Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo controlled study

Jin-Ping Zheng, Jian Kang, Shao-Guang Huang, Ping Chen, Wan-Zen Yao, Lan Yang, Chun-Xue Bai, Chang-Zheng Wang, Chen Wang, Bao-Yuan Chen, Yi Shi, Chun-Tao Liu, Ping Chen*, Qiang Li, Zhen-Shan Wang, Yi-Jiang Huang, Zhi-Yang Luo, Fei-Peng Chen, Jian-Zhang Yuan, Ben-Tong Yuan, Hui-Ping Qian, Rong-Chang Zi, Nan-Shan Zhong

Summary

Background Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation, and has many components including mucus hypersecretion, oxidative stress, and airway inflammation. We aimed to assess whether carbocisteine, a mucolytic agent with anti-inflammatory and antioxidative activities, could reduce yearly exacerbation rate and improve quality of life.

Methods We did a randomised, double-blind, placebo-controlled study of 709 patients from 22 centres in China. Participants were eligible if they were diagnosed as having COPD with a postbronchodilator FEV1/FVC of less than 0.7 and an FEV1, between 25% and 79% of the predicted value, were aged between 40 and 80 years, had a history of at least two COPD exacerbations within the previous 2 years, and had remained clinically stable for over 4 weeks before the study. Patients were randomly assigned to receive 1500 mg carbocisteine or placebo per day for a year. The primary endpoint was exacerbation rate, and analysis was by intention to treat. This trial is registered with the Japan Clinical Trials Registry (http://jcmtr.ac.jp/ctri/index/html) number UMIN-CRT C00000233.

Findings 354 patients were assigned to the carbocisteine group and 355 to the placebo group. Numbers of exacerbations per patient per year declined significantly in the carbocisteine group compared with the placebo group (1·008 [SE 0·056] vs 1·348 [SE 0·064], risk ratio 0·755 [95% CI 0·623–0·916, p=0·004]. Insignificant interactions were found between the preventive effects and COPD severity, smoking, as well as concomitant use of inhaled corticosteroids. Carbocisteine was well tolerated. Quality of life was also improved.

Interpretation Mucolytics, such as carbocisteine, should be recognised as a worthwhile treatment for prevention of exacerbations and improving quality of life in Chinese patients with COPD.

Funding Kyorin Pharmaceuticals.

Introduction Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation, and pathophysiology involves many components including mucus hypersecretion, oxidative stress, and inflammation in the airway and lungs. Therefore, agents active with mucolytic, anti-inflammatory, and antioxidative effects could offer promise for treatment.

In Europe and Asia, mucolytics such as carbocisteine have been widely used for treatment of respiratory diseases with phlegm production because of their capacity to facilitate sputum elimination. Furthermore, carbocisteine seems likely to have a role in antioxidation that might be more important than mucolysis itself for long-term management of COPD. Clinical studies have shown benefits in preventing exacerbation of COPD with carbocisteine. However, these results have been inconclusive because of certain pitfalls in study design, such as small sample size, not being double-blinded, lack of placebo control, or short period of study. Poole and Black did a systematic review of mucolytics in COPD, which has been updated with inclusion of the BRONCHUS study using N-acetylcysteine. Their results showed that mucolytics including carbocisteine were effective in reducing the number of exacerbations in COPD and improving health status in all studies except BRONCHUS. Since evidence on long-term efficacy remains insufficient, mucolytics are not recommended for regular treatment by guidelines such as that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Clinical trials that closely follow reliable research study designs are therefore warranted to clarify whether COPD patients can benefit from protracted mucolytic therapy.

The aim of this study was to assess the effectiveness in preventing exacerbation, improving quality of life, as well as the safety profiles of long-term (1-year) carbocisteine administration in patients with COPD.

