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Efficacy and Safety of Spleen Aminopeptide Oral Lyophilized Powder in Patients with Frequent Acute Exacerbations of Bronchiectasis: A Randomized, Double-blind, Placebo-controlled, Single-center Clinical Trial

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Abstract

Background: Bronchiectasis is a common chronic inflammatory and infectious disease of the airway, which has a high prevalence and frequent acute exacerbations. The treatment approaches for bronchiectasis include mucolytic agents and an immune enhancement strategy, but the latter lacks evidence from randomized controlled trials (RCTs) supporting their efficacy. Spleen Aminopeptide Oral Lyophilized Powder (SAOLP) is a bidirectional immune modulator, mainly composed of a complex of peptides and nucleotides, with an average molecular weight of around 3500. It contains various amino acids and immune regulatory factors, which can trigger and enhance cellular immune function, and promote the immune balance of the body. **Methods:** A randomized, double-blind, placebo-controlled, single-center clinical trial of SAOLP was conducted in patients with non-cystic fibrosis bronchiectasis. The participants received placebo or SAOLP 4mg/d for 3 months and were followed up for 6 months. The primary outcome was a number of acute exacerbations in 6 months. The secondary outcome was the presence of respiratory symptoms at 6 months. Adverse effects were also recorded and analyzed. **Results:** SAOLP decreased the number of acute exacerbations (corrected χ^2 test, $p = 0.038$) and alleviated respiratory symptoms ($p = 0.0141$) in non-cystic fibrosis bronchiectasis compared with placebo. There was no significant increase in adverse events in the SAOLP group ($p > 0.9999$) compared with the placebo group. **Conclusion:** Usage of SAOLP for 3 months may have potential benefits for non-cystic fibrosis bronchiectasis in reducing acute exacerbations and improve respiratory symptoms. More large and multi-center studies are needed to provide more evidence for its clinical use and determine the duration of treatment.

Keywords

Non-cystic fibrosis bronchiectasis; spleen aminopeptide; acute exacerbations; randomized clinical trial; acute exacerbation

Introduction

Bronchiectasis is a chronic inflammatory and infectious disease of the airways, characterized by permanent damage

and widening of the airways, accumulation of excess mucus, and persistent or frequent infections. The prevalence of bronchiectasis is high and still increasing. It was first described by René Laënnec in 1819 [1] and has been called "orphan lung disease" for more than a century because of its heterogeneity with multiple underlying causes [2]. Idiopathic bronchiectasis and post-infection are the two most common causes, while immune deficiency, allergic bronchopulmonary aspergillosis (ABPA), and primary ciliary dyskinesia (PCD) also cause bronchiectasis. The incidence of bronchiectasis is also affected by ethnic and regional factors [3]. A study of from China found that idiopathic bronchiectasis is the most common cause (66%) and pseudomonas aeruginosa was found in 78.2% most of the patients with idiopathic bronchiectasis [4]. Paradigmatic pathogenesis—"vicious circle" theory by Cole in 1984 proposed that "infection-inflammation-enzyme" were the three distinct factors that promote the development of secondary bronchiectasis [5]. Dysregulation of immune defense mechanisms and anti-inflammatory pathways in the lungs eventually leads to abnormal and permanent airway dilatation, which results in a variety of symptoms in the patients, such as chronic cough, productive sputum, and hemoptysis, recurrent infections, and frequent acute exacerbations [6]. Frequent acute exacerbations are the main factors leading to disease deterioration and mortality. A study conducted in 10 European clinical centers found that the more acute exacerbations of bronchiectasis per year during follow-up, the higher the mortality rate [7].

