Efficacy of budesonide/formoterol and tiotropium combination for the treatment of Chinese patients with chronic obstructive pulmonary disease

Jun-fei Feng, MMa, Guo-rong Ding, MMb, Yan-zhong Xie, MMb, Dejun Zhao, MMc,*, Xuehui Wang, MDb,*

Abstract
This study investigated the efficacy and safety of budesonide/formoterol (B/F) and tiotropium combination in the management of chronic obstructive pulmonary disease (COPD) in Chinese patients.

Between January 2015 and November 2017, 113 eligible Chinese patients with COPD were included and divided into an intervention group and a control group. Sixty-three patients in the intervention group underwent B/F combined tiotropium, while 50 patients in the control group received tiotropium alone. The primary outcome was severity of dyspnea on exertion (DOE), measured by the 6-minute walk test (6MWT) scale. The secondary outcomes included lung function, measured by the forced expiratory volume in 1 second (FEV₁), quality of life, measured by the St. George’s Respiratory Questionnaire (SGRQ), and adverse events. All outcomes were measured at the end of 12-week treatment.

B/F and tiotropium combination showed greater efficacy in DOE (P < .01), lung function (P < .01), and quality of life (P < .01), compared with tiotropium alone at the end of 12-week treatment. In addition, adverse events in both groups were similar and tolerable.

The findings suggest that B/F and tiotropium combination can be used as an effective treatment in Chinese patients with COPD.

Abbreviations: 6MWT = 6-minute walk test, B/F = budesonide/formoterol, COPD = chronic obstructive pulmonary disease, DOE = dyspnea on exertion, FEV₁ = forced expiratory volume in 1 second, GOLD = Global Initiative for Chronic Obstructive Lung Disease, LABA = long-acting β2-adrenergic agonist, SGRQ = St. George’s Respiratory Questionnaire.

Keywords: budesonide, chronic obstructive pulmonary disease, efficacy, formoterol, tiotropium

1. Introduction
Chronic obstructive pulmonary disease (COPD) is a common progressing disease, which contributes to the leading cause of morbidity and mortality around the world. It is estimated that 64 million people will suffer from COPD by 2030 according to the reports from World Health Organization. It often brings a significant burden for individuals and society, and is often associated with poor quality of life in many patients.

2. Methods and patients
2.1. Ethics
This study was approved by the Research Ethics Committee of Hangzhou Fuyang Hospital of Traditional Chinese Medicine, The People’s Hospital of Fuyang, and the First Affiliated Hospital of Heilongjiang University of Chinese Medicine. All patients provided written informed consent according to the Declaration of Helsinki.

2.2. Study design
In this retrospective study, 113 Chinese patients with COPD were included between December 2014 and November 2017. They were divided into 2 groups according to the different therapies for COPD.
they received. Of them, 63 subjects underwent B/F combined tiotropium (intervention group), while 50 patients received tiotropium alone (control group). Patients in both groups were treated for a total of 12 weeks.

### 2.3. Eligibility

All patients were confirmed diagnosis as COPD (stage II, III, or IV)\(^4\) without a history of infections or exacerbation of respiratory symptoms. In addition, they all had no signs of edema, ability to walk themselves. However, patients were excluded if they had severe cardiovascular disease, liver and renal failure, thyroid dysfunction, as well as severe mental disorder, which may affect the outcomes evaluation.

### 2.4. Intervention

Patients in both groups received tiotropium 18\(\mu\)g once daily. In addition to the tiotropium, patients in the intervention group also underwent either B/F 160/4.5 mg, twice daily for a total dose of 320/9 mg. All medications were applied for a total of 12 weeks.

