Combined inhaled corticosteroid and long-acting β2-adrenergic agonist therapy for noncystic fibrosis bronchiectasis with airflow limitation

An observational study

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Abstract

Background and objective: There is presently no clear evidence on the effect of combined treatment for non-cystic fibrosis (non-CF) bronchiectasis with inhaled corticosteroid (ICS) and long-acting β2-adrenergic agonist (LABA). The objective of this study is to assess the efficacy and safety of salmeterol-fluticasone combined inhaled therapy for non-CF bronchiectasis with airflow limitation.

Methods: An observational study was performed in 120 non-CF bronchiectasis patients diagnosed by high-resolution computed tomography (HRCT) scanning of the chest. Patients received either routine therapy or salmeterol-fluticasone (100/500 μg daily).

This work was financially supported by the National Science Foundation of China (NSFC81370103); Programs from STCSM (134119a6400), and Innovation Program of Shanghai Municipal Education Commission (13SG22), which did not play any role in the study design, literature search, study selection, collection and analysis of data, interpretation of results, or drafting of the manuscript.

Supplemental Digital Content is available for this article.

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Medicine (2016) 95:42(e5116)

Received: 4 June 2016 / Received in final form: 8 September 2016 / Accepted: 18 September 2016

http://dx.doi.org/10.1097/MD.0000000000005116
combined inhaled therapy on the basis of routine therapy. Clinical symptoms, health-related quality of life (HRQL), lung function, short-acting β2-adrenergic agonist (SABA) use, and safety were monitored throughout the study.

**Results:** Of the 120 subjects, 60 received combined inhaled therapy and 60 received routine therapy. Compared to the control group, the combined inhaled therapy group showed significant improvement in their clinical symptom scores (−2.21 vs. −0.31, *P* = 0.002) and a reduction in number of weekly SABA usage (−4.2 vs. 0.1, *P* < 0.01). In addition, patients in the inhaled therapy group achieved a significant improvement in HRQL based on mMRC (−1.51 vs. −0.31, *P* < 0.005) and SGRQ (−7.83 vs. −2.16, *P* < 0.01) scoring accompanied with no severe adverse events. There were fewer exacerbation frequencies in the combined inhaled therapy group over the 12 months of treatment compared to the control group (1 [0–2] vs. 2 [1–4], *P* = 0.017). Furthermore, stratified analysis indicated that combined inhaled therapy partially improve lung function for patients for whom it is severely impaired and those with pseudomonas aeruginosa isolated.

**Conclusion:** Our results show that salmeterol-fluticasone combined inhaled therapy should be effective and safe for non-CF bronchiectasis patients especially for those patients with poor lung function or pseudomonas aeruginosa isolated.

**Abbreviations:** COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high-resolution computed tomography, HRQL = health-related quality of life, ICS = inhaled corticosteroid, IL-6 = interleukin-6, IL-8 = interleukin-8, LABA = long-acting β2-adrenergic agonist, mMRC = modified british medical research council, non-CF = non-cystic fibrosis, SABA = short-acting β2-adrenergic agonist, SGRQ = St. George’s Respiratory Questionnaire, TNF-α = tumor necrosis factor-α.

**Keywords:** inhaled, non-CF bronchiectasis, salmeterol-fluticasone, therapy

1. Introduction

Bronchiectasis is a bronchial and bronchiolar condition in which the airways are irreversibly dilated because of persistent or recurrent infection, airway inflammation, and damage to the mucociliary system.[11–13] Patients typically suffer a persistent cough, chronic sputum expectoration, recurrent pulmonary infection, and a poor health-related quality of life (HRQL).[14,15] Chronic inflammation of the bronchial wall renders mucosal cilia clearance dysfunction, leading to long-term bacteria colonization or infection of the airway. This in turn intensified their inflammation, thus forming what is often described as a vicious cycle.[16–17] Both chronic inflammation and infection of the airway are therefore considered the core elements of bronchiectasis.

