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ORIGINAL ARTICLE

A 12-month follow-up study on the preventive effect of oral lansoprazole on acute exacerbation of chronic obstructive pulmonary disease

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Summary

The objective of this study was to evaluate the preventive effects of oral administration of lansoprazole on acute exacerbation of chronic obstructive pulmonary disease (COPD). Patients with COPD in groups C and D in the stable phase were stratified into a group with neither gastroesophageal reflux nor lansoprazole therapy (group A) and a group subjected to oral lansoprazole therapy (group B_1) and a group not subjected to oral lansoprazole therapy (group B_2). The frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) questionnaire, COPD assessment test (CAT) questionnaire, pulmonary function test and the 6-minute walk test were applied; in addition, arterial blood gas, white blood cell (WBC), hs-CRP, liver function and the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in sputum were monitored during follow-up. In the 12-month follow-up period, the frequency of exacerbation in group B_2 was statistically higher than that in groups A and B_1 ($P < 0.05$). After a 3-month follow-up, the score of groups A and B_1 in the FSSG questionnaire was significantly lower than that of group B_2 ($P < 0.05$). After the 1-year follow-up, the CAT score, FEV_1, 6-min walk test, the total number of WBC, hs-CRP, alanine aminotransferase, aspartate aminotransferase, pH of the arterial blood, PaO_2, $PaCO_2$ and the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum were statistically different in group B_2 compared with groups A and B_1 ($P < 0.05$). Oral lansoprazole therapy decreased the frequency of acute exacerbation of COPD by alleviating gastroesophageal reflux and lowering the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum.

Keywords
acute exacerbation, chronic obstructive pulmonary diseases, gastroesophageal reflux, lansoprazole

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic respiratory diseases, with a high incidence, morbidity and mortality. This has been the third major cause of death in the world by 2012. The investigation of 20,245 adults in seven geographical areas of China revealed a COPD prevalence of 8.2% in the population aged

more than 40 years (Zhong *et al.* 2007). The clinical stage of COPD involves an acute exacerbation phase (AECOPD), which refers to the acute exacerbation of dyspnoea, cough, expectoration beyond baseline level, wide variations of symptoms or the need for the adjustment of therapy, as well as a stable COPD phase, which refers to stable or mild cough, expectoration and shortness of breath (Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2013).

It has been found that proton pump inhibitors (PPIs) may have preventive effects on AECOPD because of the relationship between AECOPD and gastroesophageal reflux (GER) (Mokhlesi *et al.* 2001; Casanova *et al.* 2004; Rascon-Aguilar *et al.* 2006; Liang *et al.* 2013), which can be effectively treated with PPIs. Considering that rhinovirus infection is one of the causes of AECOPD, it has been found that lansoprazole can inhibit rhinovirus 14 activity in infected cultured airway epithelial cells by inhibiting the expression of ICAM-1 and the acidification of these cells (Sasaki *et al.* 2005), thereby further decreasing their production of cytokines such as IL-1β, IL-6, IL-8 and TNF-α (Sasaki *et al.* 2005). Therefore, the purpose of this study was to explore whether oral PPI lansoprazole could prevent AECOPD and to investigate its mechanism of action.

Subjects and Methods

Subjects

A total of 175 in patients with AECOPD, including 112 men and 63 women, admitted to the Respiratory Department of Gongli Hospital of Pudong New District in Shanghai were enrolled in the study from May 2013 to May 2014. The age range and median age of the subjects were 62–78 years and 68.5 years respectively. The inclusion criteria involved the compliance with the admission standards of AECOPD established in the guidelines of diagnosis of and treatment for COPD (Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2013). The exclusion criteria were as follows: (i) acute pulmonary embolism, (ii) congestive heart failure, (iii) renal insufficiency, (iv) coma, (v) shock; (vi) inability to complete the lung function test, (vii) inability to complete the frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) questionnaire, (viii) inability to complete the COPD assessment test (CAT) questionnaire; and (ix) diagnosis of mental disorder. All the study subjects signed the informed consent form after approval of the study by the Research Ethics Committee of Gongli Hospital.

All the subjects were stratified according to the score of the FSSG questionnaire, in which gastroesophageal reflux was defined as >8 after the dramatic improvement of their respiratory condition by the treatment of anti-infective agents, spasmolytic agents, anti-asthmatic agents and expectorant before hospital discharge (Shimizu *et al.* 2012).

