BMC Pulmonary Medicine

RESEARCH

Open Access

Effect of Broncho-Vaxom (OM-85) on the frequency of chronic obstructive pulmonary disease (COPD) exacerbations

Joon Young Choi[1], Yong Bum Park[2], Tai Joon An[3], Kwang Ha Yoo[4*†] and Chin Kook Rhee[5*†]

Abstract

Background Efforts have been made to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations using a variety of measures. Broncho-Vaxom (BV) is an immunomodulating agent that has shown potential benefit by balancing between immune stimulation and regulation in patients with COPD. In this study, we evaluated the clinical efficacy of BV for reducing the risk of COPD exacerbations.

Methods This study was based on the Korean National Health Insurance database, which contains reimbursement information for almost the entire population of South Korea. We extracted data from 2016 to 2019 for patients started on BV during 2017–2018. We collected baseline data on demographics, comorbidities, inhaler use, hospital type, and insurance type 1 year before starting BV. We also analyzed exacerbation history, starting from the year before BV initiation.

Results In total, 238 patients were enrolled in this study. Their mean age was 69.2 ± 9.14 years, 79.8% were male, and 45% experienced at least one exacerbation. BV reduced the risk of moderate (odds ratio [OR] = 0.59, 95% confidence interval [CI]: 0.38–0.91) and moderate-to-severe exacerbations compared to pre- and post-BV (OR = 0.571, 95% CI: 0.37–0.89). BV use also reduced the incidence of moderate and moderate-to-severe exacerbations (incidence rate ratio [IRR] = 0.75, $p = 0.03$; and IRR = 0.77, $p = 0.03$, respectively). The use of BV was significantly delayed moderate exacerbations (hazard ratio = 0.68, $p = 0.02$), but not with moderate-to-severe or severe exacerbations.

Conclusion The use of BV was associated with fewer moderate and moderate-to-severe exacerbations. Additionally, BV was associated with a delay in moderate COPD exacerbations.

Keywords Broncho-Vaxom, Chronic obstructive pulmonary disease, HIRA database, Oral vaccine, OM-85, Exacerbation

†Kwang Ha Yoo and Chin Kook Rhee contributed equally to this work.

*Correspondence:
Kwang Ha Yoo
khyou@kuh.ac.kr
Chin Kook Rhee
chinkook77@gmail.com
[1] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[2] Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea
[3] Division of Pulmonology and Critical Care, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[4] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University School of Medicine, 120 Neungdong-Ro, Gwangjin-Gu, Seoul 05030, Republic of Korea
[5] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seochogu, Seoul 06591, Republic of Korea

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem affecting > 300 million patients worldwide [1]. It is associated with high morbidity and mortality, and was recently ranked as the third leading cause of death worldwide [1, 2]. Among patients with COPD, those who experience frequent exacerbations have poor clinical outcomes, including reduced quality of life, accelerated decline in lung function, and increased mortality [3–6]. Additionally, healthcare costs are significantly higher in frequent exacerbators [3]. Efforts have been made to reduce exacerbation risk through pharmacological and non-pharmacological measures.

Various drugs, including bronchodilators, inhaled corticosteroids (ICS), phosphodiesterase E4 inhibitors, long-term macrolides, and mucoregulators, are effective for reducing the frequency of COPD exacerbations [7]. However, a large proportion of patients are categorized as frequent exacerbators, and are at high risk of morbidity and mortality [8, 9]. Various drugs have been investigated in terms of their efficacy for preventing exacerbations, including immunoregulators (so-called "oral vaccines" [10–13]).

Broncho-Vaxom (BV) is an immunoregulator that has been investigated for decades, mostly in patients with chronic inflammatory airway disease. BV is an oral bacterial lysate derived from eight major species of respiratory pathogens [14]. BV modulates the host immune system in various ways by balancing between immune stimulation and regulation [15–19]. It is known that immune stimulation involves both innate immunity (TLR-dependent synergism, polynuclear cell recruitment [CXCL1, 6, 8], proinflammatory response [IL-1, IL-6, TNF-α], secretion of antiviral cytokine [IL-12, IFN-α, IFN-γ], NK cell activation [CCL2, 3]) and adaptive immunity (B-cell activation [CCL2,3,20,22, BAFF, IL-6, APRIL]) [15]. Additionally, immune regulation is associated with maturation in dendritic cells (DC), specifically in pDC and moDC (CD80/CD86), and airway mucosal DC migration (CCR-7) [15]. Immune regulatory effect of BV is also known to involve the induction of regulatory T cells and local aggregation [15]. It was classified as a "grade A" treatment for chronic rhinosinusitis without nasal polyps in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 [20]. Previous studies have investigated the role of BV in COPD treatment, and showed potential benefits in terms of exacerbation risk, hospitalization duration, and antibiotic prescriptions [12, 13, 21, 22]. However, additional investigations using large databases with more comprehensive analysis are needed to reveal the beneficial effects of BV [7]. Moreover, there has been no real-world study that evaluate the effect of BV in real clinical practice.