Inhaled corticosteroid (ICS) and long-acting β2-adrenergic agonist (LABA) have proved obvious benefit for asthma or chronic obstructive pulmonary disease (COPD) patients. They have been definite to improve both the symptoms and HRQL of these patients.[18–20] Attempts have recently been made to apply these therapeutic strategies in daily clinical practice for bronchiectasis patients owing to airway inflammation and hyperresponsiveness as well. Several studies have observed that the use of ICS or bronchodilators can alleviate clinical symptoms (e.g., expectorations and wheezing), reduce sputum volume, the use of ICS or bronchodilators can alleviate clinical symptoms (e.g., expectorations and wheezing), reduce sputum volume,

2. Materials and methods

2.1. Trial design

Our study was an observational study to assess the efficacy and safety of combined inhaled ICS and LABA for non-CF bronchiectasis patients. It took place from June 2011 to June 2012 with 120 patients from Shanghai Pulmonary Hospital divided into 2 groups: the combined inhaled therapy group and the routine therapy group. The principal investigator enrolled participants and clinician assigned participants to interventions.

2.2. Participants

Participants were eligible for this study if they were at least 18 years’ old and had the following: airflow obstruction, which was defined by forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) ratio, FEV1/FVC <70%, in clinically stable phase, which was defined as having stable symptoms not requiring a new therapeutic intervention for at least 2 months precede entry the study; a proven documented diagnosis of bronchiectasis confirmed by HRCT; ≥2 exacerbations requiring systemic antibiotic or hospitalization within the past year; and the ability to complete a lung function test.

Exclusion criteria were as follows: current smokers or former smokers with a cigarette smoking history >10 pack-years; patients undergoing chronic oral steroid treatment; patients who had occupational exposure or definite COPD; cystic fibrosis, or traction bronchiectasis owing to various pulmonary fibrosis, an active pulmonary mycobacterial infection, fungal infection, active sarcoidosis, active allergic bronchopulmonary aspergillosis (ABPA), asthma as defined by the Global Initiative for Asthma (GINA)[18]; patients with severe cardiopulmonary dysfunction; with impaired hepatic or kidney function; with hypogammaglobulinemia or other autoimmune diseases; pregnant or breast-feeding women; or patients with a known intolerance for ICS or LABAs.

The study was approved by the ethics committee of Shanghai Pulmonary Hospital, Tongji University School of Medicine; written informed consent was obtained from all of participating patients, and all aspects of the study were performed in accordance with relevant guidelines and regulations.

2.3. Intervention

The inhaled therapy group received salmeterol-fluticasone (Seretide 250, GlaxoSmithKline) combined inhaled therapy twice daily on the basis of routine therapy, and the control
group received routine therapy consisting of oxygen uptake, phlegm dissipation, hemostasis postural drainage, and naturopathy. Sporadic treatment with short-acting β2-adrenergic agonist (SABA) was permitted. An exacerbation was defined as an acute deterioration in the patient’s condition requiring systemic antibiotics or hospital admission or emergency department visit. Patients who experienced an exacerbation during the study were reviewed by the study doctor to receive antibiotics or other therapy. While regular study treatment continued, all patients received the training in inhaler device use before entering the study, and were asked to bring their inhaler devices to all medical appointments to ensure correct inhalation technique and monitor compliance to their treatment. In addition, any adverse effects on inhaled therapy were strictly monitored, particularly side effects from corticosteroid use. During the entire study period, patients were permitted to directly contact the clinician over any problems derived from the study.

2.4. Outcomes

All patients underwent review at baseline entry to the study and at months 6 and 12 of treatment. Each review consists of the following assessments: clinical symptoms (cough frequency, daily sputum volume, and hemoptysis) (see Table, Supplemental Content 1, http://links.lww.com/MD/B338); HRQL, based on their dyspnea rating under the modified British medical research council (mMRC dyspnea scale) and their score on St. George’s Respiratory Questionnaire (SGRQ), self-administered quality of life measure validated for use in bronchiectasis patients, with a higher score indicating a poorer HRQL; a lung function test was performed, and FEV1, FEV1% predicted, FVC, FVC% predicted, and FEV1/FVC ratio were measured according to standardized guidelines, with the highest of 3 satisfactory measurements recorded for each patient, the amount of the SABA used in each week was recorded. Sputum specimens were collected from all patients for microbial cultures at baseline and again at month 12; exacerbations in the year preceding entry into the study and during the study period were reviewed by the investigators.