The subjects without gastroesophageal reflux did not receive lansoprazole therapy (group A, $n = 90$). The subjects with gastroesophageal reflux were stratified into a group treated orally with lansoprazole (Hubei Qianlong pharmaceutical Co., Ltd., Qianjiang, Hubei Province, China) (group B_1, 42 cases, 15 mg, qd) and a group not subjected to lansoprazole therapy (group B_2, 43 cases). All three groups were medicated with an inhaled drug (budesonide/formoterol dry-powder inhalation, 160.0/4.5 μg, two inhalations bid; Astra-Zeneca Co., Ltd., Sodertalje, Sweden) for the treatment of COPD and were monitored once every 3 months for the following 12 months. FSSG questionnaire, CAT questionnaire, pulmonary function test and the 6-minute walk test were applied, and arterial blood gas, the total number of white blood cells (WBC), high-sensitivity C-reactive protein (hs-CRP), liver function and the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum were monitored during follow-up. The frequency of acute exacerbation in the 12-month follow-up period was also recorded. There was no statistical difference in the sex composition and age composition between the three groups evaluated ($P > 0.05$). Eleven patients were lost to follow up in group A, three patients in group B_1 and five patients in group B_2 in the 12-month period. The comparison of demographic data between the three groups is shown in Table 1.

Methods

FSSG questionnaire. This questionnaire (Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease, 2011) is composed of 12 questions, which are scored to indicate the frequency of symptoms, as follows: never = 0, occasionally = 1, sometimes = 2, often = 3and always = 4. The cut-off score for the diagnosis of GER disease (GERD) was defined as 8.

CAT questionnaire. This questionnaire is composed of eight questions on six subjective symptoms – cough, sputum, chest tightness, sleep, energy and mood – and two endurance evaluation parameters – exercise tolerance and influence of daily exercise (Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease, 2011). The CAT score ranged between 0 and 40, in which 0–10 indicated a mild effect, 11–20 indicated a medium effect, 20–30 indicated a severe effect and 30–40 indicated a very severe effect. The higher was the score, the more severe was the illness.

Sputum collection and processing. After gargling, sputum was induced by the inhalation of a hypertonic 3% saline solution, and saliva was discarded; deep sputum discharges were collected into dry sterile beakers, and after the addition of the same volume of 10% dithiothreitol, the samples were rotated in a micro-oscillator at 50 ***g*** at 37°C water-soluble constant temperature oscillation box for 20 min and centrifuged for 5 min at 2,000 ***g***. The supernatant was collected and maintained at −70°C. The levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the

Table 1 Comparison of demographic data in the study groups

	Group A (n = 90)	Group B_1 (n = 42)	Group B_2 (n = 43)
Age(year)	71.2 (65–78)	67.3 (62–77)	66.5 (64–78)
Sex (male/female)	61/29	26/16	25/18
BMI (kg/m^2)	22.2 (18.1–45.2)	23.1 (16.7–39.5)	21.5 (15.2–36.8)
Ex-smoker/smoker	52/38	28/15	29/16
Packs/year	120 (0–400)	130 (0–380)	138 (0–420)
Course of COPD	21.9 (15–34)	23.4 (18–33)	18.7 (20–30)
FEV_1 (ml)	905.6 ± 130.8	915.9 ± 131.9	908.8 ± 124.8
FEV_1/predicted value(%)	40.1 (30.2–48.5)	42.5 (29.2–45.3)	38.2 (32.5–47.6)
FEV_1/FVC(%)	51.7 (28.2–62.1)	50.4 (30.5–58.7)	48.2 (32.3–62.3)
FSSG score	6.2 ± 1.3	12.7 ± 3.6$^{\triangle}$	14.2 ± 4.5$^{\triangle}$
CAT score	28.5 ± 6.6	29.2 ± 8.2	29.6 ± 5.7
6-min walk test	182.5 ± 23.6	185.3 ± 19.8	190.1 ± 25.4

$^{\triangle}$compared with group A, $P < 0.05$.

sputum were assayed using a chemiluminescence immunoassay analysis technique (Immulite automatic analyzer, DPC company, Chicago, USA).

Statistical analysis

q test was adopted for the data comparison between groups. Measurement data were presented in the form of $\bar{x}\pm$ s. Statistical Package for Social Sciences (SPSS) software, version 19.0., was applied in the analysis. $P < 0.05$ indicated significant differences.