In this study, we utilized national health insurance reimbursement data which collects medical data in almost all patients in South Korea, Our objective was to conduct a comprehensive analysis of the effects of BV on COPD exacerbations. We compared exacerbation risk, frequency, and incidence, and the time to first exacerbation, between the pre- and post-BV periods in COPD patients who used the drug. We also performed subgroup analyses to identify patients most likely to benefit from BV.

Material and methods

Study population and data collection

The Health Insurance Review & Assessment Service (HIRA) reviews the adequacy of medical cost coverage and verifies insurance claims for almost the entire population of South Korea. The HIRA collects clinical and medical patient data through medical personnel for insurance reimbursement assessment. In this study, we extracted the data of COPD patients registered in the HIRA database from January 2016 to December 2019 (Fig. 1).

The COPD patients included in this study were: 1) aged ≥ 40 years at the index date; 2) prescribed one or more medication for COPD at least twice per year during the study period [long-acting muscarinic antagonist (LAMA), long-acting beta-2 agonist (LABA), inhaled corticosteroids (ICS) plus LABA (ICS + LABA), LABA plus LAMA (LABA + LAMA), short-acting muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA), SABA plus SAMA (SABA + SAMA), phosphodiesterase-4 inhibitor (PDE4-I), systemic bronchodilator, or theophylline];; 3) had one or more inpatient or outpatient claim with the International Classification of Disease-10 (ICD-10) code for COPD (J43–J44, except J43.0), i.e., any diagnosis for an inpatient claim, or a primary or 4th secondary diagnosis for an outpatient claim, during the study period. We defined patients with COPD based on criteria 1), 2) and 3). To further select patients who are actively treated, we added a criterion of ICS/LABA or LAMA usage. The exclusion criteria were use of Uro-Vaxom® or Ismigen® during the study period; diagnosis of lung cancer, idiopathic pulmonary fibrosis, or interstitial lung disease during the study period; lung transplantation during the study period; prescription of BV during the pre-BV period or before the index date 2; death during the study period; and receiving a different type of inhaler or having a medication possession ratio < 50% for the same type of inhaler between or during the pre- and post-BV periods.