Methods

Patients Participants were eligible for inclusion if they were diagnosed as having COPD with a postbronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) of less than 0.70 and an


Guangzhou Institute of Respiratory Disease,
First Affiliated Hospital of Guangzhou Medical College,
Guangzhou, China
(Prof J-P Zheng MD, Prof N S Zhong MD); First Affiliated Hospital of China Medical University, Shenyang, China (Prof J Kang MD); Beijing Hospital, Shanghai Jiao Tong University Medical School, Shanghai, China (Prof S G Huang MD); Shenyang PLA General Hospital, Shenyang, China (P Chen MD); Peking University Third Hospital, Beijing, China (Prof W-Y Yao MD); First Affiliated Hospital, Xi’an Jiaotong University, Xi’an, China (Prof Y Yang MD); Zhongshan Hospital, Fudan University, Shanghai, China (Prof C X Bai MD); Xin Qiao Hospital, Chongqing, China (Prof C Z Wang MD); Chao Yang Hospital, Beijing, China (Prof F Wang MD); Tianjin General Hospital, Tianjin, China (B Y Chen MD); Nanjing PLA General Hospital, Nanjing, China (Sh MD); Huaxi Hospital, Chengdu, China (C T Liu MD); Second Xiangya Hospital, Changsha, China (Prof F Chen MD); Shanghai Hospital, Shanghai, China (Q Li MD); Second Affiliated Hospital of Dalian Medical University, Dalian, China (Z S Wang MD); Hainan Province Hospital, Haikou, China (Y J Huang MD); First Municipal Hospital, Foshan, China (Z Y Liu MD); Second Affiliated Hospital of Guangzhou Medical College, Guangzhou, China (F P Chen MD); Red Cross Hospital, Guangzhou, China (J Z Yuan MD); Second Municipal Hospital, Shenzhen, China (B T Yan MD); Xinhai Hospital, Guangzhou, China (H P Qian MD); and Panyu Hospital, Guangzhou, China (K C Zh MD)
FEV₁ between 25% and 79% of predicted value. The severity of COPD was defined in accordance with GOLD criteria. Patients had to be aged between 40 and 80 years, have a history of at least two COPD exacerbations within the previous 2 years, yet have remained clinically stable for over 4 weeks before the study, and have good oral and writing skills. Smoking status was recorded and verified by history; non-smokers were also included in the study.

Patients were excluded if they had a history of physician-diagnosed asthma, non-COPD respiratory disorders, lung volume reduction surgery or transplantation, other conditions likely to interfere with the study, a requirement for long-term oxygen therapy (12 h or more per day) or pulmonary rehabilitation, evidence of alcohol or drug misuse, known or suspected hypersensitivity to the study medication or part of its ingredients, current use of oral corticosteroids, involvement in an investigational drug trial during the previous 12 weeks, or onset of an exacerbation requiring systemic or oral corticosteroid therapy or hospitalisation during the run-in period. Those with a history of severe glaucoma or severe heart, liver, and kidney diseases, or diffuse bilateral bronchiectasis, and those in pregnancy or lactation were also excluded from the study.

Participants were enrolled from 22 medical centres in China, of which 20 were academic hospital-based centres and two were community-based pulmonary clinics; six were located in northern China, four in eastern China, nine in southern China, and three in western China.

The study was approved by local ethics committees and was done in compliance with the Declaration of Helsinki (1996). All patients gave written informed consent.

**Study design**

This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The study protocol was designed by an investigator steering committee and transplanted to all study sites thereafter. All investigators were trained before the trial to ensure reliable study quality, with special emphasis on understanding of the protocol, performing a spirometry test, blinding of allocation, drug management, and compliance with good clinical practice. Beijing Contract Research Organisation (Beijing, China) was exclusively responsible for data management, data analysis, and data quality control.

Randomisation was done using the predetermined computer-generated randomisation list provided by a statistician from the Beijing CRO. The processing of randomisation was stratified by study centres, based on a block size of four, to allow for a balanced number of participants in both groups at a centre level. At each centre, the enrolled participants were allocated in order of their assigned numbers to the carbocisteine group or the placebo group.