Due to the essential role of dysregulation in immune function in the incidence and development of bronchiectasis, it is of great significance to attach importance to the use of immune modulators in clinical practice. According to their effects on immunity response, immunomodulators can be divided into three classes, immune-enhancer, immune-suppressor, and bidirectional immunomodulator. Immune-enhancer is mainly used as adjuvant treatment of immune deficiency diseases, infectious diseases, and malignancies. Immune-suppressor is mainly used for autoimmune diseases and anti-transplant rejection. Bidirectional immunomodulators maintain homeostasis by regulating immune balance at multiple targets and sites. SAOLP, the lyophilized powder of poly-aminopeptidase and nucleotide substance extracted from fresh pig spleen, is one of the candidate immune modulators. The average molecular weight of SAOLP is about 3500 Dalton, and it contains 16 kinds of amino acids which are a variety of essential trace elements and immune regulatory factors [8]. SAOLP can trigger and enhance cellular immune function and promote the immune balance of the body, and therefore it has potential in the treatment of patients with low cellular immune function, immune deficiency, organ injury and tumor, autoimmune disorders (e.g. recurrent respiratory infections, bronchitis, pneumonia, asthma, etc.) [9-14]. SAOLP prevents pediatric repeated respiratory infection by regulating T lymphocyte subsets and T cell-mediated cellular immunity [15]. In adolescent patients with verruca plana, SAOLP inhibited the secretion of immune factors interleukin-2 (IL-2), and interleukin-4 (IL-4), and relieved the inhibition of IL-4 on lymphocytes and phagocytosis of macrophages [16]. However, clinical evidence of the effects of SAOLP on acute exacerbation in patients with bronchiectasis is lacking. Here we conducted a randomized, double-blind, placebo-controlled, single-center clinical trial to determine if SAOLP can reduce acute exacerbations of non-cystic fibrosis bronchiectasis in Chinese patients.

1. Materials and methods

1.1 Design and setting

This is a randomized, double-blind, placebo-controlled, single-center clinical trial. Patients were randomly cross-assigned to the SAOLP group or placebo group. The participants, physicians, and all the members of the study, were blinded to the drug assignment.

1.2 Ethical issues

The trial was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research. The trial protocol was approved by the Medical Ethics Committee of Zhongshan Hospital, Fudan University (Ethical code: B2017-085). This trial was registered with the Chinese Clinical Trial Registry at http://www.chictr.org.cn (ChiCTR-2300069002). Written informed consent was obtained from each participant or his/her legal guardian.

1.3 Study participants

A total of 72 out-patients diagnosed with non-cystic fibrosis bronchiectasis was were enrolled in the Department of Respiratory and Critical Care Medicine, Zhongshan Hospital, Fudan University. Recruitment started in August 2018 and ended in August 2019.

Patients were eligible for inclusion if they met the following criteria: (1) Male or female aged 18-80; (2) Diagnosed with non-cystic fibrosis bronchiectasis by high-resolution computed tomography (HRCT) and history of clinical manifestations; (3) At least once acute exacerbation with increased sputum volume, sputum color change, fever or hemoptysis during the past year; (4) No respiratory failure in blood gas analysis; (5) Without any other chronic airway diseases, chronic heart failure, tumors, or other life-threatening diseases; (6) Signed and dated the written informed consent; (7) Promise good compliance with the study protocol and were able to understand and complete drug treatment and follow-up.

Patients were excluded if they met any of the following criteria: (1) Experiencing acute exacerbation at the time of enrollment; (2) Pregnancy; (3) Prior history of mental illness that may prevent him/her from compliance with the study protocol; (4) Previously received SAOLP in this or another study; (5) Allergic to any composition of the study drug or placebo; (6) History of chronic alcohol or drug abuse in the past six months; (7) Used immune stimulants or immune compound drugs in the last three months; (8) History of tumors, severe cardiovascular disease, liver/renal insufficiency, active tuberculosis, immune-related diseases (e.g., rheumatoid arthritis and inflammatory bowel disease), allergic bronchopulmonary aspergillosis, and bronchiectasis associated with pulmonary fibrosis within the last three months; (9) Severe chronic respiratory failure requiring long-term non-invasive mechanical ventilation, serious pulmonary heart disease, other serious organ diseases, such as severe coronary heart disease, uncontrolled or poorly controlled hypertension and diabetes.