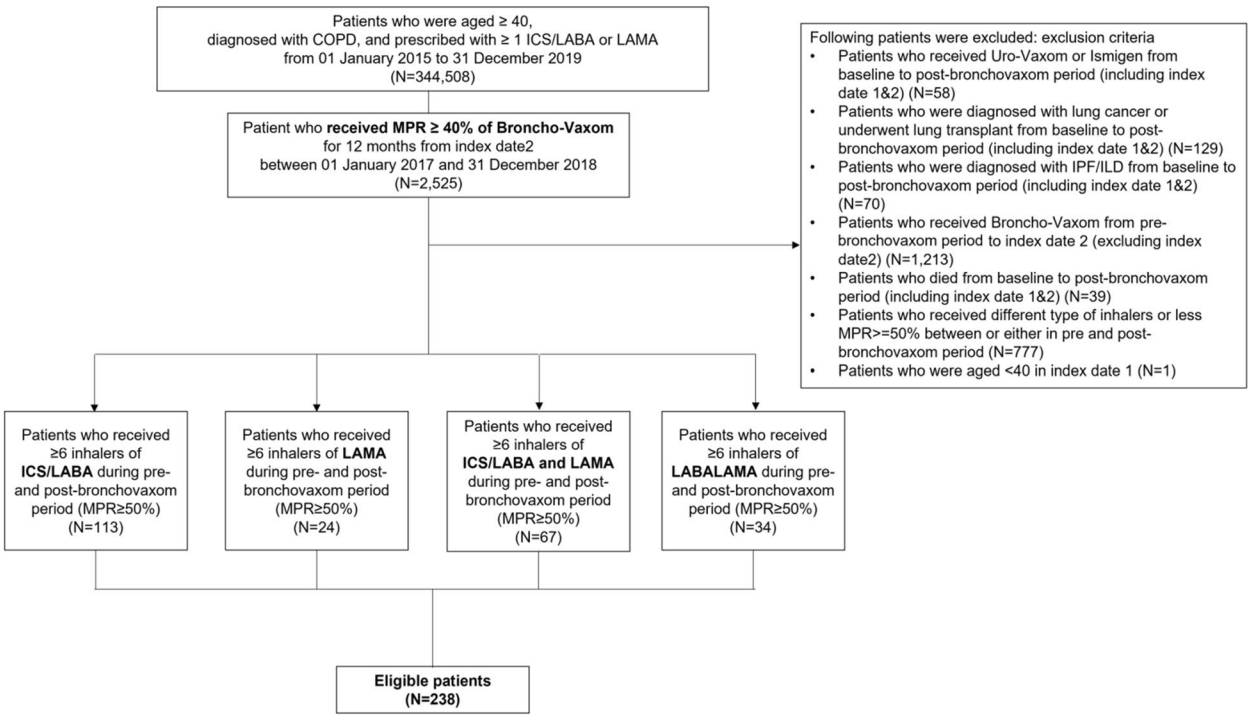

Fig. 1 Flow chart of patient selection

Study design

We selected COPD patients started on BV during 2017–2018, which we defined as the index period (Fig. 2). The date of BV initiation during the index period was called index date 2, and the 12-month date preceding index date 2 was index date 1. We collected data on demographic characteristics during the 12-month period before index date 1, defined as the baseline. We compared outcomes between the 12 months before index date 2 (pre-BV period) and 12 months after index date 2 (post-BV period).

Clinical parameters

Baseline characteristics of interest included age, sex, insurance type, hospital type, exacerbation history, history of asthma and pneumonia, modified Charlson Comorbidity Index (mCCI) score, and COPD medication

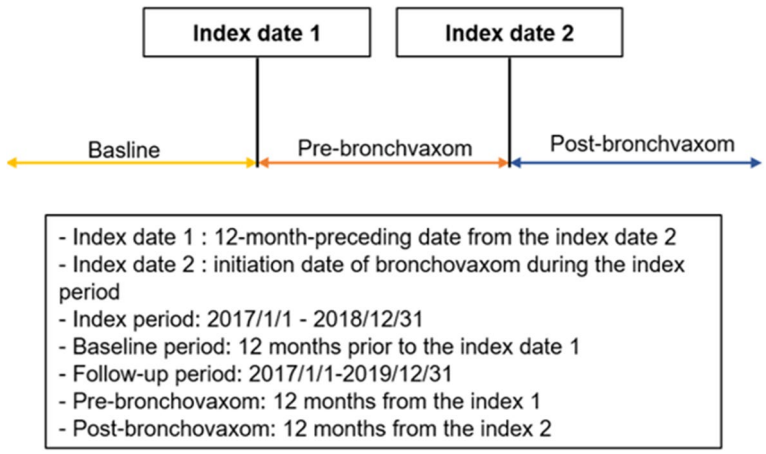

Fig. 2 Overview of study design

use. Data on exacerbation history during the pre- and post-BV periods were also collected.

COPD exacerbations were identified based on the presence of the relevant diagnostic codes and systemic steroid and/or antibiotic prescriptions during the observation period (Supplemental Material 2.2.1.1). Moderate exacerbations were defined as events that required an outpatient visit and prescription of systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as those that required an inpatient or emergency room visit for patients prescribed systemic corticosteroids and/or antibiotics. Exacerbations were also categorized according to antibiotic or oral corticosteroid (OCS) use.

Statistical analysis

All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA) using SAS Enterprise Guide version 6.1. Continuous variables are expressed as means c ± standard deviations, and categorical values as numbers and percentages. Exacerbation risk was compared between the pre- and post-BV periods using a binomial mixed model. We also used the Poisson distribution to compare exacerbation frequency, relative frequency, and incidence rate ratio (IRR) between the pre- and post-BV periods. Data on the time to first exacerbation were subjected to survival analysis. All analyses were adjusted for potential confounding variables including age, sex, insurance type, hospital type, exacerbation history, history of asthma or pneumonia, mCCI score, COPD medication use, and index year.

Results

Baseline characteristics

Among the 344,508 COPD patients in the database, 2,525 were BV users during the study period (Fig. 1) and 238 were included in the analysis. The mean age of the BV users was 69.2 ± 9.14 years, and 79.8% were male (Table 1). BV was primarily prescribed in tertiary and general hospitals. About 45% of the patients prescribed BV had a history of exacerbations during the previous year, and 9.2% had ≥ 2 moderate or ≥ 1 severe exacerbation. About half of the patients were using ICS + LABA inhalers, and 28.2% were using triple therapy.

