



Effect of OM-85 BV on reducing bronchiectasis exacerbation in Chinese patients: the iPROBE study

Jinming Gao¹, Lun Li¹, Nan Jiang², Ying Liao², Lingfei Kong³, Yuanlin Song⁴, Jinfu Xu⁵, Jie Cao⁶, Yuping Li⁷, Chengli Que⁸, Roy A. Pleasants⁹

¹Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China; ²Department of Medicine, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China; ³Department of Pulmonary and Critical Care Medicine, First Affiliated Hospital of China Medical University, Shenyang, China; ⁴Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China; ⁵Department of Pulmonary and Critical Care Medicine, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; ⁶Department of Pulmonary and Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin, China; ⁷Department of Pulmonary and Critical Care Medicine, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ⁸Department of Pulmonary and Critical Care Medicine, First Hospital of Peking University, Beijing, China; ⁹Division of Pulmonary Medicine and Critical Care, Chapel Hill, NC, USA

Contributions: (I) Conception and design: J Gao, RA Pleasants; (II) Administrative support: J Gao, L Kong, Y Song, J Xu, J Cao, Y Li, C Que; (III) Provision of study materials or patients: J Gao, L Kong, Y Song, J Xu, J Cao, Y Li, C Que; (IV) Collection and assembly of data: J Gao, L Li, N Jiang, Y Liao; (V) Data analysis and interpretation: J Gao, RA Pleasants; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jinming Gao, MD. Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, #1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. Email: gjinming@yahoo.com.

Background: Bronchiectasis is characterized by recurrent infectious exacerbations. No existing data inform preventive strategy for exacerbations beyond chronic macrolides. OM-85 BV, an immunostimulant, has been shown to prevent recurrent respiratory infections. We initiated this 1-year, multi-centered, double-blind, and controlled trial to investigate the preventive effect of OM-85 BV on Bronchiectasis Exacerbations in Chinese patients (iPROBE).

Methods: Patients with bronchiectasis aged 18 to 75 years, having at least one exacerbation in the past year, were randomized to receive, in addition to any respiratory medications, two courses of 7 mg of OM-85 BV or matching placebo (one capsule orally per day for 10 days a month) for 3 consecutive months, followed by 3 months without treatment. The primary outcomes included the number of acute infectious exacerbations and the time to first exacerbation. Secondary endpoints included patient-reported respiratory outcomes. Safety measures were also assessed.

Results: Among the 196 participants, 99 were in the OM-85 BV group and 97 in the placebo group. At week 52, the mean number of acute exacerbations per patient was equal to 0.98 and 0.75, respectively, in the two groups ($P=0.14$). Difference in the time to first pulmonary exacerbation was not statistically significant ($P=0.11$). There was no statistically significant difference in any secondary end-points. The safety profile in the two arms was good and the majority of adverse events were mild.

Conclusions: OM-85 BV did not demonstrate protection in decreasing pulmonary exacerbations of bronchiectasis in this trial performed in Chinese patients. It had good safety profile.

Keywords: OM-85 BV; bronchiectasis; immunostimulation; infection; pulmonary exacerbation

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Introduction

Non-cystic fibrosis bronchiectasis (thereafter called bronchiectasis) is a common, but, long-term neglected chronic respiratory disease in China (1,2). Indeed, prevalence of bronchiectasis in adult populations has been rising significantly around the world (3,4). Bronchiectasis represents a suppurative airway disorder with its phenotypes being highly heterogeneous and is characterized by permanent dilatation of one or more bronchi (5).

The abnormal architecture of bronchiectatic airways facilitates the chronic colonization of bacterial species such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* (6-8). Therefore, patients with bronchiectasis are prone to recurrent pulmonary exacerbations caused by bacterial infections, negatively influencing the natural history of the disease (9). Progressive airway damage and a deregulated immune response, resulting from a “vicious cycle” of recurrent bacterial infections, reflect a failure of the host defenses to maintain the homeostasis of the respiratory tract (7). Therefore, prevention of pulmonary exacerbations should be a prioritized aim of therapy. However, there is a limited evidence base to support the regimes for this goal (10).