Neither the investigator nor the patient knew the group allocation. The placebo was identical to the intervention drug in appearance, labelling and packaging, but did not contain any active ingredients.

Supplies of tablets for every patient were identified with a three-digit number. A sealed envelope that contained the randomisation code for any given patient was kept by the investigator and was not to be broken during the study, except in cases of a serious life-threatening adverse event. Opening of a certain envelope, whether intentional or accidental, had to be carefully recorded on the related case-report form, and the patient had to be withdrawn from the study. The steering committee and the independent party who did the statistics analysis were blocked from all information about treatment allocations during the study.

After a 2-week run-in period, eligible patients with COPD were randomly assigned to receive carbocisteine (2×250 mg, three times daily) or placebo (two tablets, three times daily) for 1 year. Both carbocisteine and placebo tablets were provided by Baiyunshan Pharmaceutical, China. No other medications were provided as part of the study.

After randomisation, patients were interviewed every 3 months until the end of trial to confirm their vital signs, record any unscheduled visits to a health-care provider, check their adherence to the study regimen by collecting and counting the number of remaining tablets, record adverse events, and refill study tablets for the next 3 months.

Conventional treatment for COPD, such as short-acting or long-acting bronchodilators and inhaled corticosteroids, that had been started before the study, was permitted to continue but had to be sustained during the study period. Systemic administrations of corticosteroids, antibiotics,
Outcome measures
The primary endpoint was exacerbation rate over 1 year. Exacerbation defined by Anthonisen\(^7\) was used—ie, at least 2-day persistence of at least two major symptoms (worsening dyspnoea and an increase in sputum purulence, volume, or both), or of any single major symptom plus more than one minor symptom (upper airway infection, unexplained fever, and increased wheezing). Clinical data such as difficulty breathing, the amount and trait of sputum, fever, and presence of upper airway infection were followed-up using a patient diary card, and were reviewed between the patient and his or her attending physician at each interview before final validation as an exacerbation by the steering committee.

Secondary endpoints included covariance-adjusted exacerbation rate, quality of life, lung function and arterial oxygen saturation. Exacerbation rates stratified by months on treatment (3, 6, and 9 months) were also assessed.

Quality of life was assessed by St George’s Respiratory Questionnaire (SGRQ) scores.\(^1\) The patients completed an SGRQ (using a validated Chinese version) before randomisation and at the end of study while they were clinically stable, under the supervision of clinical staff trained on questionnaire administration.

At the start and end of the study, postbronchodilator spirometry was done according to American Thoracic Society recommendations for acceptability and reproducibility.\(^6\) FEV\(_1\) was measured 20 min after inhalation of 400 μg [A: OK?] salbutamol via a spacer. Predicted FEV\(_1\) values were selected from the European Committee of Coal and Steel predictions\(^2\) and adjusted for Chinese ethnicity according to Zheng and Zhong’s recommendation\(^1\) to minimise variations from ethnic differences.

\(\text{SpO}_2\) as measured by finger pulse oximetry was taken at the end of the run-in period and at 6 and 12 months of treatment. Adverse events were reviewed at each study interview.

Statistical analysis
Accurate calculation of sample size had been an issue of great attention when planning the trial, but we were unable to do so because of a scarcity of reference data from previously published studies. Consequently, the sample size was determined on the basis of experiences of Chinese respiratory doctors and by the steering committee. The estimated sample size was deemed to be powered for this study.

All statistical analyses for baseline characteristics and outcomes were done on an intention-to-treat basis. Quantitative baseline characteristics and outcome measures were reported as means (SD) or as percentages within groups. Exacerbation rate was analysed with a negative binomial regression model including interactions between treatment and covariates (such as COPD stages, smoking status, and concomitant medications). If interaction was not significant, the treatment effect was assessed with a regression model adjusted by covariant. Risk ratio and 95% CI in the carbocisteine group versus placebo group were reported.