Table 1 Baseline characteristics of BV users

Variables	Numbers (*n* = 238)
Age	69.2 ± 9.14
Sex (male)	190 (79.8%)
Insurance type	
Health insurance	207 (87.0%)
Medical aid	31 (13.0%)
Hospital type	
Tertiary and general hospital	196 (82.4%)
Others	42 (17.6%)
History of COPD AE	
None	131 (55.0%)
1 moderate	85 (35.7%)
≥ 2 moderate or ≥ 1 severe	22 (9.2%)
History of pneumonia	63 (26.5%)
mCCI	2.62 ± 2.12
COPD medication	
LAMA	24 (10.1%)
LABA + LAMA	34 (14.3%)
ICS + LABA	113 (47.5%)
Triple	67 (28.2%)

Data are presented as n (%) or mean ± SD

BV Broncho-Vaxom, *COPD* Chronic obstructive pulmonary disease, *AE* Acute exacerbation, *mCCI* Modified Carlson Comorbidity Index, *LAMA* Long-acting muscarinic antagonist, *LABA* Long-acting beta2-agonist, *ICS* Inhaled corticosteroids

Differences in exacerbation risk between the pre- and post-BV periods

A comparison of the risk of exacerbation between the pre- and post-BV periods is shown in Table 2. The risk of moderate and moderate-to-severe exacerbations decreased significantly after using BV (odds ratio [OR] = 0.59, 95% confidence interval [CI]: 0.38–0.91]; OR = 0.57, 95% CI: 0.37–0.89, respectively). However, the reduction in the risk of severe exacerbations did not reach statistical significance. BV did not significantly modify the risk of any of the three types of exacerbations (antibiotic-, OCS-, and antibiotic/OCS-related exacerbations), except moderate OCS-related exacerbations (OR = 0.58, 95% CI: 0.34–0.99) (Supplementary Material 6.1).

Subgroup analysis revealed that the risk of moderate exacerbation decreased in patients aged > 75 years, and in those with one previous moderate exacerbation, no history of pneumonia, a history of asthma, or an mCCI score ≥ 2 (Supplementary Material 6.1.1.1). None of the subgroups benefitted from BV regarding severe exacerbation (Supplementary Material 6.2.1.2). Patients who used triple therapy, those aged > 75 years, females, and those with no history of exacerbations or pneumonia, a history of asthma, or an mCCI score ≥ 2 had a lower moderate-to-severe exacerbation risk after using BV (Supplementary Material 6.2.1.3).

Differences in exacerbation frequency and incidence

No significant difference in overall exacerbation frequency was observed between the pre-BV and post-BV periods, regardless of exacerbation severity (Supplementary Material 6.2.2). Subgroup analysis revealed that an age ≥ 75 years and mCCI score ≥ 2

Table 2 Differences of exacerbation risk between pre- and post-BV period

	Number of patient with events (%) ($n=238$)		Crude OR (95% CI)	Adjusted OR (95% CI)
	pre-BV	post-BV		
COPD exacerbation				
Moderate	127 (0.53)	104 (0.44)	0.678 (0.471–0.976)	0.591 (0.383–0.914)
Severe	91 (0.38)	81 (0.34)	0.833 (0.572–1.215)	0.818 (0.545–1.230)
Moderate to Severe	165 (0.69)	141 (0.59)	0.643 (0.440–0.941)	0.571 (0.368–0.886)

BV Broncho-Vaxom, *COPD* Chronic obstructive pulmonary disease, *OR* Odd ratio

Table 3 Incidence rate of COPD exacerbation between pre- and post-BV period

	Incidence rate per 1,000 PYs		Incidence risk ratio (IRR)	*P*-value
	pre-BV	post-BV		
COPD exacerbation				
Moderate	804.75	604.64	0.75	0.03
Severe	473.19	423.73	0.90	0.47
Moderate to Severe	1247.18	965.18	0.77	0.03

PY Person-year, *BV* Broncho-Vaxom, *COPD* Chronic obstructive pulmonary disease, *IRR* Incidence rate ratio

were associated with a significantly lower frequency of moderate and moderate-to-severe exacerbations during BV use.

The use of BV was associated with lower incidence rates of moderate and moderate-to-severe exacerbations (IRR = 0.75, $p=0.03$; and IRR = 0.77, $p=0.03$, respectively), but not of severe exacerbations (Table 3). In the subgroup analysis, patients aged > 75 years, and those with an mCCI score ≥ 2, benefitted from BV in terms of moderate and moderate-to-severe exacerbations (Supplementary Material 6.2.3).