Chronic macrolides with both antibacterial and anti-inflammatory properties have shown promise in preventing bronchiectasis exacerbations (11). Six to 12 months of treatment with these medications has shown a decreased rate of bronchiectasis exacerbations by several randomized controlled trials (RCTs) and a pooled meta-analysis (12-15). Nevertheless, chronic use of macrolides significantly increased bacterial resistance to antibiotics as well as potential adverse drug effects (14-16).

The non-specific prevention of recurrent airway infections by immunostimulating agents has gained recognition over the past decades. OM-85 BV (Broncho-vaxom, Vifor Pharma Pharmaceuticals, Geneva, Switzerland), an immunostimulant, contains of extracts of eight different bacteria thought to be commonly responsible for respiratory infections. Orally administrated OM-85 BV increases respiratory immune defense against a wide variety of pathogens by activating pulmonary macrophages, increasing the CD4/CD8 lymphocytes ratio and IFN- γ concentration in the human lung (17). OM-85 BV has been shown to effectively reduce exacerbations and improve life quality for patients with chronic obstructive pulmonary disease (COPD) in the RCTs (18-20).

Given that the majority of patients with bronchiectasis

often suffer from bacterial exacerbations (21), we implemented this investigator-initiated and -driven, multi-centered, phase 4 trial of investigation of PReventive effect of OM-85 on Bronchiectasis Exacerbations in adult Chinese patients (iPROBE).

Methods

Study design and subjects

Detailed design of this trial has been published previously (22). This study was a 52-week, randomized, double-blind, and placebo-controlled trial carried out in ten medical centers in Beijing, Tianjin, Shenyang, Shanghai, Hangzhou, and Wenzhou in China.

We enrolled bronchiectasis patients at routine outpatient visits at the time of clinical stability. Follow-ups were carried out in subspecialty clinics at study sites. Participants underwent study visits at the participating clinical centers on five separate occasions and had two follow-ups by telephone call during the 1-year trial period (*Figure 1*). The end of the study was defined by the last visit of the last participant. Tests performed during the visits were described previously (22).

The diagnosis of bronchiectasis was made as per the British Thoracic Society guidelines (21). Patients were eligible if they met the following inclusion criteria: subjects of both genders were adult patients (>18 years) with bronchiectasis shown by chest high-resolution computed tomography (HRCT) within 3 years of study inclusion and having had at least one acute exacerbation in the previous 1 year when recruiting. An exacerbation was defined as the patient reporting that an acute worsening in signs and symptoms that needing additional therapy (23). Full exclusion criteria and withdrawal criteria were provided in the published protocol (22).

Randomization and intervention

All eligible subjects were randomized using block randomization sequences generated by computer. The subjects were assigned at a 1:1 ratio with a permuted block size of four and sequential assignment, stratified by the center. Blinding continued until all analyses were completed.

The subjects were randomized to receive two courses of 7 mg of OM-85 BV or matching placebo (one oral capsule per day for 10 days a month) for 3 consecutive months, followed by 3 months without treatment. The trial lasted for 1 year (*Figure 1*).

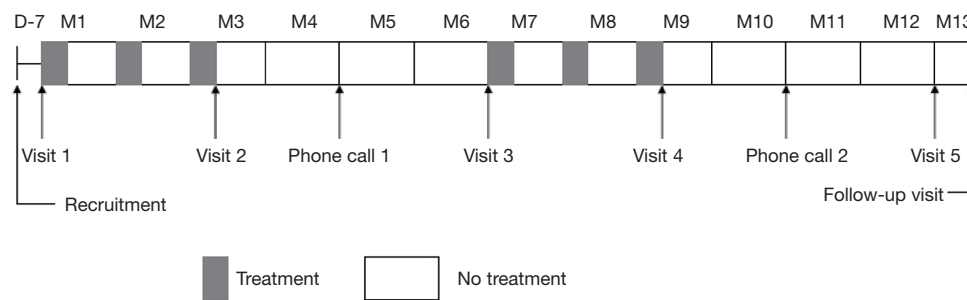


Figure 1 Treatment periods and visits.

