



Budesonide suspension nebulization treatment in Chinese pediatric patients with cough variant asthma: a multi-center observational study

Xiaojian Zhou MD, Jianguo Hong B Med, Huanji Cheng PhD, Juanjuan Xie B Med, Jianzhi Yang B Med, Qiang Chen B Med, Shaoru He MD, Yun Li MD, Xiaoqin Zhou MD & Changchong Li MD

To cite this article: Xiaojian Zhou MD, Jianguo Hong B Med, Huanji Cheng PhD, Juanjuan Xie B Med, Jianzhi Yang B Med, Qiang Chen B Med, Shaoru He MD, Yun Li MD, Xiaoqin Zhou MD & Changchong Li MD (2016): Budesonide suspension nebulization treatment in Chinese pediatric patients with cough variant asthma: a multi-center observational study, Journal of Asthma, DOI: [10.3109/02770903.2015.1111903](https://doi.org/10.3109/02770903.2015.1111903)

To link to this article: <http://dx.doi.org/10.3109/02770903.2015.1111903>



Accepted author version posted online: 30 Oct 2015.
Published online: 20 Jan 2016.



Submit your article to this journal [↗](#)



Article views: 59



View related articles [↗](#)



View Crossmark data [↗](#)



ORIGINAL ARTICLE

Budesonide suspension nebulization treatment in Chinese pediatric patients with cough variant asthma: a multi-center observational studyXiaojian Zhou, MD¹, Jianguo Hong, B Med², Huanji Cheng, PhD³, Juanjuan Xie, B Med⁴, Jianzhi Yang, B Med⁵, Qiang Chen, B Med⁶, Shaoru He, MD⁷, Yun Li, MD⁸, Xiaoqin Zhou, MD⁹, and Changchong Li, MD¹⁰

¹Department of Pediatrics, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai, P.R. China, ²Department of Pediatrics, First Affiliated People's Hospital, Shanghai Jiaotong University, Shanghai, P.R. China, ³First Affiliated Hospital, Jilin University, Changchun, Jilin, China, ⁴Wuxi City Eighth People's Hospital, Wuxi, Jiangsu, P.R. China, ⁵Children's Hospital of Quanzhou City, Quanzhou, Fujian, China, ⁶Children's Hospital of Jiangxi Province, Jiangxi, Nanchang, China, ⁷Guangdong People's Hospital, Guangzhou, Guangdong, China, ⁸People's Hospital of Hunan Province, Changsha, Hunan, P.R. China, ⁹Hubei Maternal & Child Healthcare Hospital, Wuhan, Hubei, P.R. China, and ¹⁰Second Affiliated Hospital, Wenzhou Medical College, Wenzhou, Zhejiang, P.R. China

Abstract

Objective: To describe the impact of nebulized budesonide inhalation suspension (BIS) on guardian-reported symptoms in Chinese pediatric patients with cough variant asthma (CVA). **Methods:** This was a secondary analysis of a prospective, non-interventional study conducted at 39 Chinese sites. Patients with CVA aged ≤ 5 years were classified according to the severity of baseline symptoms: mild (symptom score ≤ 3) or severe (symptom score > 3). Daytime and night-time symptom scores, disease control, use of bronchodilators, and improvements in symptoms control were compared after 1, 3, 5 and 7 weeks of treatment between groups. **Results:** Among 914 patients, 821 (89.8%) completed the 7-week treatment. Among all patients, 368 (40.3%) were classified as mild CVA and 529 (57.9%), as severe CVA. Symptom scores in the severe group were higher than those in the mild group at weeks 1, 3, and 5 ($p < 0.05$), but not at week 7 ($p > 0.05$). Further, more patients in the mild group achieved disease control at any time point (98.6% at 3 weeks and 99.7% at 7 weeks), compared with the patients in the severe group ($p < 0.001$). The proportion of patients requiring bronchodilators differed between the groups until week 5 ($p < 0.001$). No severe or drug-related adverse events were reported. **Conclusions:** Individualized BIS treatment should be formulated according to the severity of baseline symptoms in CVA patients. Patients with mild CVA showed improvement after a shorter treatment time, while patients with severe CVA might require a longer time to respond to the treatment.