Differences in time to first exacerbation between the pre- and post-BV periods

A comparison of the time to first exacerbation between the pre- and post-BV periods is shown in Fig. 3. The use of BV delayed moderate exacerbations (hazard ratio [HR] = 0.68, $p=0.02$), but not moderate-to-severe (HR = 0.77, $p=0.07$) or severe exacerbations (HR = 1.02, $p=0.03$).

Discussion

In this nationwide study, we compared pre- and post-BV exacerbations in BV users. Our results showed that the risk of moderate and moderate-to-severe exacerbations was significantly reduced by BV. Additionally, BV reduced the incidence rates of moderate and moderate-to-severe exacerbations, and delayed the time to the first moderate exacerbation. However, BV did not have a significant effect on severe exacerbations.

Various immunomodulatory substances, including BV, polyvalent mechanical bacterial lysate, pidotimod, probiotics, non-typeable Haemophilus influenza protein vaccine, and MV-130 have been introduced to treat chronic inflammatory airway diseases [10, 11, 23]. These agents are believed to exert their effects through the so-called "gut-lung axis", where the mucosal immune systems of the gut and lungs function as an integrated unit defending against pathogens that can breach either mucosa [10, 24]. Pathogens are detected by the pattern recognition receptors of dendritic cells (DCs) in mucosal membranes. DCs function as immune sentinels, activating the immune cascade and promoting the migration of innate and adaptive immune cells through the lymphatic system. During this process, not only proinflammatory cells, but

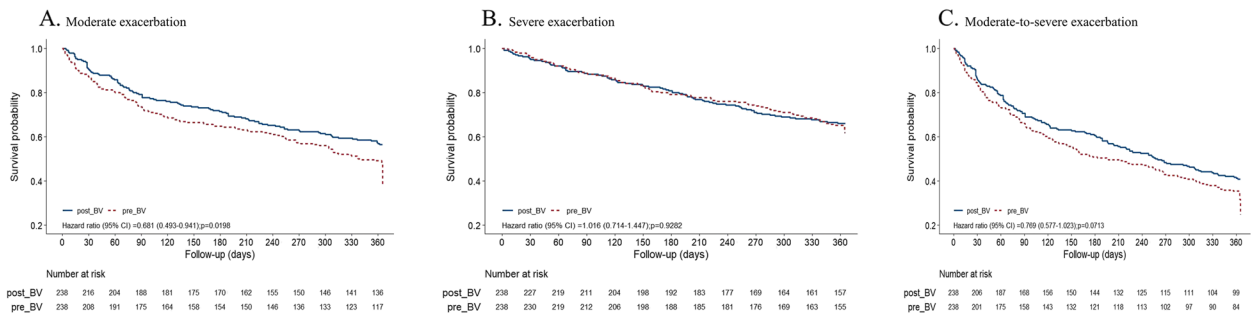

Fig. 3 Time to first COPD exacerbation. (**A** Moderate exacerbation; **B** Severe exacerbation; **C** Moderate to severe exacerbation)

also immune regulatory cells, migrate to remote mucosal membranes, which reduces inflammation. A good balance between immunostimulation and immunoregulation may optimize the response to various insults.

BV (OM-85) is an oral bacterial lysate consisting of lyophilized lysates from 21 different bacterial strains that mostly affect the human respiratory tract; they include Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis. Staphylococcus aureus, and Klebsiella pneumonia. The mechanism of action of BV has been widely studied in various experimental models. Parola et al. showed that BV selectively activates NF-kB and the MAPK-dependent pathway in human DCs, which induces chemokines (i.e., CXCL8, CXCL6, CCL3, CCL20, and CCL22) to recruit immune effector cells and enhances humoral immunity by releasing B-cell activating cytokines (i.e., IL-6, IL-10, and BAFF) [18]. Additionally, BV increases IFNα, which has an important role in defending against viral infections. In a murine model, Pasquali et al. reported a substantial decrease in viral load after 5 days in a BV group after infection with the influenza virus [19]. Moreover, the proportion of neutrophils in bronchoalveolar lavage fluid decreased, while the number of CD8 + T-lymphocytes increased, on days 5 and 10 post-infection, respectively, reflecting activation of the innate and adaptive cellular immune responses by BV. These results indicate that BV has a multi-faceted mechanism of action.