### 2.5. Outcome measurements

The primary outcome included severity of dyspnea on exertion (DOE), measured by the 6-minute walk test (6MWT).\(^2\) This tool was a modified 10-point Borg category ratio scale with the higher scores, the more severe breath condition. The secondary outcomes consisted of lung function, measured by the forced expiratory volume in 1 second (FEV\(_1\)),\(^2\) and quality of life, measured by the St. George’s Respiratory Questionnaire (SGRQ).\(^1\) In addition, any adverse events related to the treatments were also recorded. All outcomes were measured at baseline and at the end of 12-week treatment.

### 2.6. Statistical analysis

All data were analyzed by using SAS package (Version 9.1; SAS Institute Inc., Cary, NC). All the categorical data were analyzed by the Pearson Chi-square test or Fisher exact test. All the continuous data were analyzed by the t test or Mann–Whitney rank sum test. Statistical significant was defined as \(P < .05\) (2 sides).

### 3. Results

The patient characteristics at baseline are summarized in Table 1. The 2 groups did not differ significantly in all the characteristics of age, sex, body mass index, smoking status, Brinkman index, Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, GOLD stage, home oxygen therapy, anticholinergic, inhaled corticosteroid, 6MWT scale, and lung function (Table 1).

At the end of 12-week treatment, B/F combined tiotropium showed greater efficacy in enhancing the severity of DOE (\(P < .01\), Table 2), measured by the 6MWT, and lung function (\(P < .01\), Table 2) compared with tiotropium alone. Moreover, B/F combined tiotropium also exhibited significant improvements in quality of life, measured by SGRQ scale, compared with tiotropium alone (\(P < .01\), Table 2).

Adverse events are listed in Table 3. During the period of 12-week treatment, several adverse events were detected among patients in both groups (Table 3). These adverse events included severe COPD, nasopharyngitis, cough, myalgia, and pneumonia. However, no significant differences were found regarding these adverse events between the 2 groups (\(P > .05\), Table 3). No death-related treatment occurred in both groups (Table 3).

### Table 1

| Characteristics                  | Intervention group (n = 63) | Control group (n = 50) | \(P\) |
|---------------------------------|-----------------------------|------------------------|------|
| Mean age, y                     | 64.9 (7.3)                  | 66.2 (7.8)             | .37  |
| Race (Chinese)                  | 63 (100.0%)                 | 50 (100.0%)            | .--  |
| Sex                             |                             |                        |      |
| Male                            | 49 (77.8%)                  | 35 (70.0%)             | .35  |
| Female                          | 14 (22.2%)                  | 15 (30.0%)             | .35  |
| BMI, kg/m\(^2\)                 | 21.8 (3.4)                  | 21.6 (3.7)             | .77  |
| Smoking status, n               |                             |                        |      |
| Smokers                         | 34 (54.0%)                  | 26 (52.0%)             | .84  |
| Nonsmokers                      | 29 (46.0%)                  | 21 (48.0%)             | .84  |
| Brinkman index                  | 1327.5 (547.1)              | 1368.4 (592.6)         | .71  |
| GOLD criteria                   |                             |                        |      |
| II                              | 15 (23.8%)                  | 11 (22.0%)             | .82  |
| III                             | 38 (60.3%)                  | 33 (66.0%)             | .54  |
| IV                              | 10 (15.9%)                  | 6 (12.0%)              | .56  |
| GOLD stage                      | 3.0 (0.7)                   | 2.9 (0.8)              | .49  |
| Home oxygen therapy             | 18 (58.3%)                  | 16 (50.0%)             | .69  |
| Anticholinergic                 | 36 (83.3%)                  | 33 (88.9%)             | .34  |
| Inhaled corticosteroid          | 15 (52.8%)                  | 13 (58.3%)             | .79  |
| 6MWT scale                      | 4.7 (2.2)                   | 4.9 (2.4)              | .65  |
| Pulmonary function              |                             |                        |      |
| FVC, L                          | 2.8 (0.8)                   | 2.7 (0.9)              | .54  |
| FEV\(_1\), % predicted          | 45.1 (16.9)                 | 44.3 (17.1)            | .80  |

\(BMI=\) body mass index; 6MWT = 6-minute walk test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV\(_1\) = forced expiratory volume in 1 s; FVC = forced vital capacity.