1.4 Intervention

Excel was used to generate a set of random numbers with serial numbers 1-72, and then the random numbers were arranged in ascending order, with the first 36 for the SAOLP group and the last 36 for the placebo group. Then put the serial number in ascending order. The group assignments were performed in a double-blind manner, in which the study designer arranged and controlled all the trials, and neither the participants nor the investigators were aware of the trial-group assignments. Both groups received standard therapy (such as mucolytics) decided by the attending physicians according to the European Respiratory Society guidelines for the management of adult bronchiectasis [17]. The participants were randomized to a placebo or SAOLP group. The SAOLP group participants received SAOLP (Zhejiang Feng'an Bio-pharmaceutical Co., Ltd., National drug approval number H20068132) 4 mg once a day before bed for 3 months. The placebo was a lyophilized powder of mannitol, which has similar appearance and taste as SAOLP. Patients who were intolerant to SAOLP or showed SAOLP-related adverse events or disease deterioration were withdrawn and treated as appropriate. Patients treated for less than 3 months were only included in the safety analysis.

1.5 Data collection and follow-up processes

Patients' general information, including gender, age, body mass index (BMI), history of allergies, smoking history, other disease conditions, respiratory medications, diagnosis of bronchitis, and acute exacerbations, was recorded at enrollment. The severity of bronchiectasis was assessed using multiple score scales including FACED (FEV1, age, chronic Pseudomonas colonization, extension of disease radiographically, dyspnea), Modified Medical Research Council (mMRC) Dyspnea Scale, COPD (Chronic Obstructive Pulmonary Disease) Assessment Test (CAT), Patients Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorde-7 (GAD-7) [18-21]. Blood routine examination, liver function, kidney function, immunologic function, inflammatory factors, sputum smear, sputum culture, and lung function examination were performed at enrollment. Participants had two follow-up visits at the end of the third (3M) month in the out-patient clinic and at the end of the sixth (6M) month by telephone, respectively. Respiratory and systemic symptoms, signs, and numbers of acute exacerbations since enrollment were recorded. At the two follow-up visits, adverse events (AE) during the study period were recorded. All AEs were recorded by physicians. Serious AEs were reported to study managers within 24 hours and treated as appropriate.

1.6 Outcome measurements

The primary outcome is the percentage of participants who experienced at least one acute exacerbation. The secondary outcome was the percentage of participants with respiratory symptoms.

1.7 Statistical analyses

The sample size and test efficiency were calculated by PASS 2021 software. Thirty-six participants per arm were

required to detect a treatment effect on primary outcome with a power of 80% and a two-sided significance level of 5%. Because the actual dropout rate was higher than the predicted rate, test power was recomputed using binomial enumeration of all possible outcomes. Continuous variables were expressed as mean, SD and were compared by the unpaired t-test between the two groups. Categorical variables were reported as frequencies with percentages and were compared by χ^2 test or Fisher's exact test. Statistical analyses were performed using GraphPad Prism 8.4.2 software. A two-sided *p-value* < 0.05 was considered statistically significant.

2. Results

2.1 Participants characteristics

Figure 1 shows the flowchart of the study. A total of 72 patients were screened and 10 of them were excluded according to exclusion criteria. Of the remaining 62 subjects, 33 were randomly assigned to the placebo group and 29 to the SAOLP group. In the subsequent six months, six in the placebo group and eight in the SAOLP group lost follow-up due to lost of contact to participants. Finally, 27 participants in the placebo group and 21 in the SAOLP group were included in the final analysis. Participants treated for less than 3 months were included in the safety assessment. Table 1 shows the baseline demographic and clinical characteristics of participants (27 in the placebo group and 21 in the SAOLP group). There were no significant differences in baseline characteristics between the two groups. The mean number of acute exacerbations during the past year was 4.22 in the placebo group and 4.14 in the SAOLP group.