Keywords

Baseline symptoms, budesonide suspension nebulization treatment, cough variant asthma

HistoryReceived 8 April 2015
Revised 14 October 2015
Accepted 18 October 2015
Published online 18 January 2016**Introduction**

Cough variant asthma (CVA) is considered as a specific type of bronchial asthma, which occurs at all ages that is usually unrecognized, leading to under-diagnosis and under-treatment [1]. In children, CVA is often over-diagnosed, and shares with typical asthma eosinophilic airway inflammation resulting in bronchial hyper-responsiveness [2]. CVA is one of the principal causes of chronic cough in children in China [3]. Approximately 30% of the pediatric patients with CVA may progress to clinically typical bronchial asthma [4].

Inhaled corticosteroids are currently the main drugs used to control bronchial asthma, and may improve the clinical symptoms of pediatric patients. Meanwhile, early intervention with inhaled corticosteroids may prevent irreversible airway

remodeling. It is known that airway remodeling may not only occur in typical asthma, but also in CVA [5]. Therefore, it is reasonable to believe that inhaled corticosteroids may play a role in early treatment and protection of pediatric patients with CVA. Studies have shown that early use of inhaled corticosteroids may delay the progression of CVA to typical asthma [6]. Inhaled corticosteroids may also effectively improve airway hyper-reactivity [7]. Budesonide reduces the percentage of eosinophils in induced sputum in CVA patients [8]. Budesonide inhalation suspension (BIS) is the only nebulized glucocorticosteroid for inhalation that is approved by the FDA for young children aged above 12 months, and is also the only inhaled corticosteroid approved for use during pregnancy (pregnancy category B) [9], with potent airway anti-inflammatory effects. Compared with oral therapy, nebulized inhalation may deliver the drug directly to the lesion site, with rapid onset and minor systemic side effects. Moreover, it does not require the patients to perform active inspiration, and therefore, is particularly suitable for young

Correspondence: Jianguo Hong, Department of Pediatrics, First Affiliated People's Hospital, Shanghai Jiaotong University, Shanghai 200080, China. Tel: +86-13501803655. Fax: +86-21-37798435. E-mail: hongjianguo@hotmail.com

children, elderly and infirm patients, or acute-stage patients [10]. However, the use of corticosteroids is not completely harmless [11], and there might be a need for individualization of the dosage in order to optimize the harm/benefit ratio. CVA may be graded according to its severity [12], and this could be used to direct corticosteroid treatment. Indeed, the FENOTYPE trial in classical asthma showed the benefit of personalized corticosteroid treatment [13].

To the best of our knowledge, currently, no data are available regarding the tailoring of budesonide in the treatment of pediatric patients with CVA. The present non-interventional study was designed to describe the impact of nebulized BIS on subjective guardian-reported symptoms in Chinese CVA patients aged ≤ 5 years.

Methods

Study design

This was a secondary analysis of a previous prospective, observational, non-interventional multicenter study. Pediatric patients with CVA were included from 39 sites over China. In the original observational study, pediatric patients had received BIS treatment according to the judgment of their treating physician. The type and dose of any relieving agent or other therapeutic drugs were determined by the treating physician. Patients were assessed at weeks 1, 3, 5 and 7 after starting BIS during their visits to the outpatient department or by phone.

The study was approved by the Ethics Committee of each participating hospital. The need for individual consent to this secondary analysis was waived by the committee.