### Table 2

| Outcome measurements     | Intervention group (n = 63) | Control group (n = 50) | Difference | \(P\) |
|---------------------------|----------------------------|------------------------|------------|------|
| 6MWT scale                | -4.1 (5.4, -1.9)           | -1.9 (-3.2, -1.1)      | -2.2 (-3.0, -1.4) | <.01 |
| FVC, L                    | 0.19 (0.11, 0.26)          | 0.06 (0.01 0.10)       | 0.14 (0.05, 0.22) | <.01 |
| FEV\(_1\), % predicted    | 3.4 (1.1, 4.7)             | 1.2 (0.4, 2.1)         | 2.2 (1.3, 3.1) | <.01 |
| SGRQ score                |                             |                        |            |      |
| Total                     | -14.9 (-20.2, -8.3)        | -6.1 (-9.9, -2.7)      | -8.8 (-11.2, -6.5) | <.01 |
| Symptom                   | -22.6 (-30.4, -13.7)       | -10.3 (-19.6, -3.4)    | -12.4 (-18.9, -5.3) | <.01 |
| Activity                  | -13.3 (-20.6, -4.5)        | -4.2 (-9.4, -0.9)      | -9.1 (-16.6, -4.2) | <.01 |
| Impact                    | -12.8 (-19.5, -5.9)        | -4.7 (-8.1, -1.0)      | -8.2 (-13.3, -5.4) | <.01 |

6MWT = 6-minute walk test, FEV\(_1\) = forced expiratory volume in 1 s, FVC = forced vital capacity, SGRQ score = St George Respiratory Questionnaire Scores.
that tiotropium can improve the clinical symptoms of COPD and a long duration of action.\(^{[25]}\) The clinical evidence proved anticholinergic drug with a dissociation half-life of up to 24 hours contrary, tiotropium bromide is a new type of long-acting alone, and were consistent with the results of previous studies.\(^{[26]}\) On the reported to have a good coordination effect.\(^{[23,24]}\) Thus, the combination of both medications is selective effect.\(^{[23,24]}\) Thus, the combination of both medications is

5. Conclusion

The results of this retrospective study demonstrated that B/F combined tiotropium can either enhance DOE and lung function, and improve quality of life in Chinese patients with COPD.

Author contributions

Conceptualization: Dejun Zhao, Jun-fei Feng, Xue-hui Wang, Guo-rong Ding.

Data curation: Dejun Zhao, Jun-fei Feng, Xue-hui Wang, Guo-rong Ding.

Formal analysis: Xue-hui Wang.

Investigation: Xue-hui Wang.

Methodology: Xue-hui Wang.

Project administration: Jun-fei Feng, Yan-zhong Xie.

Resources: Dejun Zhao, Jun-fei Feng, Yan-zhong Xie.

Software: Yan-zhong Xie.

Supervision: Yan-zhong Xie.

Validation: Dejun Zhao, Guo-rong Ding.

Visualization: Guo-rong Ding.

Writing – original draft: Dejun Zhao, Jun-fei Feng, Xue-hui Wang, Guo-rong Ding, Yan-zhong Xie.

Writing – review & editing: Dejun Zhao, Jun-fei Feng, Xue-hui Wang, Guo-rong Ding, Yan-zhong Xie.

References

[1] Cortopassi F, Gurung P, Pinto-Plata V. Chronic obstructive pulmonary disease in elderly patients. Clin Geriatr Med 2017;33:539–52.

[2] Chuang ML, Lin IF, Lee CY. Clinical assessment tests in evaluating patients with chronic obstructive pulmonary disease: a cross-sectional study. Medicine (Baltimore) 2016;95:e5471.