2.5. Statistical analysis

The statistical package SPSS, version 19.0 (SPSS Inc, Chicago, IL), was used for the statistical analysis. Data are presented as mean and standard deviation for quantitative variables and absolute numbers and percentages for qualitative variables. Only patients who completed the study were included in the final analysis. Student t test was used to analyze normally distributed variables and the Mann–Whitney U test was used to analyze nonnormally distributed variables. Qualitative variables were compared using the chi-square test. A 2-tailed P value of <0.05 was considered statistically significant.

3. Results

3.1. Patients

Of 125 patients initially screened, 120 patients took part in the study, with 60 received routine therapy and inhaled therapy, and the other 60 received routine therapy. The inhaled therapy group had 2 withdrawals owing to failure to return. The control group had 3 withdrawals, 2 of whom did not commit to the study reviews, and a third who suffered a severe exacerbation. There were no deaths during the study. In total, 115 patients completed the study, with 58 in the inhaled therapy group and 57 in the control group (Fig. 1). The baseline characteristics for each group in the analysis, including disease course, clinical symptoms, pulmonary function, and comorbidities, are shown in Table 1. There were no statistically significant differences between 2 groups.

3.2. Clinical symptoms and HRQL assessments

At baseline, there were no significant differences in clinical symptom score (See Table, Supplemental Content 1, http://links.lww.com/MD/B338), mMRC score, and SGRQ score between the 2 groups. At the end of 12 months’ treatment, patients receiving combined inhaled therapy showed significant improvement in their symptom scores (−3.21 vs. −2.31, P = 0.002) and a reduction in number of weekly SABA usage (−2.16 vs. −0.1, P < 0.01) compared to the control group. In addition, patients in the combined inhaled therapy group achieved a significant improvement in HRQL based on mMRC (−1.51 vs. −0.31, P < 0.005) and SGRQ (−7.83 vs. −2.16, P < 0.01) scoring. Furthermore, the inhaled therapy group showed significant improvement in both clinical symptoms and HRQL throughout the treatment, whereas control group seemed to have no improvement. Figure 2 shows the changes in clinical parameters for both groups at each of the study time points.

3.3. Pulmonary function test

There was no observed effect on FEV1, FEV1% predicted, or FEV1/FVC in either the combined inhaled therapy or control groups. The mean changes in FEV1 from baseline to the end of treatment were similar for both groups (0.03 vs. −0.1, P = 0.041) (See figure, Supplemental Content 2, http://links.lww.com/MD/B338). Stratification analysis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline on lung function hierarchical grouping indicated that lung function improved significantly after 12 months of combined inhaled therapy. In severe lung function subgroup, significant differences were seen between the 2 treatment groups for changes in FEV1 (0.76 vs. −0.1, P = 0.001) (Fig. 3D), although changes in FEV1% predicted and FEV1/FVC remained similar between the 2 groups (Fig. 3E and F). There was no significant improvement in lung function for patients in moderate subgroup (Fig. 3A–C). Further study found that among patients with *Pseudomonas aeruginosa* isolated, FEV1 and FEV1% predicted showed slight increases in

![Flow diagram of the study. Two groups in the figure 1 should be: 60 received inhalation therapy and routine therapy; 60 received routine therapy only.](http://links.lww.com/MD/B338)
the inhaled therapy group and declined slightly in control group, although the observed difference was not considered striking. As the mean change of FEV1/FVC was more distinct in the combined inhaled therapy group than in the control group (2.4 vs. 2.03, respectively, \( P = 0.02 \)) (See figure, Supplemental Content 3, http://links.lww.com/MD/B338). Therefore, long-term combined inhaled therapy may induce delayed pulmonary function decline for bronchiectasis patients with poor pulmonary function or patients with \( P aeruginosa \) isolated.