Outcomes

The primary goals of this study include two domains during 12-month period: (I) the number of event-based acute exacerbation; (II) time to first acute exacerbation.

The secondary efficacy variables included: life quality assessed by the St. George's Respiratory Questionnaire (SGRQ) (24); cough severity using Leicester Cough Questionnaire (LCQ) score (25); change in lung function parameters reflected by forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC; serum C-reactive protein (CRP); duration of antibiotics use; use of a rapid-acting bronchodilator; and bacteria clearance of spontaneously expectorated sputum.

Sample size

To detect a true difference in the primary outcome measures of number of bronchiectasis exacerbations and time to first exacerbation, a total of 244 subjects (122 per arm) were screened. This calculation was based on the 80% probability of detecting the statistically and clinically significant difference in the number of bronchiectasis exacerbations and time to the first exacerbation (22).

Ethical approval

The study was approved by the Human Research Ethics Board at Peking Union Medical College Hospital (REB number S-474) and was registered with www.clinicaltrials.gov (identifier number NCT01968421). Informed written consent was obtained from each participant.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), the International Conference for Harmonization (ICH) principles of Good Clinical Practice (GCP) and the Declaration of

Tokyo (2004). The investigators conducted all aspects of this study in accordance with all national and regional laws of the pertinent regulatory authorities.

Statistics

There were three analysis populations in the study: Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Set. The primary endpoints were analyzed on FAS, which was the primary population and supported by PPS. The secondary endpoint and baseline information were analyzed on FAS. Safety analyses were performed on Safety Set.

The primary efficacy variable was analyzed on FAS population and supported by PPS population. Statistical description and statistical inference were conducted. Mean \pm standard deviation (SD) was presented as a statistical description by study group.

Statistical inference consisted of parameter estimation and hypothesis test. For categorical variables, frequency and proportion were summarized by groups. Comparisons between two groups were performed using Student's *t*-test or Wilcoxon rank-sum test depending on data distribution. Two-tailed 95% confidence interval of the difference between groups was also presented.

The categorical data were analyzed by Pearson chi-square test or Fisher exact test. The change after and before treatment within each group was described and tested by paired *t*-test or signed ranks test.

The interval to the first time of acute exacerbation was analyzed as survival data. Kaplan-Meier curve of two groups was presented and log-rank test was used to test the difference between two groups.

All analyses followed the intention-to-treat principle. We employed the following methods to minimize the potential effects of missing data or dropout. First, when the study treatment was discontinued, we tried to obtain consent from

the participants to collect data on treatments and outcomes. We used an estimating equation method to impute missing data in our primary analysis and we conducted a sensitivity analysis by using simple imputation methods (26). All reported P values are two-sided. All data analyses were performed using SAS 9.4 (SAS Institute Inc.).

Safety analysis

Analysis on safety was done using safety set. All adverse events (AEs) were coded using the version of MedDRA. Total frequency and incidence of AE and severe AE (SAE) were described. The frequency of AE in each group was tabulated by system organ class. The severity and relationship with the study were summarized by each group.

Results

Study participants

The first patient was enrolled March 1, 2015 and the last visit was on December 22, 2017. Between January 2, 2015 and January 9, 2018, a total of 244 clinically stable subjects with a diagnosis of bronchiectasis were recruited from ten medical centers (Table 1). Of these, 196 patients from ten study sites were randomized into OM-85 BV group (n=99) or placebo group (n=97), and 175 (89.3%) completed the treatment and trial. All participants reported more than one exacerbation in the previous 1 year at recruitment. Figure 2 shows the reasons for trial withdrawal.

