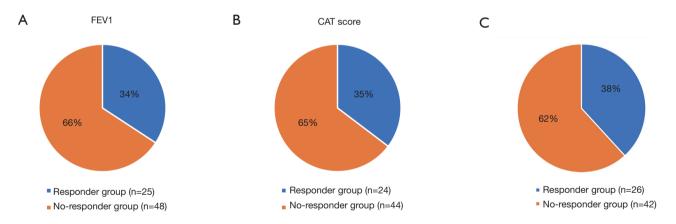| Events	Period during 3 months after treatment start	Period during 3 months after 3 months treatment	P value
Pneumonia	8	9	1.000
Bronchitis	6	5	1.000
Antibiotics therapy	14	17	0.648

Figure 1 Rate of therapeutic response to high-dose budesonide/formoterol combination therapy evaluated by improvement of FEV1 or CAT score. (A) Thirty-four percent of patients showed an increase in FEV1 ≥100 mL; (B) 35% showed a decrease ≥2 points; (C) twenty-six (38.2%) patients were included in the therapeutic response group. FEV1, forced expiratory volume in 1 second; CAT, COPD assessment test.

COPD before the onset of BOS. The onset of BOS may have exaggerated symptoms in some patients with potentially underlying pre-clinical COPD/asthma. The use of high-dose budesonide/formoterol may have resolved underlying pre-clinical COPD/asthma. However, there are several advantages to this study. The first was that medical care and management were standardized by a single expert using the same protocol. The second was that this is the first study to compare the effects of budesonide/formoterol 160/4 and 320/9 µg applied to patients with BOS in the real world. Finally, more than 70 patients with BOS, a very rare disease, were enrolled.

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Kim et al. Efficacy and safety of budesonide/formoterol 320/9 µg with BOS patients

Our study failed to show superior effect of high-dose budesonide/formoterol (320/9 µg) compared with low-dose. However, high-dose budesonide/formoterol was safe and there was no lung function deterioration. Identifying subgroups of patients that have a good response to high dose budesonide/formoterol should be considered to improve the management and survival of patients with BOS after HSCT.

Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-19-3475). CKR serves as an unpaid editorial board member of *Journal of Thoracic Disease*. CKR reports personal fees from MSD, personal fees from AstraZeneca, personal fees from GSK, personal fees from Novartis, personal fees from Takeda, personal fees from Mundipharma, personal fees from Boehringer-Ingelheim, personal fees from Teva, personal fees from Sanofi, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional ethic committee/review board of Seoul St. Mary's Hospital, which waived the requirement for informed consent due to the retrospective nature of the study (IRB No. KC19RESI0661).

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