[3] Yin HL, Yin SQ, Lin QY, et al. Prevalence of comorbidities in chronic obstructive pulmonary disease patients: A meta-analysis. Medicine (Baltimore) 2017;96:e6836.

[4] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: Updated 2013. London, UK: Global Initiative for Chronic Obstructive Lung Disease; 2013. Available at: http://www.goldcopd.org. Accessed March 10, 2017.

[5] World Health Organization. World Health Statistics. 2008. Available at: http://www.who.int/gho/publications/world_health_statistics/EN _WHS08_Full.pdf. Accessed June 1, 2017.

[6] Wei X, Shi Z, Cui Y, et al. Impulse oscillometry system as an alternative diagnostic method for chronic obstructive pulmonary disease. Medicine (Baltimore) 2017;96:8543.

[7] Rossi A, Botorace-Petanjek B, Chlou M, et al. Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research: a consensus document from six scientific societies. Int J Chron Obstruct Pulmon Dis 2017;12:2593–610.

[8] Jin J, Yu W, Li X, et al. Factors associated with bronchectasis in patients with moderate-severe chronic obstructive pulmonary disease. Medicine (Baltimore) 2016;95:e4219.

[9] D’Urzo A, Donohue JF, Price D, et al. Dual bronchodilator therapy with aclidinium bromide/formoterol fumarate for chronic obstructive pulmonary disease. Expert Rev Respir Med 2015;9:519–32.

[10] Pelsia G, Muzzio CC, Vatrella A, et al. Pharmacological basis and scientific rationale underlying the targeted use of inhaled corticosteroid/long-acting (2-adrenergic agonist combinations in chronic obstructive pulmonary disease treatment. Expert Opin Pharmacother 2015;16:2009–21.

[11] Horita N, Goto A, Shibata Y, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 2017;2:CD012066.

[12] Rojas-Reyes MX, García Morales OM, Dennis RJ, et al. Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2016;6:CD008532.

[13] Mastrodicasa MA, Drooge CA, Mulhall AM, et al. Long acting muscarinic antagonists for the treatment of chronic obstructive pulmonary disease: a review of current and developing drugs. Expert Opin Investig Drugs 2017;26:161–74.

[14] Global initiative for chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Bethesda, MD: GOLD; 2011.

[15] Ferguson GT, Tashkin DP, Skárby T, et al. Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: the 6-month, randomized RISE (Revealing the Impact of Symptom in reducing Exacerbations in COPD) study. Respir Med 2017;112:31–41.
[16] Lin YH, Liao XN, Fan LL, et al. Long-term treatment with budesonide/formoterol attenuates circulating CRP levels in chronic obstructive pulmonary disease patients of group. PLoS One 2017;12:e0183300.

[17] Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;9:CD009552.

[18] Alvarado-Gonzalez A, Arce L. Tiotropium bromide in chronic obstructive pulmonary disease and bronchial asthma. J Clin Med Res 2015;7:831–9.

[19] Ramadan WH, Kabbara WK, El Khoury GM, et al. Combined bronchodilators (tiotropium plus olodaterol) for patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:2347–56.

[20] Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.

[21] American Thoracic Society Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107–36.

[22] Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St George’s Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321–7.

[23] Won KS, Kook RC, Jin KY, et al. Therapeutic effect of budesonide/formoterol, montelukast and N-acetylcysteine for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Resp Res 2016;17:63.

[24] Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. Chest 2017;151:340–57.

[25] Bühling F, Lieder N, Kühlmann UC, et al. Tiotropium suppresses acetylcholine-induced release of chemotactic mediators in vitro. Respir Med 2007;101:2386–94.

[26] Szafinski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74–81.

[27] Lee SD, Xie CM, Yunus F, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: a randomized, multicentre study in East Asia. Respirology 2016;21:119–27.

[28] Trudo F, Kern DM, Davis JR, et al. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. Int J Chron Obstruct Pulmon Dis 2015;10:2055–66.