The two treatment arms were generally comparable in terms of sex, age, smoking status, length of bronchiectasis-related symptoms, number of acute exacerbations in the past year, lung function parameters, and serum inflammatory markers (Table 1). The OM-85 BV group differed from the placebo group in more patients (64.6%) with bronchiectasis for more than 10 years (P=0.02). The significantly higher percentage of patients using inhaled anticholinergics in OM-85 BV group compared with placebo group (37.2% vs. 24.0%, P=0.047). No chronic exposure to antibiotics was reported among subjects in the two groups.

In this trial, *Pseudomonas aeruginosa* was the most often isolated pathogen in sputum, seen in 32.9% in OM-85 BV group and 25.9% in placebo group. Group A *Streptococcus* in sputum was the secondary most common isolated bacteria, where it was present in 9.8% of patients in OM-85 BV group and 12.9% of patients in the placebo group.

Efficacy

Primary outcomes

Over the 1-year study period, the number of one or more episodes of acute exacerbation per patient per 6 months, did not differ between the two groups OM-85 BV or placebo (0.57 ± 0.76 vs. 0.42 ± 0.66 , P=0.16) (Table 2). At week 52, the mean rate of acute exacerbation episodes was equal to 0.98 ± 1.19 and 0.75 ± 0.98 , respectively, in the two groups (P=0.14) (Table 2).

Because there was no beneficial effect for OM-85 BV on bronchiectasis exacerbation, we next analyzed the impact of inhaled corticosteroids (ICS) on pulmonary exacerbations in OM-85 BV group. In the OM-85 BV group, 24.5% of patients had taken ICSs and found that patients never on ICSs had fewer, not statistically significant, exacerbations than that ever on ICSs at week 24 (0.40 ± 0.66 vs. 0.73 ± 0.70 , P=0.08), however, this effect was not shown at week 52 (0.72 ± 1.01 vs. 1.00 ± 0.78 , P=0.33) (Table 3).

Also, there was no difference in the time to first exacerbation after 1 year between the two groups (P=0.11) (Figure 3). In a prior study, local airway immune response was modified by oral delivery of OM-85 BV after 3 months (27). We further assessed the difference in the time to the second flare-up between the two groups, the difference was not statistically significant (data not shown).

Secondary outcomes

At weeks 26 and 52, there were no statistically significant differences between OM-85 BV group and placebo group for any secondary efficacy outcomes including cough severity assessed by LCQ, life quality expressed by St. George scores, lung function measures, and serum inflammatory indices (Table 4). Likewise, there were no statistically significant differences in duration of acute exacerbation (8.84 ± 4.44 vs. 9.11 ± 4.15 days, P=0.723) and days of antibiotics administration (9.19 ± 4.48 vs. 9.20 ± 3.82 days, P=0.989) throughout the study course (Table 5). Also, the use of rapid-acting bronchodilators as rescue medication did not differ in the two groups (data not shown).

Safety analysis

The safety profile and tolerability of OM-85 BV in this study were generally good as reported in previous studies performed in COPD exacerbation trials (19,20,28). Sixteen AEs were reported totally (7 in OM-85 BV group and 9 in placebo group) (Table 6). Most AEs were mostly mild,