Ethical Approval statement

All the subjects signed the informed consent form after the approval of the study by the Research Ethics Committee of Gongli Hospital.

Results

Comparison of multiple observational results between the three groups evaluated in the 12-month follow-up

The results of Table 2 indicate that during the 12-month follow-up, the frequency of acute exacerbation was significantly higher in group B_2 compared with groups A and B_1 ($P < 0.05$), but not significantly different between groups B_1 and A. At enrolment, the FSSG score in groups B_1 and B_2 was significantly higher than that in group A ($P < 0.05$). After 3-, 6-, 9- and 12-month follow-up, the FSSG score was significantly different than that at enrolment in group B_1 ($P < 0.05$), but not in group A ($P > 0.05$). After a 3-month follow-up, the FSSG score was significantly lower in groups A and B_1 compared with group B_2 ($P < 0.05$).

Table 2 Comparison of multiple observational data between the three groups evaluated in the 12-month follow-up ($\bar{x}\pm s$)

Observational data	Frequency of acute exacerbation per year	FSSG score	CAT score	FEV_1 (mL)	6-min walk test (min)
Group A					
At enrolment (n = 90)	2.5 ± 0.6	6.2 ± 1.3	28.5 ± 6.6	905.6 ± 130.8	182.5 ± 23.6
After 3 months (n = 90)		5.5 ± 1.6$^{\triangledown}$	29.1 ± 5.1$^{\triangledown}$	880.5 ± 126.9$^{\triangledown}$	173.3 ± 33.4$^{\triangledown}$
After 6 months (n = 90)		4.8 ± 0.9$^{\triangledown}$	30.2 ± 7.3$^{\triangledown}$	865.7 ± 122.3$^{\triangledown}$	164.4 ± 28.3$^{\triangledown}$
After 9 months (n = 90)		6.7 ± 0.8$^{\triangledown}$	30.9 ± 7.9$^{\triangledown}$	850.2 ± 117.7$^{\triangle}$	168.9 ± 24.9$^{\triangledown}$
After 1 year (n = 79)		7.1 ± 1.2$^{\triangledown}$	31.5 ± 8.4$^{\triangledown}$	845.8 ± 119.5$^{\triangle}$	157.6 ± 21.5$^{\triangledown}$
Group B_1					
At enrolment (n = 42)	3.2 ± 0.8$^{\blacktriangledown}$	12.7 ± 3.6$^{\triangle}$	29.2 ± 8.2$^{\triangledown}$	915.9 ± 131.9$^{\triangledown}$	185.3 ± 19.8$^{\triangledown}$
After 6 months (n = 42)		6.4 ± 1.1$^{\diamond}$	30.5 ± 8.6$^{\blacklozenge}$	883.6 ± 134.9$^{\blacklozenge}$	177.5 ± 20.1$^{\blacklozenge}$
After 9 months (n = 42)		6.2 ± 1.4$^{\diamond}$	31.7 ± 6.9$^{\blacklozenge}$	862.2 ± 119.3$^{\blacklozenge}$	161.3 ± 25.4$^{\blacklozenge}$
After 1 year (n = 39)		4.8 ± 1.0$^{\diamond\star}$	32.6 ± 5.4$^{\blacklozenge\star}$	850.7 ± 120.7$^{\diamond\star}$	150.7 ± 24.7$^{\blacklozenge\star}$
Group B_2					
At enrolment (n = 43)	5.1 ± 1.1$^{\blacktriangle}$	14.2 ± 4.5$^{\triangle\blacklozenge}$	29.6 ± 5.7$^{\triangledown\blacklozenge}$	908.8 ± 124.8$^{\triangledown\blacklozenge}$	190.1 ± 25.4$^{\triangledown\blacklozenge}$
After 3 months (n = 43)		15.3 ± 4.8$^{\blacksquare}$	30.3 ± 6.9$^{\blacksquare}$	875.9 ± 133.6$^{\blacksquare}$	172.4 ± 30.7$^{\blacksquare}$
After 6 months (n = 43)		16.4 ± 5.0$^{\blacksquare}$	34.7 ± 9.9$^{\square}$	852.7 ± 117.8$^{\square}$	154.6 ± 26.1$^{\square}$
After 9 months (n = 43)		13.8 ± 3.4$^{\blacksquare}$	36.2 ± 8.4$^{\square}$	823.6 ± 129.2$^{\square}$	134.4 ± 25.1$^{\square}$
After 1 year (n = 38)		14.5 ± 3.1$^{\blacksquare\star *}$	37.6 ± 9.7$^{\square\star *}$	775.3 ± 107.4$^{\square\star *}$	102.5 ± 24.9$^{\square\star *}$