### 3.4. Exacerbations

A total of 33 patients (56.9%) in the combined inhaled therapy group had exacerbations during the 12 months of treatment,

| Parameters          | All patients (N=120) | Salmeterol-Fluticasone Group (n=60) | Control group (n=60) | \( P \)  |
|---------------------|-----------------------|-------------------------------------|----------------------|--------|
| Age, y              | 55.34±10.54           | 53.95±10.22                         | 56.77±10.86          | 0.146  |
| Female (%)          | 79 (68.70)            | 38 (63.33)                          | 41 (68.33)           | 0.564  |
| Disease course, y   | 20.65±5.57            | 21.12±5.86                          | 20.18±5.26           | 0.357  |
| Smoking, pack-y     | 5.38±2.11             | 5.74±2.23                           | 5.01±1.98            | 0.06   |
| Clinical symptom score | 8.42±3.28            | 8.23±3.12                           | 8.62±3.45            | 0.517  |
| Lung segment involved | 3.5±1.5              | 3.4±1.8                             | 3.6±1.2              | 0.475  |
| mMRC score          | 3.92±1.35             | 3.87±1.45                           | 3.98±1.23            | 0.655  |
| SGRO total          | 42.84±10.08           | 43.24±10.34                         | 42.45±9.8            | 0.668  |
| Exacerbation        | 3 (2.5)               | 3 (2.5)                             | 3 (2.5)              | 0.933  |
| FEV1 (L)            | 1.77±0.60             | 1.79±0.57                           | 1.74±0.62            | 0.138  |
| FEV1 (%)            | 55.29±14.68           | 55.09±14.42                         | 55.50±14.94          | 0.879  |
| FVC (L)             | 2.84±0.9              | 2.85±0.9                            | 2.83±0.89            | 0.537  |
| FVC (%)             | 79.54±15.38           | 79.11±12.44                         | 79.97±18.31          | 0.355  |
| FEV1/FVC (%)        | 61.02±7.38            | 60.66±7.71                          | 61.38±7.04           | 0.594  |

Comorbidities

- Diabetes          | 5 (4.17%)             | 1 (1.67%)                           | 4 (6.67%)            | 0.364  |
- Hypertension       | 7 (5.83%)             | 3 (5%)                              | 4 (6.67%)            | 1.000  |
- Chronic heart disease | 5 (4.17%)          | 2 (3.33%)                           | 3 (5%)               | 1.000  |
- Tumour             | 1 (0.83%)             | 1 (1.67%)                           | 0 (0%)               | 1.000  |

FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, mMRC = modified British Medical Research Council, SGRO = St. George’s Respiratory Questionnaire. Data are represented as the mean ± standard deviation or number (percent) or median (interquartile).

**Figure 2.** Improvement of clinical symptoms and health-related quality of life in two groups throughout the study. * represents intra-group comparison, # represents inter-group comparison, \( ^* P < 0.05, ^{**}P < 0.01; ^{##}P < 0.05, ^{###}P < 0.01 \). S-F = salmeterol-fluticasone.
compared to 48 (84.2%) in the control group \( (P < 0.001) \). All required antibiotic therapy. Thirty-eight patients required hospitalization, including 9 in the inhaled therapy group and 29 in the control group \( (P < 0.001) \). There were fewer exacerbation frequency in the combined inhaled therapy group over the 12 months of treatment compared to the control group \( (1 [0–2] \text{ vs. } 2 [1–4], P = 0.017) \) (Fig. 4A). Furthermore, our results demonstrated that for patients with \( P. aeruginosa \) isolated, the frequency of exacerbations significantly reduced \( (4 [2–6] \text{ vs. } 2 [1–3], P = 0.021) \) in combined inhaled group, whereas the control group was not (Fig. 4B), and that overall exacerbation frequency was more in the \( P. aeruginosa \) subgroup than the other 2 subgroups (See Table, Supplemental Content 4, http://links.lww.com/MD/B338). However, there was no obvious difference in exacerbation frequency between 2 groups for patients with other positive microorganism isolated or negative isolated. These results suggested that inhaled ICS and LABA are more effective to reduce exacerbation for patients with \( P. aeruginosa \) isolated.