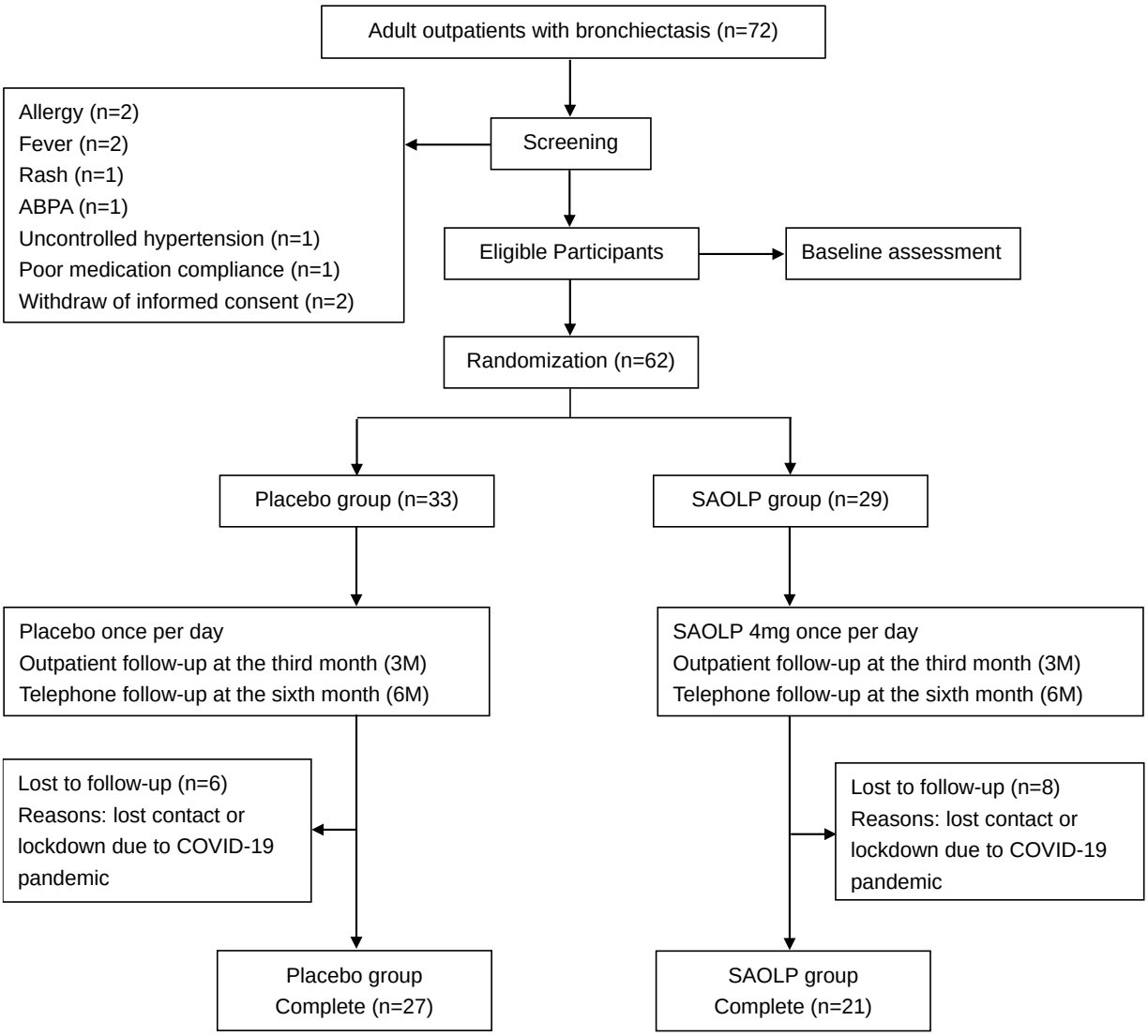

Figure 1. Study flow diagram.

Table 1. Baseline demographic and clinical characteristics of participants between placebo and SAOLP groups