Compared with group A, $^{\blacktriangle}P < 0.05$, $^{\blacktriangledown}P > 0.05$; compared with group A at enrolment, $^{\triangle}P < 0.05$, $^{\triangledown}P > 0.05$; compared with group B_1 at enrolment, $^{\diamond}P < 0.05$, $^{\blacklozenge}P > 0.05$; compared with group B_2 at enrolment, $^{\square}P < 0.05$, $^{\blacksquare}P > 0.05$; compared with group A after the 1-year follow-up, $^{\star}P < 0.05$, $^{\star}P > 0.05$; compared with group B_1 after the 1-year follow-up, $^{*}P < 0.05$.

The results of the CAT score, FEV_1 and 6-minute walk test were not statistically different between the three study groups at enrolment and after the 3-month follow-up ($P > 0.05$), although the FSSG score in group B_1 significantly decreased after the 3-month follow-up. After the 1-year follow-up, these parameters were significantly different in group B_2 compared with groups A and B_1 ($P < 0.05$), but not significantly different between groups A and B_1 ($P > 0.05$).

Comparison of multiple observational results in blood samples between the three groups evaluated in the 12-month follow-up

Table 3 shows that there was no statistical difference in WBC count, hs-CRP, alanine aminotransferase, aspartate aminotransferase, pH, PaO_2 and $PaCO_2$ between the three groups evaluated at enrolment and after the 3-month follow-up ($P > 0.05$), although the FSSG score in group B_1 significantly decreased in the 3-month follow-up. After the 1-year follow-up, only pH and $PaCO_2$ were significantly different in group B_2 compared with group A or B_1 ($P < 0.05$), but these parameters were not significantly different between groups A and B_1 ($p > 0.05$).

Comparison of multiple observational results in sputum samples between the three groups evaluated in the 12-month follow-up

Table 4 shows that there was no significant difference in the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum between the three groups evaluated at enrolment ($P > 0.05$); however, these levels were significantly different in group B_2 compared with groups A and B_1 both 9 months and 1 year after enrolment ($P < 0.05$), but were not significantly different between groups A and B_1 in the same period ($P > 0.05$).

Table 3 Comparison of multiple observational data in blood samples between the three groups evaluated in the 12-month follow-up ($\bar{x} \pm s$)