### 3.5. Sputum microorganism results

As shown in Table 2, no significant changes were observed in the microorganism isolates of either group throughout the study. At the baseline, the most common separation bacteria were \( P. aeruginosa \), followed by \( K. pneumonia \). After 12 months’ treatment, no significant fungal isolations were seen because of the corticosteroid administered in the inhaled therapy group.

### 3.6. Adverse effects

The patients with adverse effects were few in total \( (15.52\% \text{ vs. } 8.77\%, P = 0.269) \) (Table 3) and no significant differences were observed between the 2 groups. The side effects observed were those commonly associated with inhaled steroids, including oropharyngeal discomfort, dental ulcers and dysphonia, with marginally greater prevalence in the inhaled therapy group. Two patients in each group reported palpitation. Nevertheless, there were no withdrawals owing to adverse effects from either group.

![Figure 3. Changes of pulmonary function in moderate and severe pulmonary function subgroup after treatment. #Represents inter-group comparison, ##P < 0.01. S-F = salmeterol-fluticasone.](image-url)
3.7. Discussion

Bronchiectasis has been no longer regarded as a rare disease, but there is still no authoritative therapy guideline for normative treatment. Most of the treatment is based on the empirical treatment for COPD or asthma. As the similar disease characteristics of COPD, chronic bronchial inflammation in bronchiectasis is characterized by the infiltration of mononuclear cells and neutrophils, whose abundant secretion of elastase and inflammatory factors, including interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α), causes damage to the airflow, resulting in chronic bronchial airflow obstruction and hyperresponsiveness. Corticosteroids play the potential anti-inflammatory effects by reducing inflammatory cell infiltration of the airway, inhibiting the activation of various inflammatory cells and release of inflammatory cytokines and chemokines. As several studies have reported, high-dose ICS treatment is clearly effective for certain clinical symptoms and improves the HRQL of bronchiectasis patients by decreasing the inflammatory parameters in the patient’s bronchial mucosa.

Furthermore, ICS and LABA are known to show a synergistic effect when administered together. ICS has been observed to enhance LABA action by upregulating the amount of beta receptors on the cell surface, whereas LABAs activate glucocorticoid receptors and accelerate their anti-inflammatory effects (e.g., suppressing T-lymphocyte proliferation), alleviating neutrophil chemoattraction and decreasing the concentrations of IL-6, IL-8, TNF-α, all of which are key in the inflammatory cascade observed in bronchiectasis. It is therefore feasible to practice the combined use of ICS and LABA in bronchiectasis patients with airflow limitation. We excluded patients with cystic fibrosis in this study because it is very rare in the Chinese population.

According to our research, combined inhaled therapy resulted in a significant improvement in our patients’ clinical symptoms and HRQL, as measured by their clinical symptom score, mMRC score, and SGRQ score. In addition, there was a distinct reduction of SABA used per week compared to the control group. As other authors have reported, combined inhaled therapy can also better alleviate sputum production, dyspnea, and other symptoms, with resultant improvement to patient’ quality of life.

Moreover, our research observed that combined inhaled therapy did not impact pulmonary function, which is consistent with the findings of previous studies. However, further studies are needed to validate these findings in a larger patient population.