Characteristics	Placebo group	SAOLP group	*p*
Participants, n	27	21	
Age, years, mean (SD)	59.41 (15.08)	56.43 (16.82)	0.5217
Gender			
Male, n (%)	10 (37.04)	4 (19.05)	0.2135
Female, n (%)	17 (62.96)	17 (80.95)	
BMI, kg/m^2, mean (SD)	20.69 (3.55)	21.57 (3.96)	0.4195
Family history, n (%)	6 (22.22)	4 (19.05)	>0.9999
Comorbidities			
Rash, n (%)	2 (7.41)	2 (9.52)	>0.9999
Nasosinusitis, n (%)	3 (11.11)	3 (14.29)	>0.9999
Tuberculosis, n (%)	1 (3.70)	4 (19.05)	0.1534
Hypertension, n (%)	4 (14.81)	4 (19.05)	0.7155
Number of acute exacerbations during the past year, mean (SD)	4.22 (3.54)	4.14 (3.52)	0.9389
Laboratory findings			
Pseudomonas aeruginosa in sputum culture, n (%)	8 (29.63)	4 (19.05)	0.5101
Peripheral lymphocyte (%), mean (SD)	32.54 (9.78)	28.74 (6.86)	0.1375
TNF (pg/ml), mean (SD)	7.56 (2.75)	8.24 (4.21)	0.5053
IL-8 (pg/ml), mean (SD)	9.11 (6.86)	7.00 (2.81)	0.1919
Pulmonary function test			
FEV1 pred (%), mean (SD)	67.94(25.23)	66.30 (23.25)	0.8179
FEV1/FVC (%), mean (SD)	65.54 (11.85)	68.59 (13.28)	0.4103
Severity indexes			
FACED score, mean (SD)	2.59 (1.61)	2.87 (1.64)	0.5603
mMRC score, mean (SD)	1.83 (0.95)	2.11 (0.89)	0.2947
CAT score, mean (SD)	17.52 (9.60)	19.25 (6.13)	0.4757
PHQ-9 score, mean (SD)	6.48 (6.62)	6.20 (3.80)	0.8636
GAD-7 score, mean (SD)	4.69 (5.40)	4.25 (4.69)	0.7671

BMI, body mass index; TNF, tumor necrosis factor; IL, interleukin; FEV1 pred, forced expiratory volume in first second; FVC, forced vital capacity; FACED score, Forced expiratory volume in 1 s (FEV1), Age, Chronic colonization, Extension, and Dyspnea score; mMRC score, modified medical research council score; CAT, COPD Assessment Test; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7.

2.2 Acute exacerbations

The primary outcome of the trial is the percentage of participants who experienced at least once acute exacerbation. As shown inclusion criteria, all participants had at least one acute exacerbation in the past year. Acute exacerbations occurred at least once in 6 patients in the placebo group and 1 patient in the SAOLP group at 3M follow-up. Seven patients in the placebo group had acute exacerbations at 6M follow-up, compared with 1 patient in the SAOLP group. The percentage of participants who had at least one acute exacerbation during the sixth-month intervention was significantly lower in the SAOLP group than in the placebo group (corrected χ^2 test, $p = 0.038$, Table 2).

Table 2. Comparison of the number of participants with ≥1 acute exacerbation between the placebo group and SAOLP group

	Placebo group (n=27)	SAOLP group (n=21)	*p**
3-month follow-up			
Number of patients with ≥1 exacerbation, n(%)	6 (22.2)	1 (4.8)	0.072
Non-exacerbation, n (%)	21(87.8)	20(95.2)	
6-month follow-up			
Number of patients with ≥1 exacerbation, n(%)	7 (25.93)	1 (0.00)	0.038
Non-exacerbation, n (%)	20 (74.07)	20(100.00)	

* Corrected χ^2 test.

2.3 Respiratory symptoms

The secondary outcome was the percentage of participants with respiratory symptoms. More subjects in the SAOLP group had improvement in symptoms than those in the placebo group (Figure 2). Sputum color was classified as white or colored (e.g., yellow, green, and yellow-green), where colored sputum generally indicates that the patient was experiencing bacterial infections. At enrollment, the percentage of colored sputum was 18/21 (85.71%) in the SAOLP group and 22/27 (81.48%) in the placebo group. After medical treatment, removing subjects without phlegm, the percentage of colored sputum in the SAOLP group was lower than that in the placebo group, 15/20 (75.00%) vs 24/26 (92.31%) in the third month, and 14/19 (73.68%) vs 23/26 (88.46%) in the sixth month (Figure 2A).