Observational data	WBC ($\times 10^9$/L)	hs-CRP (mg/L)	AST (U/L)	ALT (U/L)	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)
Group A							
At enrolment ($n = 90$)	8.5 ± 1.9	5.5 ± 0.8	32.5 ± 7.6	27.5 ± 5.3	7.37 ± 0.56	72.5 ± 11.6	54.5 ± 9.6
After 3 months ($n = 90$)	9.1 ± 2.6$^{\triangledown}$	6.4 ± 1.2$^{\triangledown}$	35.6 ± 8.6$^{\triangledown}$	32.3 ± 8.6$^{\triangledown}$	7.36 ± 0.48$^{\triangledown}$	73.2 ± 13.2$^{\triangledown}$	57.2 ± 10.4$^{\triangledown}$
After 6 months ($n = 90$)	7.5 ± 1.6$^{\triangledown}$	8.5 ± 1.9$^{\triangledown}$	29.3 ± 6.4$^{\triangledown}$	35.3 ± 4.6$^{\triangledown}$	7.38 ± 0.45$^{\triangledown}$	71.3 ± 15.2$^{\triangledown}$	52.2 ± 8.5$^{\triangledown}$
After 9 months ($n = 90$)	6.8 ± 1.7$^{\triangledown}$	7.4 ± 1.1$^{\triangledown}$	38.5 ± 8.6$^{\triangledown}$	28.7 ± 5.6$^{\triangledown}$	7.39 ± 0.48$^{\triangledown}$	69.5 ± 14.3$^{\triangledown}$	49.5 ± 9.2$^{\triangledown}$
After 1 year ($n = 79$)	8.4 ± 2.0$^{\triangledown}$	10.2 ± 2.7$^{\triangledown}$	36.6 ± 5.5$^{\triangledown}$	38.2 ± 6.2$^{\triangledown}$	7.39 ± 0.54$^{\triangledown}$	73.5 ± 11.6$^{\triangledown}$	51.4 ± 7.6$^{\triangledown}$
Group B_1							
At enrolment ($n = 42$)	7.6 ± 1.5$^{\triangledown}$	4.5 ± 0.4$^{\triangledown}$	37.2 ± 8.6$^{\triangledown}$	34.3 ± 4.6$^{\triangledown}$	7.36 ± 0.47$^{\triangledown}$	73.6 ± 14.3$^{\triangledown}$	55.2 ± 10.6$^{\triangledown}$
After 3 months ($n = 42$)	6.3 ± 1.6$^{\blacklozenge}$	6.7 ± 0.9$^{\blacklozenge}$	28.7 ± 6.4$^{\blacklozenge}$	26.6 ± 6.4$^{\blacklozenge}$	7.35 ± 0.56$^{\blacklozenge}$	71.4 ± 14.5$^{\blacklozenge}$	58.5 ± 11.3$^{\blacklozenge}$
After 6 months ($n = 42$)	7.2 ± 0.9$^{\blacklozenge}$	8.2 ± 1.2$^{\blacklozenge}$	33.5 ± 6.9$^{\blacklozenge}$	33.0 ± 6.3$^{\blacklozenge}$	7.38 ± 0.68$^{\blacklozenge}$	72.2 ± 19.4$^{\blacklozenge}$	52.2 ± 8.2$^{\blacklozenge}$
After 9 months ($n = 42$)	8.3 ± 1.3$^{\blacklozenge}$	7.7 ± 1.0$^{\blacklozenge}$	35.3 ± 8.2$^{\blacklozenge}$	27.5 ± 5.6$^{\blacklozenge}$	7.39 ± 0.53$^{\blacklozenge}$	74.3 ± 15.8$^{\blacklozenge}$	50.7 ± 8.4$^{\blacklozenge}$
After 1 year ($n = 39$)	9.2 ± 1.8$^{\blacklozenge\star}$	9.3 ± 1.6$^{\blacklozenge\star}$	41.3 ± 7.6$^{\blacklozenge\star}$	36.2 ± 9.6$^{\blacklozenge\star}$	7.40 ± 0.66$^{\blacklozenge\star}$	70.3 ± 17.4$^{\blacklozenge\star}$	48.3 ± 9.2$^{\blacklozenge\star}$
Group B_2							
At enrolment ($n = 43$)	8.5 ± 1.3$^{\triangledown\blacklozenge}$	6.8 ± 1.2$^{\triangledown\blacklozenge}$	33.3 ± 5.6$^{\triangledown\blacklozenge}$	33.5 ± 9.6$^{\triangledown\blacklozenge}$	7.38 ± 0.59$^{\triangledown\blacklozenge}$	76.3 ± 19.3$^{\triangledown\blacklozenge}$	57.4 ± 14.3$^{\triangledown\blacklozenge}$
After 3 months ($n = 43$)	5.6 ± 1.2$^{\blacksquare}$	5.3 ± 0.7$^{\blacksquare}$	35.2 ± 7.8$^{\blacksquare}$	38.3 ± 7.2$^{\blacksquare}$	7.36 ± 0.59$^{\blacksquare}$	73.8 ± 14.2$^{\blacksquare}$	59.4 ± 8.4$^{\blacksquare}$
After 6 months ($n = 43$)	7.3 ± 1.4$^{\blacksquare}$	8.1 ± 1.6$^{\blacksquare}$	27.4 ± 5.4$^{\blacksquare}$	27.3 ± 4.4$^{\blacksquare}$	7.35 ± 0.90$^{\blacksquare}$	72.0 ± 15.0$^{\blacksquare}$	57.5 ± 10.6$^{\blacksquare}$
After 9 months ($n = 43$)	8.5 ± 1.3$^{\blacksquare}$	9.3 ± 0.6$^{\blacksquare}$	35.4 ± 7.2$^{\blacksquare}$	38.2 ± 8.6$^{\blacksquare}$	7.35 ± 0.67$^{\blacksquare}$	68.3 ± 14.7$^{\blacksquare}$	60.3 ± 13.4$^{\blacksquare}$
After 1 year ($n = 38$)	5.4 ± 0.9$^{\blacksquare\star}$	7.5 ± 1.3$^{\blacksquare\star}$	39.2 ± 8.4$^{\blacksquare\star}$	26.3 ± 5.4$^{\blacksquare\star}$	7.34 ± 0.45$^{\blacksquare\star *}$	65.2 ± 11.4$^{\square\star}$	64.1 ± 15.6$^{\blacksquare\star *}$