Log-rank test was used to compare the difference of exacerbation in percentages between groups. SGRQ scores (total, symptom, activity, and impact score) and postbronchodilator FEV\(_1\) were analysed as changes from baseline values with Wilcoxon’s rank-sum test. χ\(^2\) test or

### Table 1: Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Carbocisteine n=353</th>
<th>Placebo n=354</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>273 (77.3%)</td>
<td>282 (79.7%)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>65.40 (9.17)</td>
<td>64.95 (8.58)</td>
</tr>
<tr>
<td>Duration of COPD in years, mean (SD)</td>
<td>8.76 (8.71)</td>
<td>9.61 (9.19)</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>265 (75.1%)</td>
<td>262 (74.0%)</td>
</tr>
<tr>
<td>Baseline spirometry, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>1.07 (0.41)</td>
<td>1.12 (0.43)</td>
</tr>
<tr>
<td>FEV(_1), percentage of predicted value</td>
<td>43.93% (15.40)</td>
<td>45.10% (15.23)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.20 (0.74)</td>
<td>2.28 (0.75)</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>49.61% (12.75)</td>
<td>50.11% (12.57)</td>
</tr>
<tr>
<td>GOLD stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>167 (47.2%)</td>
<td>177 (50.0%)</td>
</tr>
<tr>
<td>III</td>
<td>139 (39.4%)</td>
<td>140 (39.6%)</td>
</tr>
<tr>
<td>IV</td>
<td>47 (13.3%)</td>
<td>37 (11.4%)</td>
</tr>
<tr>
<td>SGRQ total score, mean (SD)</td>
<td>41.57 (19.05)</td>
<td>42.83 (19.34)</td>
</tr>
</tbody>
</table>

Medications for COPD before study
- \(\beta\), agonists: 76 (21.53%) 61 (17.23%)
- Anticholinergic agents: 40 (11.33%) 36 (10.17%)
- Inhaled corticosteroids: 64 (18.13%) 54 (15.25%)
- Xanthines: 113 (30.01%) 95 (26.84%)

Data are number (%) unless otherwise specified. COPD=chronic obstructive pulmonary disease. FEV\(_1\)=forced expiratory volume in 1 second. FVC=forced vital capacity. SGRQ=St George’s Respiratory Questionnaire.

Figure 2: Kaplan-Meier plot of probability of being exacerbation-free at each time point through the study
Risk ratio of exacerbation affected by GOLD-defined COPD severity and treatment with carbocisteine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV/stage II</td>
<td>1·442</td>
<td>1·072–1·938</td>
<td>0·015</td>
</tr>
<tr>
<td>Stage III/stage II</td>
<td>1·245</td>
<td>1·013–1·530</td>
<td>0·037</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbocisteine/placebo</td>
<td>0·736</td>
<td>0·607–0·892</td>
<td>0·002</td>
</tr>
</tbody>
</table>

Table 2: Risk ratio of exacerbation affected by GOLD-defined COPD severity and treatment with carbocisteine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carbocisteine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>41·57 (19·05)</td>
<td>42·83 (19·34)</td>
<td>0·430</td>
</tr>
<tr>
<td>After treatment</td>
<td>37·51 (21·39)*</td>
<td>42·78 (22·91)</td>
<td>0·046</td>
</tr>
<tr>
<td>Change</td>
<td>−4·06 (16·43)</td>
<td>−0·05 (19·01)</td>
<td>0·130</td>
</tr>
<tr>
<td>Symptoms</td>
<td>50·30 (20·80)</td>
<td>49·19 (23·25)</td>
<td>0·564</td>
</tr>
<tr>
<td>After treatment</td>
<td>38·96 (20·88)*</td>
<td>45·65 (26·02)</td>
<td>0·015</td>
</tr>
<tr>
<td>Change</td>
<td>−1·34 (22·52)</td>
<td>−3·54 (23·49)</td>
<td>0·004</td>
</tr>
<tr>
<td>Activity</td>
<td>51·27 (20·08)</td>
<td>50·24 (22·04)</td>
<td>0·994</td>
</tr>
<tr>
<td>After treatment</td>
<td>47·94 (23·14)*</td>
<td>50·04 (24·29)</td>
<td>0·428</td>
</tr>
<tr>
<td>Change</td>
<td>−3·33 (19·42)</td>
<td>−0·20 (21·50)</td>
<td>0·321</td>
</tr>
<tr>
<td>Impacts</td>
<td>33·93 (21·59)</td>
<td>35·25 (21·70)</td>
<td>0·511</td>
</tr>
<tr>
<td>After treatment</td>
<td>33·44 (24·44)</td>
<td>35·61 (26·59)</td>
<td>0·562</td>
</tr>
<tr>
<td>Change</td>
<td>−0·49 (21·18)</td>
<td>0·36 (23·19)</td>
<td>0·830</td>
</tr>
</tbody>
</table>