COPD exacerbations are associated with a greater disease burden, including reduced quality of life, increased healthcare costs, an accelerated decline of lung function, and increased mortality [3–6]. Among the various methods used to reduce the risk of exacerbations, BV administration has shown promising outcomes, consistent with our results. Soler et al. performed a double-blind randomized placebo-controlled trial in patients with chronic bronchitis or mild COPD [21]. The BV group had a lower cumulative rate of exacerbations (relative risk [RR] = 0.71, $p = 0.03$) and greater proportion of patients free from exacerbations ($p = 0.01$) compared to the control group at the 6-month follow-up. Li et al. performed a double-blind randomized controlled trial of patients with chronic bronchitis and mild COPD. At the 1-year follow-up, the BV group had fewer, shorter-duration and less severe exacerbations, and a shorter duration of antibiotic use [25]. Pan et al. performed a meta-analysis showing that BV decreased the risk of exacerbations (RR = 0.80, 95% CI: 0.65–0.97) [13]. Our study showed that the risk of moderate-to-severe exacerbations decreased in response to BV (OR = 0.57).

Our results indicated that BV may be more effective in reducing moderate than severe exacerbations, and thus may be more effective in those with a lower disease burden. Most of the RCTs that showed favorable effects of BV in terms of reducing the risk of exacerbations included patients with mild COPD; RCTs that included only severe COPD patients failed to show significant reductions in exacerbation risk [21, 22, 25]. Furthermore, the duration of hospitalization did not differ between BV users and non-users in the subgroup analysis of the meta-analysis by Pan et al., which accorded with our result that BV had no beneficial effect on severe exacerbations [13]. Additionally, our study showed that BV had a more significant effect on exacerbations in those aged ≥ 75 years with a high comorbidity burden. As no study has definitively identified subgroups that may benefit from BV, further investigations are needed.

This study had some limitations. First, it was a retrospective observational study, and several types of bias may thus be present. However, because the HIRA database includes almost all patients in South Korea and has minimal missing data, selection and observer biases were probably well controlled. Nevertheless, the single-arm design and inclusion only of patients who used BV may have led to some selection bias. Second, we analyzed 1-year follow-up data of patients who used BV; longer-term outcomes should be investigated in a future study. Third, since COPD was defined by the ICD-10 code and drug usage, there is a possibility that some patients might have been misdiagnosed with COPD. We relied on our operational definition for COPD due to the absence of lung function data in the HIRA database. Nevertheless, this definition has been frequently utilized in prior research [26–40].Strengths of our study included the careful selection of patients from a database including almost all patients in South Korea, based on inclusion criteria that have been used in previous studies; we excluded subjects whose data may have confounded the results. Second, we analyzed the effects of BV on the risk of exacerbations according to severity and type. We also performed a subgroup analysis to identify patients most likely to benefit from BV.

In conclusion, we analyzed the nationwide HIRA database to determine the efficacy of BV for reducing exacerbations in COPD patients. BV use was associated with a significantly lower risk of moderate and moderate-to-severe exacerbations, and a delay in the first moderate exacerbation. However, no effect on severe exacerbations was detected. Given the need to prevent exacerbations in COPD patients, our data are important in showing that BV may reduce the exacerbation risk if used as an adjunct to standard therapy.

Abbreviations

COPD Chronic obstructive pulmonary disease
BV Broncho-Vaxom

ICS	Inhaled corticosteroid
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
HIRA	Health Insurance Review & Assessment Service
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
ICD-10	International Classification of Disease-10
mCCI	Modified Charlson Comorbidity Index
IRR	Incidence rate ratio
OCS	Oral corticosteroid
OR	Odd ratio
DC	Dendritic cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-023-02665-4.

Additional file 1.

Acknowledgements
None.

Authors' contributions
Conceptualization: Park YB, Yoo KH, Rhee CK. Methodology: Choi JY, An TJ, Yoo KH, Rhee CK. Formal analysis: Yoo KH, An TJ, Rhee CK. Data curation: Park YB, Yoo KH, Rhee CK, Investigation: All authors. Writing-original draft preparation: Choi JY. Writing-review and editing: All authors. Approval of final manuscript: All authors.

Funding
This study was supported by the Aju Pharm Co., Ltd., Seoul, Republic of Korea. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Availability of data and materials
The data that support the findings of this study are available from the Health Insurance Review & Assessment Service in Korea, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, the data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Konkuk University Hospital, Republic of Korea with registration number KUMC 2021–02-001–003. Informed consent from patients was waived by the Institutional Review Board of Konkuk University Hospital. We confirm that all methods were performed in accordance with the Declaration of Helsinki and the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
CK Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. JY Choi, TJ An, YB Park, KH Yoo had no competing interests.