AST: aspartate aminotransferase; ALT: alanine aminotransferase; compared with group A at enrolment, $^{\triangle}P < 0.05$, $^{\triangledown}P > 0.05$; compared with group B_1 at enrolment, $^{\diamond}P < 0.05$, $^{\blacklozenge}P > 0.05$; compared with group B_2 at enrolment, $^{\square}P < 0.05$, $^{\blacksquare}P > 0.05$; compared with group A after the 1-year follow-up, $^{*}P < 0.05$, $^{\star}P > 0.05$; compared with group B1 after the 1-year follow-up, $^{*}P < 0.05$.

Table 4 Comparison of multiple observational data in sputum samples between the three groups evaluated in the 12-month follow-up ($\bar{x} \pm s$)

Observational data	IL-1β [lg (pg/mL)]	IL-6 [lg (pg/mL)]	IL-8 [lg (pg/mL)]	TNF-α [lg (pg/mL)]	GM-CSF [lg (pg/mL)]
Group A					
At enrolment (n = 90)	3.58 ± 0.48	2.45 ± 0.32	6.78 ± 0.67	1.98 ± 0.21	4.23 ± 0.88
After 3 months (n = 90)	4.26 ± 0.59$^{\triangledown}$	3.78 ± 0.50$^{\triangledown}$	5.64 ± 0.46$^{\triangledown}$	2.45 ± 0.38$^{\triangledown}$	3.69 ± 0.54$^{\triangledown}$
After 6 months (n = 90)	5.21 ± 0.76$^{\triangledown}$	4.11 ± 0.37$^{\triangledown}$	4.49 ± 0.33$^{\triangledown}$	1.58 ± 0.24$^{\triangledown}$	3.34 ± 0.47$^{\triangledown}$
After 9 months (n = 90)	3.33 ± 0.58$^{\triangledown}$	3.54 ± 0.47$^{\triangledown}$	6.23 ± 0.76$^{\triangledown}$	2.47 ± 0.36$^{\triangledown}$	2.97 ± 0.32$^{\triangledown}$
After 1 year (n = 79)	4.76 ± 0.75$^{\triangledown}$	4.34 ± 0.78$^{\triangledown}$	8.45 ± 0.77$^{\triangledown}$	3.08 ± 0.54$^{\triangledown}$	3.78 ± 0.58$^{\triangledown}$
Group B_1					
At enrolment (n = 42)	3.23 ± 0.33$^{\triangledown}$	2.89 ± 0.45$^{\triangledown}$	7.05 ± 0.69$^{\triangledown}$	2.15 ± 0.36$^{\triangledown}$	3.45 ± 0.56$^{\triangledown}$
After 3 months (n = 42)	2.67 ± 0.54$^{\blacklozenge}$	2.44 ± 0.38$^{\blacklozenge}$	5.56 ± 0.54$^{\blacklozenge}$	1.23 ± 0.27$^{\blacklozenge}$	2.44 ± 0.78$^{\blacklozenge}$
After 6 months (n = 42)	4.15 ± 0.67$^{\blacklozenge}$	2.67 ± 0.47$^{\blacklozenge}$	4.75 ± 0.64$^{\blacklozenge}$	2.47 ± 0.38$^{\blacklozenge}$	2.23 ± 0.65$^{\blacklozenge}$
After 9 months (n = 42)	5.23 ± 0.59$^{\blacklozenge}$	3.57 ± 0.65$^{\blacklozenge}$	3.56 ± 0.55$^{\blacklozenge}$	2.89 ± 0.46$^{\blacklozenge}$	3.16 ± 0.89$^{\blacklozenge}$
After 1 year (n = 39)	5.57 ± 0.69$^{\blacklozenge\bigstar}$	4.15 ± 0.80$^{\blacklozenge\bigstar}$	5.56 ± 0.48$^{\blacklozenge\bigstar}$	3.16 ± 0.57$^{\blacklozenge\bigstar}$	4.67 ± 0.76$^{\blacklozenge\bigstar}$
Group B_2					
At enrolment (n = 43)	4.17 ± 0.48$^{\triangledown\blacklozenge}$	3.05 ± 0.64$^{\triangledown\blacklozenge}$	6.54 ± 0.53$^{\triangledown\blacklozenge}$	2.34 ± 0.43$^{\triangledown\blacklozenge}$	4.13 ± 0.48$^{\triangledown\blacklozenge}$
After 3 months (n = 43)	6.23 ± 0.57$^{\blacksquare}$	3.78 ± 0.58$^{\blacksquare}$	8.22 ± 1.28$^{\blacksquare}$	3.56 ± 0.67$^{\blacksquare}$	6.55 ± 0.68$^{\blacksquare}$
After 6 months (n = 43)	7.26 ± 0.56$^{\blacksquare}$	5.45 ± 0.47$^{\blacksquare}$	10.57 ± 1.98$^{\blacksquare}$	5.45 ± 0.89$^{\blacksquare}$	7.55 ± 0.89$^{\blacksquare}$
After 9 months (n = 43)	8.65 ± 0.64$^{\square}$	7.55 ± 0.69$^{\square}$	12.57 ± 2.64$^{\square}$	7.54 ± 1.63$^{\square}$	9.51 ± 1.26$^{\square}$
After 1 year (n = 38)	11.25 ± 0.87$^{\square *}$*	9.45 ± 1.12$^{\square *}$*	15.68 ± 3.06$^{\square *}$*	10.35 ± 2.67$^{\square *}$*	12.56 ± 2.64$^{\square *}$*