Subjects

A total of 914 pediatric patients diagnosed with CVA and aged ≤ 5 years were enrolled from 4 Apr 2008, to 22 March 2009. Of 914 patients, 11 were excluded from the study for various reasons; not having cough persistently for eight weeks, had abnormal chest X ray, history of classic asthma, respiratory infection and other diseases. CVA was diagnosed according to the recommendations of the Japanese Cough Research Society [12]. Patients were included (i) if they had cough for at least eight weeks without wheezing, no wheezing on auscultation of chest, (ii) no past history of asthma symptoms such as wheezing or dyspnea, (iii) no history of upper respiratory infection within previous eight weeks, (iv) increased airway responsiveness, (v) effective response to bronchodilator therapy, (vi) no increase in cough sensitivity, and (vii) no abnormal findings on CXR. Pediatric patients who were prescribed nebulized BIS (Pulmicort Respules, AstraZeneca, London, UK) entered the screening process. Patients who had received a leukotriene modifier two weeks prior to the study or who had planned to use it during the study, patients who had received systematic or inhaled glucocorticoids two weeks prior to the study, children of the staff involved in the research plan and implementation, and patients who had participated in any other clinical studies in the 30 days preceding this study were excluded.

Throughout the study, any controlling agent, relieving agent, and other concomitant drugs required by the pediatric

patients were prescribed by the judgment of the investigator, and its use was recorded by the guardian of the pediatric patient. The dosage of BIS was decided in accordance with the product monograph, and the duration of treatment was seven weeks for each patient. The recommendation for urgent use of reliever medication was ≤ 2 times per week for controlled asthma and for those with uncontrolled asthma, it is > 2 times per week.

Methods of assessment

The symptoms of CVA were scored by daytime cough frequency and severity, and nighttime cough frequency and severity (Table 1). The mean score of daytime cough was calculated as the (sum of daytime frequency scores + sum of daytime cough severity scores)/total number of days. The mean score of nighttime cough was calculated as the (sum of nighttime frequency scores + sum of sleep disorder scores due to nighttime cough)/total number of days. The total symptoms score was calculated as the (sum of mean score of daytime cough + mean score of nighttime cough). Good compliance indicates that the medications used are in accordance with the doctor's order in 80% or more treatment days, while poor compliance indicates medications that are used in accordance with the doctor's order in less than 80% treatment days. The assessments for disease control were conducted by each investigator and were judged as controlled, partially controlled, and uncontrolled, based on the daytime and nighttime cough control observed in the period between every two follow-ups. Controlled CVA was defined as patients: (1) experiencing no nocturnal symptoms; (2) have no limitations on their activities; (3) have no (or ≤ 2 times) requirement of relieving agent in a week. Partially controlled CVA was defined as one of the following: (1) existence of limitation of activity per week; (2) existence of nocturnal symptoms; or (3) need of relieving agent (> 2 times) in a week. Uncontrolled CVA was defined as the existence of at least three or more features of partially controlled asthma in a week. The assessment criteria for disease control by the investigator are provided in Table 2 [14]. The condition of the patient such as, controlled, partially controlled, and not controlled was assessed by the guardian of the pediatric patient, based on the daytime and nighttime cough control in the period between every two adjacent days.

Adverse events

The investigator reported any adverse events to the regulatory authorities.

Statistical analysis

Patients were classified according to the severity of baseline symptoms: mild symptoms (symptom score ≤ 3) or severe symptoms (symptom score > 3) (Table 1). Continuous data are presented as means $\pm$ standard deviation; baseline values were analyzed using the Student's *t*-test. Categorical variables are presented using proportions and were analyzed using the chi-square test. The indicators at different time points were tested using repeated measures analysis of variance, with two-sided $\alpha = 0.05$ as the significance level. All

Table 1. Symptom scores of pediatric patients with CVA.

Score	Daytime cough frequency	Daytime cough severity	Nighttime cough frequency	Sleep disorder due to nighttime cough
0	None (<3 times)	None	None (<3 times)	None
1	3–5 times	Mild	3–5 times	Mild
2	6–10 times	Obvious, but not influencing activities	6–10 times	Obvious, but not influencing sleep
3	More than 10 times	Severe and influencing activities	More than 10 times	Severe and influencing sleep

Table 2. Assessment criteria for disease control by the investigator [14].