Table 2

| Pathogens       | Control group Before (n=60) | After (n=57) | S-F group Before (n=60) | After (n=58) | P   |
|-----------------|-----------------------------|--------------|-------------------------|--------------|-----|
| P aeruginosa    | 25 (41.7)                   | 23 (40.4)    | 22 (36.7)               | 22 (37.9)    | 0.575|
| K pneumoniae    | 8 (13.3)                    | 7 (12.3)     | 7 (11.7)                | 7 (12.1)     | 0.783|
| E coli          | 3 (5)                       | 3 (5.3)      | 3 (5)                   | 2 (3.45)     | 1.000|
| S aureus        | 2 (3.3)                     | 1 (1.75)     | 3 (5)                   | 2 (3.45)     | 1.000|
| A baumannii     | 0 (0)                       | 0 (0)        | 1 (1.25)                | 1 (1.72)     | 1.000|
| R acinetobacter | 1 (1.25)                    | 1 (1.75)     | 0 (0)                   | 0 (0)        | 1.000|
| S maltophilia   | 1 (1.25)                    | 1 (1.75)     | 0 (0)                   | 0 (0)        | 1.000|
| K oxytoca       | 0 (0)                       | 0 (0)        | 1 (1.25)                | 1 (1.72)     | 1.000|
| Aspergillus     | 0 (0)                       | 0 (0)        | 1 (1.25)                | 1 (1.72)     | 1.000|
| Total           | 40 (66.7)                   | 36 (63.2)    | 38 (63.3)               | 36 (62.1)    | 0.702|

Before means at baseline; after means after 12 months treatment. P value means intergroup comparison. S-F = salmeterol-fluticasone.
with it reported by Martinez-García et al.[17] Although the inhaled therapy group saw some improvement, the control group had a slight decrease. Nevertheless, Mostafapour et al.[16] have reported that using salmeterol-fluticasone significantly improves lung function parameters in bronchiectasis patients. Furthermore, stratification analysis found a significant improvement in FEV1 by inhaled therapy for patients with severe lung function. We are the first to perform population stratification analysis among these studies. Our results indicate that combined inhaled therapy plays potential protection effect against the deterioration of lung function.

During the following treatment, we found that patients suffered significant fewer exacerbations compared with the previous year in the inhaled group than the control group, which differs from previous report.[17] It may be that, our research only previous year in the inhaled group than the control group, which suffered signifcant fewer exacerbations and significant improvement in FEV1/FVC were also observed in inhaled therapy group relative to the control group.

These results further illustrated that for bronchiectasis patients with poor lung function or chronic P. aeruginosa colonization, combined inhaled therapy can delay lung function decline, reduce exacerbations and decrease the burden of the disease.

As we all know, the presence of chronic colonization and/or infection with P. aeruginosa bronchiectasis patients who share a more relevant inflammatory status, a more severe disease, worse clinical, functional characteristics, and worse quality of life and long-term outcomes.[27–29] Those, P. aeruginosa chronic infection, relative severe inflammatory and poor lung function, are interaction and mutual influence, which lead to frequent exacerbations. It seems to be a vicious circle. According to our results, salmeterol-fluticasone combined inhaled therapy showed a better clinical effectiveness and safety profile for non-CF bronchiectasis patients with airflow limitation. For patients with poor lung function or P. aeruginosa chronic infection, it should be a better therapy strategy.

No changes were observed in microbiological profile of patient sputum over 12 months of treatment, especially an absence of any fungus growths may be induced by corticosteroid application. Moreover, few side effects attributable to inhaled steroids, such as oropharyngeal discomfort, dental ulcer, and dysphonia, were present in the inhaled therapy group. There were no withdrawals because of side effects.

A number of limitations exist in this study at present. First, as a single-center observational study, the power of the conclusion is reduced as it lack of blind and placebo control. Second, some score results are derived from patient questionnaire and reviews, making subjective confounding factors inevitable. Third, a few participants in control group used long-acting muscarinic antagonist (LAMA) in a short time during the trial, which may have some influence on outcomes of this trial. Finally, owing to practical difficulties, some significant parameters such as the changes of cytokines in the sputum and the duration to the first exacerbation were unfortunately not analyzed.

4. Conclusion

In conclusion, for bronchiectasis patients with varying degrees of airflow limitation, salmeterol-fluticasone combined inhaled therapy can significantly improve clinical symptoms and reduce exacerbation frequencies, without risking severe adverse events.

For patients with severe lung function and or P. aeruginosa colonization, long-term combined inhaled therapy can delay the decline of pulmonary function and may be an ideal strategy for treating these patients.

Acknowledgments

We thank Arthur Zhang for his critical language editing on this manuscript.

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