Received: 1 December 2022 Accepted: 19 September 2023
Published online: 07 October 2023

References

1. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016;21(1):14–23.
2. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J. 2006;27(2):397–412.
3. Larsson K, Janson C, Lisspers K, Ställberg B, Johansson G, Gutzwiller FS, Mezzi K, Bjerregaard BK, Jorgensen L. The Impact of Exacerbation Frequency on Clinical and Economic Outcomes in Swedish COPD Patients: The ARCTIC Study. Int J Chron Obstruct Pulmon Dis. 2021;16:701–13.
4. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925–31.
5. Suzuki M, Makita H, Ito YM, Nagai K, Konno S, Nishimura M. Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. Eur Respir J. 2014;43(5):1289–97.
6. Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. Respir Med. 2017;128:85–91.
7. Global initiative for chronic obstructive lung disease (GOLD) guidelines, global strategy for the diagnosis, management and prevention of chronic obstructive lung disease (2022).https://goldcopd.org/2022-gold-reports/.
8. Wu YK, Su WL, Yang MC, Chen SY, Wu CW, Lan CC. Characterization Associated with the Frequent Severe Exacerbator Phenotype in COPD Patients. Int J Chron Obstruct Pulmon Dis. 2021;16:2475–85.
9. McGarvey L, Lee AJ, Roberts J, Gruffydd-Jones K, McKnight E, Haughney J. Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. Respir Med. 2015;109(2):228–37.
10. Feleszko W, Rossi GA, Krenke R, Canonica GW, Van Gerven L, Kalyuzhin O. Immunoactive preparations and regulatory responses in the respiratory tract: potential for clinical application in chronic inflammatory airway diseases. Expert Rev Respir Med. 2020;14(6):603–19.
11. Wilkinson TMA, Schembri S, Brightling C, Bakerly ND, Lewis K, MacNee W, Rombo L, Hedner J, Allen M, Walker PP, et al. Non-typeable Haemophilus influenzae protein vaccine in adults with COPD: a phase 2 clinical trial. Vaccine. 2019;37(41):6102–11.
12. Tang H, Fang Z, Saborío GP, Xiu Q. Efficacy and Safety of OM-85 in Patients with Chronic Bronchitis and/or Chronic Obstructive Pulmonary Disease. Lung. 2015;193(4):513–9.
13. Pan L, Jiang XG, Guo J, Tian Y, Liu CT. Effects of OM-85 BV in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. J Clin Pharmacol. 2015;55(10):1086–92.
14. Orcel B, Delclaux B, Baud M, Derenne JP. Oral immunization with bacterial extracts for protection against acute bronchitis in elderly institutionalized patients with chronic bronchitis. Eur Respir J. 1994;7(3):446–52.
15. Kearney SC, Dziekiewicz M, Feleszko W. Immunoregulatory and immunostimulatory responses of bacterial lysates in respiratory infections and asthma. Ann Allergy Asthma Immunol. 2015;114(5):364–9.
16. Dang AT, Pasquali C, Ludigs K, Guarda G. OM-85 is an immunomodulator of interferon-β production and inflammasome activity. Sci Rep. 2017;7:43844.
17. Huber M, Mossmann H, Bessler WG. Th1-orientated immunological properties of the bacterial extract OM-85-BV. Eur J Med Res. 2005;10(5):209–17.
18. Parola C, Salogni L, Vaira X, Scutera S, Somma P, Salvi V, Musso T, Tabbia G, Bardessono M, Pasquali C, et al. Selective activation of human dendritic cells by OM-85 through a NF-kB and MAPK dependent pathway. PLoS One. 2013;8(12):e82867.
19. Pasquali C, Salami O, Taneja M, Gollwitzer ES, Trompette A, Pattaroni C, Yadava K, Bauer J, Marsland BJ. Enhanced mucosal antibody production and protection against respiratory infections following an orally administered bacterial extract. Front Med (Lausanne). 2014;1:41.
20. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1–12.
21. Solèr M, Mütterlein R, Cozma G. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration. 2007;74(1):26–32.
22. Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute

Respiratory Infection by an Immunostimulant. Am J Respir Crit Care Med. 1997;156(6):1719–24.
23. Nieto A, Mazón A, Nieto M, Calderón R, Calaforra S, Selva B, Uixera S, Palao MJ, Brandi P, Conejero L, et al. Bacterial Mucosal Immunotherapy with MV130 Prevents Recurrent Wheezing in Children: A Randomized, Double-Blind, Placebo-controlled Clinical Trial. Am J Respir Crit Care Med. 2021;204(4):462–72.
24. de Boer GM, Żółkiewicz J, Strzelec KP, Ruszczyński M, Hendriks RW, Braunstahl GJ, Feleszko W, Tramper-Stranders GA: Bacterial lysate therapy for the prevention of wheezing episodes and asthma exacerbations: a systematic review and meta-analysis. Eur Respir Rev 2020, 29(158).
25. Li J, Zheng JP, Yuan JP, Zeng GQ, Zhong NS, Lin CY. Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease. Chin Med J (Engl). 2004;117(6):828–34.
26. Kim Y, Kim K, Rhee CK, Ra SW. Increased hospitalizations and economic burden in COPD with bronchiectasis: a nationwide representative study. Sci Rep. 2022;12(1):3829.
27. Lee J, Lee JH, Kim JA, Rhee CK. Trend of cost and utilization of COPD medication in Korea. Int J Chron Obstruct Pulmon Dis. 2017;12:27–33.
28. An TJ, Kim Y, Park YB, Kim K, Cho DY, Yoo KH, Rhee CK. Inhaled corticosteroid is not associated with a poor prognosis in COVID-19. Respirology. 2021;26(8):812–5.
29. Kim J, Rhee CK, Yoo KH, Kim YS, Lee SW, Park YB, Lee JH, Oh Y, Lee SD, Kim Y, et al. The health care burden of high grade chronic obstructive pulmonary disease in Korea: analysis of the Korean Health Insurance Review and Assessment Service data. Int J Chron Obstruct Pulmon Dis. 2013;8:561–8.
30. Kim JA, Lim MK, Kim K, Park J, Rhee CK. Adherence to inhaled medications and its effect on healthcare utilization and costs among high-grade chronic obstructive pulmonary disease patients. Clin Drug Investig. 2018;38(4):333–40.
31. Kim Y, An TJ, Park YB, Kim K, Cho DY, Rhee CK, Yoo KH. Chronic obstructive pulmonary disease is not associated with a poor prognosis in COVID-19. Tuberc Respir Dis (Seoul). 2022;85(1):74–9.
32. Lee EG, Kim Y, Hwang YI, Yoo KH, Lee SE, Jung KY, Lee D, Park YB, Rhee CK. Comparison of pneumonia incidence between long-acting muscarinic antagonist and inhaled corticosteroid plus long-acting beta agonist in patients with COPD. Sci Rep. 2023;13(1):8183.
33. Lee YJ, Rhee CK, Hwang YI, Yoo KH, Lee SE, Lee D, Park YB, Kim Y: Escalation Time to Open Triple Combination Therapy from the Initiation of LAMA versus ICS/LABA in COPD Management: Findings from Comparing the Incidence of Tiotropium and ICS/LABA in Real-World Use in South Korea (CITRUS) Study. J Pers Med 2021, 11(12).
34. Park HJ, Byun MK, Kim T, Rhee CK, Kim K, Kim BY, Ahn SI, Jo YU, Yoo KH. Frequent outpatient visits prevent exacerbation of chronic obstructive pulmonary disease. Sci Rep. 2020;10(1):6049.
35. Park HJ, Byun MK, Rhee CK, Kim K, Kim HJ, Yoo KH. Significant predictors of medically diagnosed chronic obstructive pulmonary disease in patients with preserved ratio impaired spirometry: a 3-year cohort study. Respir Res. 2018;19(1):185.
36. Park HY, Kang D, Lee H, Shin SH, Kang M, Kong S, Rhee CK, Cho J, Yoo KH. Impact of chronic obstructive pulmonary disease on mortality: a large national cohort study. Respirology. 2020;25(7):726–34.
37. Park HY, Kang D, Shin SH, Choi H, Jang SH, Lee CH, Kim H, Kwon OJ, Rhee CK, Cho J. Pulmonary tuberculosis and the incidence of lung cancer among patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2022;19(4):640–8.
38. Park HY, Kang D, Shin SH, Yoo KH, Rhee CK, Suh GY, Kim H, Shim YM, Guallar E, Cho J, et al. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study. Thorax. 2020;75(6):506–9.
39. Park SC, Kim DW, Park EC, Shin CS, Rhee CK, Kang YA, Kim YS. Mortality of patients with chronic obstructive pulmonary disease: a nationwide populationbased cohort study. Korean J Intern Med. 2019;34(6):1272–8.
40. Park SC, Kim YS, Kang YA, Park EC, Shin CS, Kim DW, Rhee CK. Hemoglobin and mortality in patients with COPD: a nationwide population-based cohort study. Int J Chron Obstruct Pulmon Dis. 2018;13:1599–605.

Publisher's Note