Most patients with branch enlargement have difficulty in sputum drainage. Therefore, it is also an important clinical problem to reduce the viscosity of sputum and make it easy to cough up. At enrollment, the distribution of purulent, mucopurulent, and mucus sputum was similar in the two intervention groups. At 6M follow-up, the percentage of mucus sputum in the SAOLP group was higher than that in the placebo group, 15/19 (78.95%) vs 10/26 (38.46%), and the difference between the two groups was statistically significant ($p = 0.0141$) (Figure 2B).

Hemoptysis is an indication of deterioration of bronchiectasis. At enrollment, the percentage of hemoptysis was slightly higher in the SAOLP group (11/21,52.3%) than in the placebo group (12/27, 44.4%). At 3M and 6M follow-up, hemoptysis was reduced both in the two groups. Specifically, none of the patients in the SAOLP group had hemoptysis, while the percentage of patients with hemoptysis in the placebo group was 11.1% and 7.4% at the 3M and 6M follow-up (Figure 2C). The symptom improvement rate was 100% and 83.3% for SAOLP and placebo groups, respectively. These data suggested that SAOLP can relieve respiratory symptoms to some extent, especially in reducing the viscosity of sputum.

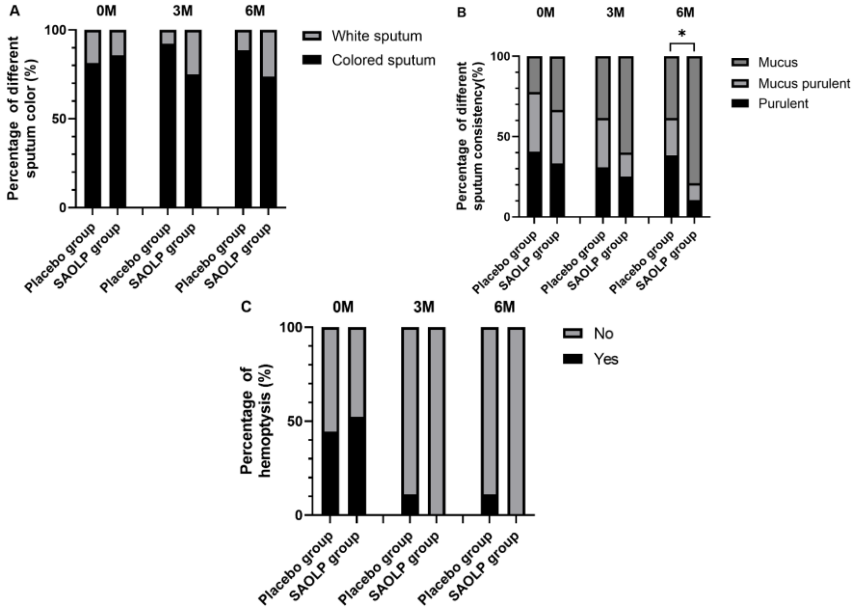

Figure 2. Comparison of the percentage of patients with different respiratory symptoms in placebo and SAOLP groups in the third month (3M) and the sixth month (6M), including sputum color (A), sputum consistency (B), and hemoptysis (C).

2.4 Drug safety evaluation

There were no significant differences in AEs among patients in the placebo and SAOLP groups, 3/36 (8.33%) vs 4/36 (11.11%) ($p > 0.9999$). In the placebo group, allergic reactions occurred in two participants, and stomachaches in one patient. In the SAOLP group, fever was seen in two patients (9.52%), rash in one patient (4.76%), and hypertension in one patient (4.76%). Among their adverse events, fever, and hypertension were considered not to be associated with the trial drug. After drug withdrawal in this patient, he/she recovered well from adverse reactions.