Table 1 Patient demographics and baseline clinical characteristics

Variables	OM-85	Placebo	P value
Male, n (%)	46/99 (46.5)	40/97 (41.2)	0.46
Age (years)	55.2±12.6	56.3±11.8	0.52
Smoking history, n (%)			
Never smokers	78/98 (79.6)	77/96 (80.2)	0.98
Ex-smokers	11/98 (11.2)	11/96 (11.5)	
Current smokers	9/98 (9.2)	8/96 (8.3)	
Time of bronchiectasis-related symptoms at screening, n (%)	17.9±15.4	15.2±16.5	0.33
<10 years	23/65 (35.4)	36/65 (55.4)	0.02
≥10 years	42/65 (64.6)	29/65 (44.6)	
Time since bronchiectasis diagnosis (years)	9.7±13.1	7.1±11.2	0.13
Numbers of exacerbations in the previous year	2.7±1.9	3.0±2.9	0.28
Respiratory medications, n (%)			
Any	63/99 (63.6)	59/97 (60.8)	0.68
Inhaled corticosteroids	24/98 (24.5)	17/94 (18.1)	0.28
Inhaled β ₂ agonists	27/98 (27.6)	23/95 (24.2)	0.60
Inhaled anticholinergics	35/94 (37.2)	23/96 (24.0)	0.047
Leukotriene receptor antagonist	4/98 (4.1)	0	0.12
Mucolytic	56/96 (58.3)	57/97 (58.8)	0.95
Influenza vaccination, n (%)	6/98 (6.1)	2/94 (2.1)	0.28
Leicester score	12.3±4.3	13.2±4.3	0.18
St. George's Respiratory Questionnaire score	31.6±17.1	29.4±14.7	0.40
Lung functions measurements (pre-bronchodilator)			
FEV ₁ /pred (%)	59.1±24.5	64.6±21.3	0.10
FVC/pred (%)	77.6±42.9	76.5±16.5	0.80
FEV ₁ /FVC (%)	64.2±15.6	68.4±15.0	0.06
Blood white counting and differential			
Total white (10 ⁹ /L)	7.3±2.7	7.1±2.1	0.45
Neutrophils (%)	63.2±10.9	63.1±10.3	0.96
Eosinophils (%)	2.2±3.0	1.9±1.5	0.33
CRP (mg/L)	14.6±30.6	9.7±14.2	0.15
ESR (mm/h)	26.5±22.7	26.6±20.8	0.98
LnTlgE	3.6±1.6	3.4±1.5	0.29
RF (IU/mL)	20.1±45.6	18.2±40.6	0.78

FEV₁/pred, forced expiratory volume in first second/predicated; FVC/pred, forced vital capacity/predicated; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; LnTlgE, log-transformed IgE.

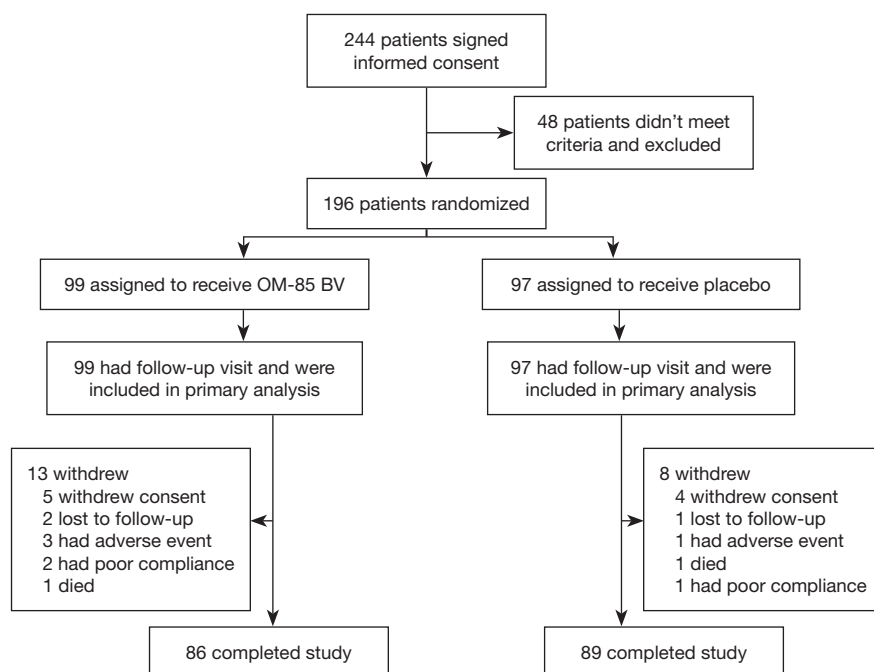


Figure 2 Study flow.