Table 3: SGRQ scores in carbocisteine and placebo groups

Fisher’s exact test were used to compare the difference in percentages between groups.

Safety profiles were assessed by safety set analysis. All hypothesis tests were two-sided, and p<0·05 was defined as significant. No interim analysis was planned. All statistical analyses were done with a validated software package (SAS version 9.1, Cary, NC, USA).

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment ran from June 1 to Sept 30, 2005, and the study was completed by Oct 15, 2006. 709 patients underwent randomisation (figure 1). Of these, two patients (one in each group) were excluded because of ineligibility, but were included in the safety analysis. Insignificant difference was found in the withdrawal rate between these two groups (13·60% vs 12·15%, χ²=0·332; p=0·565).

The two groups were similar in patient demographics, including history of smoking, duration and severity of COPD, baseline pulmonary function, quality of life, and baseline medication (table 1). COPD stages II and III accounted for 88·1% (623 of 707) of the patients, with the rest being stage IV. Before this study, the most common bronchodilator used was xanthines, followed by beta-agonists and anticholinergics, whereas inhaled corticosteroids were prescribed in only 16·7% (118 of 707) of patients.

Patient compliance was similar between the groups. The mean treatment duration was 341·2 days (SD 71·5) in the carbocisteine group and 342·6 days (SD 71·3) in the placebo group, with insignificant difference between each other (Z=−0·099, p=0·549).

The 1-year cumulative number of exacerbations was 325 in the carbocisteine group and 439 in the placebo group, corresponding to 1·008 (SE 0·056) exacerbations per patient-year with carbocisteine treatment versus 1·348 (SE 0·064) with placebo (a 24·5% reduction). The risk ratio of exacerbation was 0·755 (95% CI 0·623–0·916, p=0·004). A Kaplan-Meier plot of the number of patients who were exacerbation-free at each time point through the study is shown in figure 2.

By analysing the covariance factors in our regression model, only two factors—COPD staging and concomitant therapy (theophylline and inhaled corticosteroids)—were found to significantly affect COPD exacerbation. There were no significant interactions between treatment and COPD stages (p=0·190 for treatment×COPD stage IV/stage II; and p=0·159 for treatment×COPD stage III/stage II). After adjusting for COPD stages, analysis of regression model excluding interaction showed favourable reduction in the numbers of exacerbations in carbocisteine group compared with the placebo group (table 2). Similarly, no significant interaction was noted between treatment and concomitant inhaled corticosteroids or inhaled corticosteroids naive. Fewer exacerbations were seen in the carbocisteine group than placebo group (risk ratio 0·755; 95% CI 0·624–0·916, p=0·004). The risk ratio adjusted by xanthines was 0·734 (95% CI 0·606–0·889, p=0·002). The advantage of carbocisteine over placebo in preventing an exacerbation was remarkable even after such adjustment.

There were no significant interactions between treatment and smoking status, and the risk ratio in exacerbation adjusted for smoking status was 0·741, 95% CI 0·642–0·856, p=0·0001.