	Controlled (the following conditions are met)	Partially controlled (one of the following items is met in 1 week)	Not controlled (in any 1 week)
Limited activities	None	Existing	There were ≥ 3 symptoms of partially controlled asthma
Nighttime symptoms	None	Existing	
Requirement for a relieving agent/emergency visit	None (≤ 2 times/week)	>2 times/week	

statistical analyses were carried out by SAS 9.1.3 (SAS institute, Cary, NY).

Results

Baseline characteristics

A total of 914 patients were enrolled and 903 fulfilled the inclusion criteria. However, six patients did not complete the first diary card, leaving 897 patients for analysis. The study flowchart is presented in Figure 1. More than half of the pediatric patients (67.77%) had previously used one or more agents (antibiotics, bronchodilators and antihistamines), of which, antibiotics was used by highest proportion of patients (58.47%), while bronchodilators were used by 39.42% of patients [15]. As shown in Table 3, patients with mild baseline symptoms (symptom score ≤ 3 , mild group) and those with severe baseline symptoms (symptom score >3 , severe group) showed significant differences in morbidity of allergic dermatitis and symptom scores (p values <0.05). There was no statistical difference in other indicators between the mild and severe groups.

Cough symptom scores

Among the 897 included pediatric patients, 821 completed the seven-week BIS treatment. There were differences in symptom scores (including total score, daytime score, and nighttime score) between the mild and severe groups at and before five weeks of treatment (all p values <0.001). However, after seven weeks of treatment, this difference disappeared in all symptom scores (Table 4).

Symptom scores at different time points in the same group were compared in order to investigate the effect of sustained treatment. As shown in Table 3, in the mild group, there were differences between week 3 versus week 1 ($p < 0.05$), but not between week 5 versus week 3 and week 7 versus week 5. However, in the severe group, all comparisons (week 3 versus week 1, week 5 versus week 3, and week 7 versus week 5) showed significant differences (all p values <0.001). Therefore, patients in the mild group did not achieve further improvements in symptom score after five weeks of

treatment; however, the severe group still achieved further improvement after five weeks of BIS treatment.

To compare the extent of improvement between the two groups, the decreases in symptom scores at weeks 3, 5 and 7 were compared with week 1 between the groups (Table 3). Compared with the mild group, the decreases of all symptom scores (including total score, daytime score and nighttime score) at all points (weeks 3, 5 and 7) in the severe group were much more significant (all p values <0.001) than in the mild group.

Disease control assessment

When the symptom control rate (partially controlled + controlled) was assessed between the two treatment groups, the control rate was significantly higher in the mild group at all-time points (weeks 1, 3, 5 and 7) than the control rates in the severe group ($p < 0.001$) (Table 5).

Use of bronchodilators and improvements in symptom control

The proportion of patients who required adjuvant bronchodilators gradually dropped from 55.8% at week 1 to 14.1% at week 7 in the mild group. Patients in the severe group showed a similar trend, with bronchodilator requirement dropping from 75.0% at week 1 to 26.7% at week 7 (Figure 2). These trends suggested the improvement of symptoms control in pediatric patients after BIS treatment. In less than seven weeks of treatment, the proportions of patients prescribed bronchodilators in the severe group were higher than those in the mild group (all p values <0.001). After seven weeks of treatment, there were no differences between the groups ($p = 0.149$). This result may suggest that patients with severe symptoms may achieve more improvements in symptom control with longer administration of BIS.

Adverse events

No severe or drug-related adverse events were recorded during the seven-week BIS treatment. Other events were mild and required no extra treatment (data not shown).

Figure 1. Study flowchart.