Table 2 Cumulative number of acute exacerbations per patient

Period (months)	OM-85		Placebo		Difference mean (95% CI)	P value
	N	Mean ± SD	N	Mean ± SD		
0–6	97	0.57±0.76	95	0.42±0.66	−0.15 (−0.35, 0.06)	0.16
6–12	86	0.46±0.76	90	0.34±0.58	−0.12 (−0.32, 0.08)	0.24
0–12	97	0.98±1.19	95	0.75±0.98	−0.23 (−0.54, 0.08)	0.14

SD, standard deviation; CI, confidence interval.

Table 3 Impact of ICSs on cumulative number of acute exacerbations per patient

Period (months)	No ICSs		ICSs		Difference mean (95% CI)	P value
	N	Mean ± SD	N	Mean ± SD		
0–6	73	0.40±0.66	15	0.73±0.70	−0.33 (−0.71, 0.04)	0.08
6–12	72	0.33±0.58	14	0.36±0.63	−0.03 (−0.37, 0.32)	0.89
0–12	72	0.72±1.01	14	1.00±0.78	−0.28 (−0.85, 0.29)	0.33

ICS, inhaled corticosteroids; SD, standard deviation; CI, confidence interval.

including common cold, abdominal discomfort, nausea, and arthralgia. SAEs were observed in OM-85 BV group (n=2) and placebo group (n=1), no serious AEs were attributed to the medication and no significant laboratory changes were observed.

Discussion

This 52-week, randomized, double-blind trial evaluated the potential of OM-85 BV in reducing the number of acute exacerbations of bronchiectasis in Chinese patients. OM-

Table 4 Summary of secondary efficacious end-points

End-points	Change from baseline to follow-up		Placebo-OM-85 difference (95% CI)	P value
	OM-85 BV	Placebo		
Follow-up after 6 months				
Leicester scores	1.61	2.51	0.90 (-2.02, 3.82)	0.525
St. George scores	-7.94	-6.56	1.38 (-8.95, 11.70)	0.785
Lung functions measures (pre-bronchodilator)				
FEV1/pred (%)	0.67	0.55	-0.12 (-2.33, 2.10)	0.918
FVC/pred (%)	-3.42	0.61	4.03 (-5.45, 13.52)	0.401
FEV1/FVC (%)	-0.66	-0.83	-0.17 (-1.99, 1.66)	0.859
Blood tests				
White cells counting (10 ⁹ /L)	-0.07	-0.17	-0.10 (-0.67, 0.47)	0.729
Neutrophil (%)	-0.04	-1.75	-1.71 (-4.40, 0.98)	0.212
CRP (mg/L)	-5.01	-0.96	4.05 (-2.61, 10.71)	0.231
ESR (mm/h)	-2.48	-3.21	-0.73 (-5.51, 4.05)	0.763
Follow-up after 12 months				
Leicester score	3.58	2.08	-1.50 (-5.42, 2.42)	0.430
St. George's Respiratory Questionnaire score	-12.29	-11.75	-0.54 (-12.40, 11.32)	0.925
Lung function measures (before bronchodilator)				
FEV1/pred (%)	1.15	-0.12	-1.27 (-4.22, 1.69)	0.398
FVC/pred (%)	-2.75	0.91	3.66 (-7.18, 14.49)	0.504
FEV1/FVC (%)	-0.73	-1.44	-0.71 (-3.29, 1.88)	0.590
Blood tests				
White cells counting (10 ⁹ /L)	0.08	-0.08	-0.16 (-0.95, 0.62)	0.676
Neutrophil (%)	-1.02	-2.54	-1.52 (-4.96, 1.92)	0.385
CRP (mg/L)	-1.34	-3.13	-1.79 (-9.02, 5.43)	0.625
ESR (mm/h)	-4.36	-7.98	-3.62 (-9.49, 2.25)	0.225

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV1/pred, forced expiratory volume in first second/predicated; FVC/pred, forced vital capacity/predicated; CI, confidence interval.