Compared with group A at enrolment, $^{\triangle}P < 0.05$, $^{\triangledown}P > 0.05$; compared with group B_1 at enrolment, $^{\diamond}P < 0.05$, $^{\blacklozenge}P > 0.05$; compared with group B_2 at enrolment, $^{\square}P < 0.05$, $^{\blacksquare}P > 0.05$; compared with group A after the 1-year follow-up, $^{*}P < 0.05$, $^{\bigstar}P > 0.05$; compared with group B_1 after the 1-year follow-up, $*P < 0.05$.

Discussion

The causes of AECOPD include common cold, infections with all kinds of pathogens, air pollution, and improper drug application. GER has been reported to be associated with AECOPD (Mokhlesi *et al.* 2001; Casanova *et al.* 2004; Rascon-Aguilar *et al.* 2006; Liang *et al.* 2013). GER refers to the reflux of contents from the stomach and duodenum to the oesophagus, mouth, throat or even the lower respiratory tract. GERD includes a variety of symptoms caused by content reflux and can be treated with proton pump inhibitors. GER symptom assessment scale (GSAS), reflux disease questionnaire (RDQ), GERD questionnaire (GERDQ) and frequency scale for the symptoms of GERD (FSSG) have been adopted to objectively evaluate the symptoms of GERD because of the importance of subjective symptoms in the diagnosis of GERD (Kusano *et al.* 2004).

COPD is often accompanied by the complications of GER, which in turn can induce acute exacerbation of COPD, leading to an unmanageable condition and a vicious cycle (Wang *et al.* 2004; DeVault & Castell 2005; Garca Rodrguez *et al.* 2008). It has been found that GERD, with an incidence of 28% (39987/141057), is becoming an important cause of hospitalization or emergency admission due to acute exacerbation in patients with COPD (Kim *et al.* 2013). It has also been found that the incidence of GER in patients with COPD is higher than that in normal individuals (Sakae *et al.* 2013); moreover, some drugs prescribed to patients with COPD, such as theophylline and β_2-agonists, can promote the secretion of gastric acid (Sakae *et al.* 2013) or reduce the lower oesophageal sphincter pressure, respectively, thereby aggravating GER (Crowell *et al.* 2001). The possible mechanisms of GER involved in the acute exacerbation or recurrence of COPD include the reflux content, which can be aspirated into the airways and directly stimulate and damage the airway mucosa; acid reflux content, which can stimulate the oesophagus, leading to oesophageal mucosal inflammation, which in turn increases airway responsiveness by the vagus nerve reflex; in this respect, reflux content can directly stimulate vagus nerve receptors in the respiratory tract and thereby increase the tension of tracheal smooth muscles. It has been found that GER is closely associated with airway inflammation, which can be evaluated by assaying inflammatory cytokines such as IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum of patients with COPD (Carpagnano *et al.* 2006; Tangedal *et al.* 2014; Asai *et al.* 2015; Ishikawa *et al.* 2015).