Analysis of the length of treatment revealed that the prevention of exacerbation acted at month 6, when the risk ratio began to show statistical differences between groups (risk ratio 0·703 [95% CI 0·564–0·879], p=0·108 at 3 months; 0·792 [0·596–1·153], p=0·002 at 6 months; p=0·002 at 9 months 0·730 [0·597–0·892]).

Table 3 summarises the pretreatment and post-treatment quality of life in both groups. After a year of treatment, significant changes from baseline in SGRQ total score (−4·06 units), symptom score (−1·11 units), and activity score (−3·33 units) were detected in patients treated with carbocisteine but not placebo. The improvements in...
Prevention of acute exacerbations of COPD could lead to substantial savings in terms of healthcare use. Inhaled corticosteroids, long-acting β₂ agonists, and anticholinergics would be preferable for better outcomes, yet mucolytics could be more affordable, and will continue to have a role in treatment of COPD, particularly for long-term use. For instance, the annualised cost per patient for carbocisteine-treated patients compared with placebo after adjustment for smoking status. As such, the effects of carbocisteine would be more readily identified in our patients, with modest use of concomitant inhaled corticosteroids, than in the BRONCHUS study. Secondly, carbocisteine showed a unique picture in terms of pharmacokinetics and drug actions (including probable inhibition of viral adherence to the airway), and hence its different efficacy from N-acetylcysteine. Thirdly, the role of ethnicity in response to a treatment should be noted. The Chinese differ from Europeans in dietary patterns, nutritional status, and lifestyle, which might specifically affect certain therapies. For instance, significant differences in theophylline pharmacokinetic constants were reported between American and Chinese children with asthma. Zhou and colleagues also showed that low-dose administration of theophylline significantly reduced the time to first exacerbation and improved SGRQ scores in Chinese patients with COPD, which had not been reported in studies in white patients.

As the most important source of noxious, oxidant radical-rich gas, tobacco smoke represents a major risk factor for COPD. However, not all patients develop COPD because of smoking. In rural areas of developing countries like China, biomass fuel is also an important source of indoor air pollution. Unfortunately, non-smoking patients are excluded from many clinical studies related to COPD. Potential differences between smoking or non-smoking populations in the treatment of COPD were therefore not fully addressed. In a study by Zheng and co-workers, combination therapy with salmeterol and fluticasone was seen to provide more benefits in COPD smokers than in non-smokers. We know of no study that has so far compared the effects of carbocisteine between smoking and non-smoking individuals. Our results showed significantly fewer COPD exacerbations in carbocisteine-treated patients compared with placebo after adjustment for smoking status.

SGRQ total score and symptom score were regarded as clinically relevant. The SGRQ impact score did not show any change from baseline in either group. Postbronchodilator FEV₁ measurements were similar in each group before and after treatment, with no significant difference between these two groups, as was difference in SpO₂ between the two treatments at each interview. For the safety profiles, 113 adverse events were reported during the study period (57 in the carbocisteine group and 56 in the placebo group). The most common adverse events reported (five events or more) were gastrointestinal and cardiac problems (14 cases and nine cases in the carbocisteine group vs five cases each in the placebo group). Table 4 summarises the adverse events. No deaths were reported in the study.

Discussion

The results of our study support previous findings that long-term use of carbocisteine reduced the rate of exacerbations of COPD. The advantage of carbocisteine over placebo in prevention of an exacerbation was noteworthy, even after adjustment for COPD severity and concomitant therapy. We found no difference in exacerbation rate between the carbocisteine group and placebo group at early treatment (3 month), suggesting that longer use of carbocisteine was more effective for preventing exacerbations of COPD.

In addition to preventing COPD exacerbations, carbocisteine was shown to improve the patients’ quality of life. After 1 year of treatment with carbocisteine, significant improvements over placebo were achieved in SGRQ (total and symptom scores). The activity score also seemed favourable with carbocisteine versus placebo.