3. Discussion

This study was designed to evaluate the efficacy and safety of SAOLP in reducing acute exacerbation and alleviating respiratory symptoms in patients with non-cystic fibrosis bronchiectasis. Exacerbations and chronic respiratory symptoms including purulent sputum and hemoptysis were the main causes of disease burden for patients with bronchiectasis. Preventing exacerbations is of great importance in these patients because frequent exacerbations promote a detrimental disease course and higher mortality [22]. SAOLP or placebo was used for the first 3 months and the follow-up continued for the subsequent 3 months. The results showed that the treatment of SAOLP reduced the percentage of patients who experienced at least one acute exacerbation during a 6-month follow-up. It suggested that SAOLP may have maintained a therapeutic effect for at least 3 months. The sustained benefits were also determined in the assessment of respiratory symptoms. Colored sputum, purulent sputum, and hemoptysis were also improved in the SAOLP group compared with the placebo group. These results indicate that the addition of SAOLP treatment may benefit patients with frequent exacerbations of bronchiectasis by reducing exacerbations and also alleviating major symptoms. In addition, there was no significant increase in the frequency of adverse events in patients treated with SAOLP compared to those receiving a placebo.

SAOLP is a complex powder extracted from the spleen of a pig, which contains polypeptides and nucleotides. A previous study has shown the addition of SAOLP to recombinant human interferon α-2b ointment reduced peripheral CD8+ T cells and the level of IL-4 in patients with verruca plana [23]. In another study, SAOLP enhanced antiviral immunity in children with cytomegalovirus infection when combined with ganciclovir [24]. In addition, it has been reported that SAOLP combined with vitamins A and E was beneficial in the treatment of recurrent respiratory tract infections in children [10]. These studies indicated the potential effects of SAOLP in immunity modulation. Bronchiectasis exacerbations are associated with bacterial and viral pathogens and dysregulated host immune responses, where modulation of the inflammatory response should be part of the integrated clinical treatment [25]. In our study, the results showed that the patients with frequent exacerbations of bronchiectasis may benefit from SAOLP treatment due to the reduced exacerbations and symptoms, which suggests the efficacy of SAOLP as a supplementary treatment for this patient population.

In recent years, immunoregulators that have been proven to be used for the treatment of bronchiectasis include macrolide antibiotics (erythromycin, clarithromycin, roxithromycin, azithromycin), synthetic peptides (thymosin), vaccines (influenza vaccine, pneumococcal vaccine) and bacterial lysate (broncho-vacom). In a randomized, double-blind, placebo-controlled trial, 83 patients with bronchiectasis were assigned to receive 250mg of azithromycin or placebo orally once daily for 12 months. This study confirmed that azithromycin reduced the number of acute exacerbations of bronchiectasis. It also found that low-dose azithromycin improved FEV1 and FVC and quality-of-life scores in patients with bronchiectasis [26]. The immunomodulatory effect of azithromycin may be related to the following factors: (1) inhibition of IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α; (2) reeducation of nuclear factor κB (NF-κB) by regulating the expression of TLR4; (3) inhibition of airway mucus secretion [27, 28]. We hypothesized that SAOLP might act as an immunomodulatory agent through a similar mechanism. Moreover, we found that SAOLP helped patients to eliminate sputum easily.

There are several limitations to this study. First, this was a single-center study with a small sample size which resulted in limited diversity and quantity of enrolled participants. Second, the duration of follow-up was six months, thus the confounding factors such as climate, temperature, and humidity of different seasons cannot be ruled out. Finally, discontinuation of medication due to voluntary withdrawal and adverse events, and loss of follow-up due to contact phone changes and COVID-19 outbreak may also affect the final analysis. Multi-center, large-sample, longer-term follow-up studies are required to confirm the safety and efficacy of SAOLP in patients with non-cystic fibrosis bronchiectasis in the future.

4. Conclusions

In this double-blind, placebo-controlled, single-center RCT, the addition of SAOLP to standard, guideline-adherent treatment showed statistically significant improvement in reduction of the risk of acute exacerbation in patients with non-cystic fibrosis bronchiectasis and frequent exacerbations in the past year. It also alleviated respiratory symptoms such as colored sputum, purulent sputum, and hemoptysis. There was no significant increase in the frequency of adverse events in the SAOLP group. SAOLP may be an alternative drug for treating non-cystic fibrosis bronchiectasis with frequent exacerbations.

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Authorship

All authors contributed to the study's conception, design, and implementation. Material preparation, patient enrollment, and data collection was performed by LZ, and ZL. Data analysis was performed by ML and DH. The manuscript was written by ML and DH. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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