CAT proved to be a comprehensive questionnaire, with good repeatability for the evaluation of clinical symptoms of COPD, and therefore can be effectively used to evaluate disease progression in patients with COPD once every 2 or 3 months. The 2011 GOLD guidelines (Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease, 2011) and the updated version of the 2013 GOLD guidelines (Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2013) recommended the use of this questionnaire to assess clinical symptoms and the influence on the state of life and to predict the risk of death in patients with COPD. Considering the frequency of acute exacerbation in patients with COPD in groups A and B was once or less per year, whereas the frequency in groups C and D was twice or more per year (Global strategy for the diagnosis, management, and prevention of chronic obstruc-

tive lung disease, 2011), patients with COPD in groups C and D were enrolled as the control subjects. The lansoprazole chosen as the antacid drug and previously used in studies conducted overseas is characterized as a PPI, with specific therapeutic effects, little adverse reactions and low cost (Sasaki *et al.* 2011).

Our results showed that the frequency of acute exacerbation in group B_2 was significantly higher than that in groups A and B_1; however, this frequency was not significantly different between groups B_1 and A in the 12-month follow-up. In addition, at enrolment (discharge from hospital), the score of the FSSG questionnaire in groups B_1 and B_2 was significantly higher than that in group A; however, after 3-, 6-, 9- and 12-month follow-up, the score was significantly different from that at enrolment in group B1, but not in groups A and B_2. In groups A and B_1, this score was significantly lower than that in group B_2 after a 3-month follow-up. These results indicate that after 3 months of oral lansoprazole therapy, the reflux symptoms in group B_1 were effectively alleviated along with the decrease in the frequency of acute exacerbation, but this frequency was not statistically different from that in group A in the 12-month follow-up period.

There were no statistical differences in the CAT score, FEV_1, 6-min walk test, WBC count, hs-CRP, alanine aminotransferase, aspartate aminotransferase, pH, PaO_2, $PaCO_2$ and the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum between the three groups at enrolment ($P > 0.05$). Nine months and one year after enrolment, the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum in group B_2 were significantly different from those in groups A and B_1. One year after enrolment, the results of CAT score, FEV_1, 6-minute walk test, pH and $PaCO_2$ were significantly different in group B_2 compared with groups A and B_1, but were not significantly different between groups A and B_1. These results indicate that (i) in the follow-up period, the levels of inflammatory biomarkers IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum of the patients with GER, but without lansoprazole therapy, in group B_2 were significantly higher than those in groups A and B_1, whereas these levels in the patients subjected to lansoprazole therapy in group B_1 were significantly lower than those of group B_2, but similar to those of group A. Similar to the results of a study by Sasaki, we have found that the oral administration of lansoprazole could lower the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum without knowing its specific mechanism, which still needs to be elucidated (Sasaki *et al.* 2011), (ii) one year after enrolment, the results of CAT score, FEV_1, 6-min walk test, pH and $PaCO_2$ were significantly different in group B_2 compared with groups A and B_1, but were not significantly different between groups A and B_1. On the one hand, this indicates that GER can aggravate the symptoms as well as impair lung function, physical health and CO_2 retention; on the other hand, this indicates that antacid therapy can improve symptoms, delay the deterioration of lung function, decrease physical decline and prevent CO_2 retention, (iii) liver damage was not observed in patients with COPD after 1 year of oral lansoprazole therapy.

In conclusion, for COPD patients with GER, oral lansoprazole therapy can prevent acute exacerbation because of its efficacy in inhibiting gastric acid secretion, reduce gastroesophageal reflux and lower the levels of IL-1β, IL-6, IL-8, TNF-α and GM-CSF in the sputum. Moreover, oral lansoprazole therapy is safe. The limitation of this study lies in its small sample size and single-centre mode, which increases the need for multicentre studies with considerably larger sample sizes. The absence of a placebo group is also another imperfection which needs to be remedied in future studies.

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Conflict of Interest

There are no conflicts of interest among all the authors.

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