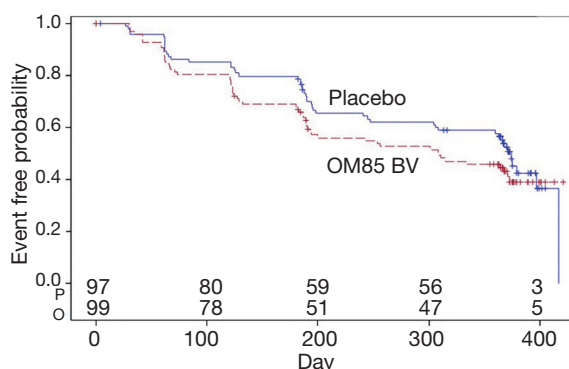
Table 5 Comparison of duration of acute exacerbations and antibiotics use

Variable	OM-85 BV (n=116)	Placebo (n=117)	P value
AE (days)	8.84±4.44	9.11±4.15	0.723
Antibiotics use (days)	9.19±4.48	9.20±3.82	0.989

AE, acute exacerbation.

Table 6 Summary of adverse events

Adverse events categorized by organ	OM-85 (n=99), n (%)	Placebo (n=97), n (%)	Total (n=196), n (%)
Any adverse events	7 (7.07)	9 (9.28)	16 (8.16)
Severe adverse events	2 (1.01)	1 (1.03)	3 (1.53)
Palpitation	0 (0)	1 (1.03)	1 (0.51)
Nausea	0	1 (0.85)	1 (0.43)
Abdominal discomfort	1 (1.01)	2 (2.06)	3 (1.53)
Common cold	3 (3.03)	4 (4.12)	7 (3.57)
Arthralgia	0	1 (1.03)	1 (0.51)
Miscellaneous	3 (3.03)	0 (0)	3 (1.53)

**Figure 3** Kaplan-Meier curve of the time to first pulmonary exacerbation of any severity in the modified intention-to-treat (mITT) population. P: placebo; O: OM-85 BV.

85 BV did not demonstrate any clinically relevant beneficial effects on cumulative number of acute exacerbations, the time to first exacerbation, lung function improvement, cough symptoms and quality of life using the Leicester and the SGRQ scores (FAS analysis). Similar observations were recorded in the per protocol analysis.

Although the present study failed to demonstrate a benefit for OM-85 in bronchiectasis exacerbations, it is nonetheless a valid negative study.

It may be speculated multiple pathways involving in pulmonary exacerbations of bronchiectasis.

We propose several possibilities to explain our negative results. First this relates to the mechanism of action for OM-85 BV through direct activation of lung macrophages by OM-85 BV in the respiratory tract (29,30). Bronchiectasis is a chronic suppurative lung disease characterized by neutrophil-predominant airways inflammation (31). Data from animal experiment showed

that OM-85 BV had little effect on neutrophils evidenced by a failure to bacterial clearance in *Klebsiella pneumoniae*-induced pneumonia, thus, no protective effect in a recurrent infection with this bacterium (32). This might suggest that alveolar macrophage activation by systemic administration with OM-85 BV is not sufficient for the protection for neutrophilic inflammation in respiratory tract bacterial infection (32). Similarly, one large randomized placebo-controlled trial performed in COPD patients showed that OM-85 didn't reduce the total number of exacerbations compared with placebo (28). OM-85 BV was shown to be more efficacious for COPD patients with a history of current or ex-smokers in decreasing exacerbations (19). Our present individual study included a small number of current smokers, thus, we were unable to perform the meaningful subgroup analysis.

The nature of disease heterogeneity may account for the difficulty in achieving endpoints in clinical trials (33). This clinical trial failed to demonstrate the additional benefit of OM-85 BV to prevent acute exacerbation of bronchiectasis on basis of the regular therapies, on the hand, reflecting the complex and heterogeneity of this disorder. It may be that recognizing the treatable traits of bronchiectasis would be of clinical relevance (34), therefore, the study with the objective aiming to identify the subgroups of patients (i.e., those having at least 3 exacerbations in the previous year) in whom OM-85 has beneficial effect is needed.