The role of long-term mucolytic and antioxidation or anti-inflammation therapy in COPD has attracted interest. Poole and Black did a systematic review in which significant reduction of the exacerbation rate by N-acetylcysteine was shown only in patients without concomitant use of inhaled corticosteroids. Several explanations might be reasonable for such difference. Firstly, inhaled corticosteroids were administered in only 16–7% of our study participants (table 1), compared with 70% of the BRONCHUS participants. Additionally, therapeutic inhaled corticosteroids are generally prescribed in smaller doses to Chinese patients. As such, the effects of carbocisteine would be more readily identified in our patients, with modest use of concomitant inhaled corticosteroids, than in the BRONCHUS study. Secondly, carbocisteine showed a unique picture in terms of pharmacokinetics and drug actions (including probable inhibition of viral adherence to the airway), and hence its different efficacy from N-acetylcysteine. Thirdly, the role of ethnicity in response to a treatment should be noted. The Chinese differ from Europeans in dietary patterns, nutritional status, and lifestyle, which might specifically affect certain therapies. For instance, significant differences in theophylline pharmacokinetic constants were reported between American and Chinese children with asthma. Zhou and colleagues also showed that low-dose administration of theophylline significantly reduced the time to first exacerbation and improved SGRQ scores in Chinese patients with COPD, which had not been reported in studies in white patients.

As the most important source of noxious, oxidant radical-rich gas, tobacco smoke represents a major risk factor for COPD. However, not all patients develop COPD because of smoking. In rural areas of developing countries like China, biomass fuel is also an important source of indoor air pollution. Unfortunately, non-smoking patients are excluded from many clinical studies related to COPD. Potential differences between smoking or non-smoking populations in the treatment of COPD were therefore not fully addressed. In a study by Zheng and co-workers, combination therapy with salmeterol and fluticasone was seen to provide more benefits in COPD smokers than in non-smokers. We know of no study that has so far compared the effects of carbocisteine between smoking and non-smoking individuals. Our results showed significantly fewer COPD exacerbations in carbocisteine-treated patients compared with placebo after adjustment for smoking status.
combined treatment for conventional therapy, less-expensive mucolytics such as carbocisteine might be an important option, especially in low-income countries and regions. In our study, the direct cost of exacerbation was not analysed because of the incomplete data recorded from the study. Unlike in Europe and the USA, only a small percentage of people in China are covered by health insurance and reimbursement, and most have to pay for their medical services themselves. Since the uninsured group might not seek treatment because of financial distress, we were unable to accurately calculate the medical costs.

There was no significant improvement in lung function in the carbocisteine group compared with the placebo group after 1 year of treatment, which indicates that the reduced rates of exacerbations and improvements in quality of life were not due to bronchodilatation effects. These findings were similar to those in other studies of mucolytics.13

Our study showed that the nature and incidence of adverse events were similar across the carbocisteine and placebo groups for 1 year, which were consistent with other studies using the same carbocisteine regimen. These results indicated that long term use of carbocisteine was well tolerated.

In conclusion, the 1-year management of carbocisteine was effective for COPD patients in terms of reductions in exacerbations and improvements in quality of life. There were no interactions between treatment and COPD severity, smoking status, and concomitant use of inhaled corticosteroids. Mucolytics, such as carbocisteine, should be recognised as a worthwhile treatment for the long-term management of COPD.

Contributors
N-SZ and JK chaired the steering committee, designed the study protocol, organised the study, and ensured the intrinsic quality of the study. All other authors enrolled participants, collected data, and took responsibility for their own centres. All authors contributed equally to this paper.

Conflict of interest statement
Jin-ping Zheng won a Best Poster Travel Grant for COPD research from European Respiratory Society (ERS) annual conference 2007 due to this work. We declare that we have no other conflict of interest. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Acknowledgments
We would like to thank Kyorin Pharmaceutical, Japan, for financial support for the study; Mei Jiang (Guangzhou Institute of Respiratory Disease), and Beijing CRO Co, (Beijing, China) for the statistical analysis; and Guang-qiao Zeng (Guangzhou Institute of Respiratory Disease) for his help with the manuscript.

References