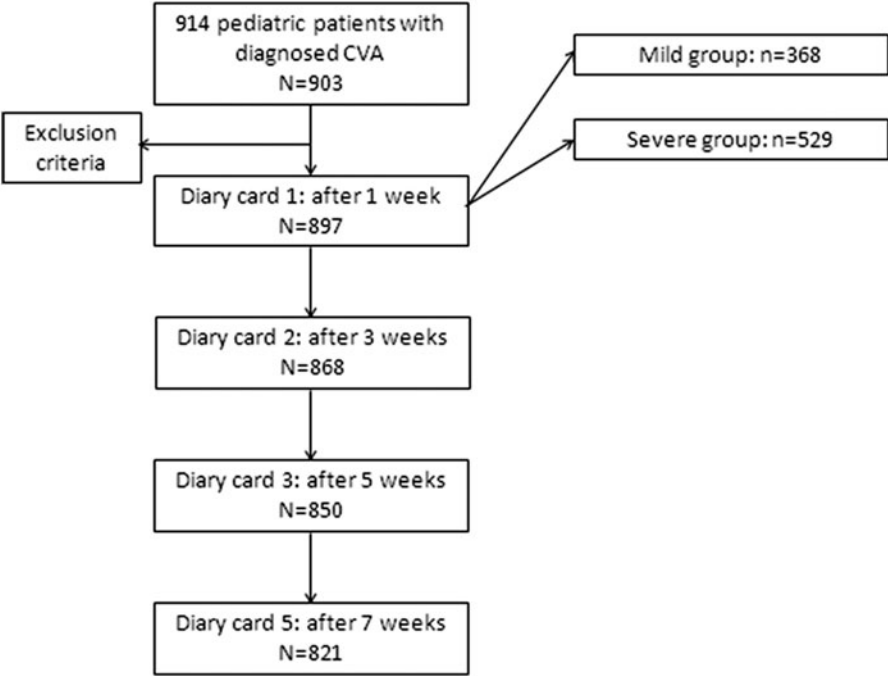


Table 3. Baseline characteristics of CVA patients.

Group (N = 897)	Mild group (symptom scores ≤3) N = 368	Severe group (symptom scores >3) N = 529	p value
Male (%)	59.0%	60.0%	0.774
Age (months)	110.3 ± 13.5	109.9 ± 14.4	0.852
Disease history related to CVA			
Allergic rhinitis (%)	32.3	26.8	0.075
Allergic dermatitis (%)	14.4	20.2	0.025
Allergic conjunctivitis (%)	8.2	6.4	0.324
Treatment history related to CVA			
Antibiotics (%)	58.4	61.1	0.428
Bronchodilators (%)	31.3	27.0	0.170
Antihistamine (%)	30.4	25.3	0.092
Baseline symptom score	1.67	5.3	-
Daytime symptom score	1.10	3.3	-
Nighttime symptom score	0.28	2.10	-
Baseline total symptom score (mean ± SD)	1.57 ± 0.950	5.64 ± 2.028	<0.001
Daytime symptom score (mean ± SD)	1.15 ± 0.790	3.32 ± 1.117	<0.001
Nighttime symptom score (mean ± SD)	0.42 ± 0.495	2.33 ± 1.375	<0.001

Mean score of daytime cough = (sum of daytime frequency scores + sum of daytime cough severity scores)/total number of days; mean score of nighttime cough = (sum of nighttime frequency scores + sum of sleep disorder scores due to nighttime cough)/total number of days. Total symptom score = mean score of daytime cough + mean score of nighttime cough.

Discussion

CVA is a phenotype of asthma presenting clinical symptoms of chronic and non-productive cough without wheezing, which is different from the typical asthma. The causes of CVA are unclear; nevertheless, bronchodilators such as β₂-agonists, and anti-inflammatory drugs such as inhaled corticosteroids and leukotriene receptor antagonists are recommended to treat CVA [3]. However, the severity of CVA varies among patients, and there is a need to optimize the harm/benefit ratio for each individual patient.