One potential reason why OM-85 BV did not lead to a significant decrease in bronchiectasis exacerbations is that it does not include bacterial lysates, *Pseudomonas aeruginosa*, which was the most common pathogen in Chinese patients with bronchiectasis (1,2). In contrast, OM-85 BV has been shown to decrease COPD exacerbations, where the most

common bacterial etiologies include those lysates included in this oral formulation. The similarly modest decrease in the number of exacerbation was observed in both groups. This might underline the importance of the increased awareness of the disease and daily care for bronchiectasis patients. We have to point out that existence of a ceiling effect might be an alternative explanation for the negative results of OM-85 BV in this trial. It was evidenced by the high rate of prescriptions for concomitant respiratory medications at the time recruitment and throughout the entire study period. However, we can't exclude the possibility of underreporting of events that might attribute to the negative result.

The strength of this current trial was the study design, which to a larger extent, replicated the methods previously adopted in trials with the objective of decreasing acute exacerbation of COPD and bronchiectasis (12-14,19,28). This trial lasted for 12 months, a period long enough to avoid bias due to seasonal variability in exacerbation frequency and time interval required for the typical patient to experience an exacerbation. These indicated that the trial design was sufficient to demonstrate the preventive property of OM-85 in bacterial exacerbations of bronchiectasis.

There were limitations to this study design. One might be related to the inclusion of ten medical centers in geographically different regions across China, leading to assessment of the potentially heterogeneous populations. The method for the assessment of acute events was pragmatic, information reported from both self-report by the patients and medical records. However, the blinded nature of this evaluation and the study size made us believe that these observations were not likely to be invalid. Demographic differences between the study drug and placebo groups at baseline were thought likely to affect the primary outcome of the study. It has been shown that more patients (64.6%) had a longer duration of disease when recruiting in OM-85 BV group than those in placebo group in this current trial. In addition, there was heterogeneity in the number of acute exacerbations at baseline exemplified by recruitment of patients having at least 1 exacerbation. In spite of the modest size of enrolled subjects, the iPROBE study was a large bronchiectasis trial compared with other studies of reducing bronchiectasis exacerbations by macrolides (12-14).

We did not find any significant difference in SGRQ and LCQ scorings between two groups during the trial. This is likely due to the fact that scorings evaluated at designated

times distant from the exacerbation might insensitive to the effect of the drug on decreasing pulmonary exacerbations. Also, there was similar change in lung function measurements in both groups after 1-year trial. These results are consistent with those observed in the trial of reducing exacerbations of COPD by OM-85 BV (28).

OM-85 BV has been widely used to prevent recurrent respiratory infections and has demonstrated a favorable AEs profile. Our trial confirms this safety profile. The majority of the documented AEs shown in *Table 5* were not severe, self-limited, and resolved fully. The total number and the distribution of events were similar in the two groups and compatible with what has been observed previously in COPD exacerbation trials (18,20,28).

In summary, the iPROBE study was not able to demonstrate the benefit for OM-85 BV, on the basis of regular treatment, in the prevention of acute exacerbation of bronchiectasis in Chinese patients. However, our negative results don't necessarily invalidate the strategy of enhancing the host body immunity against airway infections. Therefore, a logic stratified approach to treatment will be required in future. In particular, longer-term efficacy of OM-85 BV with the treatment period of more than 1 year in carefully phenotyped patients may provide additional insight into the role of this therapy for bronchiectasis.

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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-20-1662>). The 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) and the Harmonized Tripartite Guideline for GCP from the International Conference on Harmonization. The study was reviewed and approved by the Human Research Ethics Board at Peking Union Medical College Hospital (REB number S-474). All patients enrolled completed the informed consent form.

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