Therefore, the aim of the present study was to evaluate the efficacy of BIS in Chinese pediatric patients with CVA and to compare its efficacy among patients with different baseline

symptoms. The results showed that among all patients, 368 were classified as mild CVA (symptom scores ≤3) and 529, as severe CVA (symptom scores >3). Symptom scores in the severe group were higher than the symptom scores in the mild group at weeks 1, 3 and 5, but not at week 7. After five weeks, patients in the mild group reported no further improvements; however, patients in the severe group still achieved improvements at week 7. Furthermore, more patients in the mild group achieved disease control at any time point, compared with the severe group. A randomized, parallel, controlled multicenter study has shown that a combination of procaterol and inhaled budesonide was more effective in improving cough symptoms and quality of life compared to

Table 4. Symptom scores after nebulized BIS treatment (mean $\pm$ SD).

Symptom score	Mild group	Severe group	<i>p</i> value
Week 0–1, <i>N</i> = 897	368	529	
Total symptom score	1.57 $\pm$ 0.950	5.64 $\pm$ 2.028	<0.001
Daytime symptom score	1.15 $\pm$ 0.790	3.32 $\pm$ 1.117	<0.001
Nighttime symptom score	0.42 $\pm$ 0.495	2.33 $\pm$ 1.375	<0.001
Weeks 1–3, <i>N</i> = 868	354	514	
Total symptom score	0.83 $\pm$ 1.32	2.15 $\pm$ 1.973	<0.001
Daytime symptom score	0.60 $\pm$ 0.886	1.34 $\pm$ 1.187	<0.001
Nighttime symptom score	0.23 $\pm$ 0.566	0.811 $\pm$ 0.998	<0.001
Weeks 3–5, <i>N</i> = 850	344	506	
Total symptom score	0.65 $\pm$ 1.255	0.96 $\pm$ 1.513	0.018
Daytime symptom score	0.45 $\pm$ 0.875	0.60 $\pm$ 0.935	<0.001
Nighttime symptom score	0.20 $\pm$ 0.491	0.36 $\pm$ 0.695	0.001
Weeks 5–7, <i>N</i> = 821	337	484	
Total symptom score	0.54 $\pm$ 1.11	0.53 $\pm$ 1.251	0.695
Daytime symptom score	0.36 $\pm$ 0.720	0.34 $\pm$ 0.811	0.799
Nighttime symptom score	0.18 $\pm$ 0.481	0.19 $\pm$ 0.551	0.887

Mean score of daytime cough = (sum of daytime frequency scores + sum of daytime cough severity scores)/total number of days; mean score of nighttime cough = (sum of nighttime frequency scores + sum of sleep disorder scores due to nighttime cough)/total number of days. Total symptom score = mean score of daytime cough + mean score of nighttime cough.

Table 5. Symptom control after treatment (mixed evaluation from both the investigator and patients' parents).

Controlled + Partially Controlled	Mild group (<i>n</i> = 368)	Severe group (<i>n</i> = 529)	<i>p</i> value (mild group versus severe group, χ^2 test)
Week 1 (%)	94.0	76.5	<i>p</i> < 0.001
Week 3 (%)	98.6	89.3	<i>p</i> < 0.001
Week 5 (%)	99.4	87.3	<i>p</i> < 0.001
Week 7 (%)	99.7	93.3	<i>p</i> < 0.001

corticosteroid alone after eight weeks of treatment, and these effects could still be observed for two weeks after discontinuation of treatment [16]. Another randomized, parallel, controlled multicenter study has shown that the salmeterol/fluticasone propionate combination (SFC) and inhaled salmeterol for 12 weeks considerably relieved the symptoms and improved the pulmonary function, but SFC showed more pronounced effects and added efficacy in decreasing sputum eosinophil counts and eosinophil cationic protein contents [17]. However, after discontinuation of treatment for 12 weeks, CVA relapsed and most indicators returned to the baseline levels [17]. In the present study, treatment using bronchodilators was avoided as much as possible, and bronchodilator prescriptions were used as an indicator for the efficacy of BIS treatment. The proportion of patients requiring bronchodilators differed between the groups until week 5. No severe or drug-related adverse events were reported.

Inhaled corticosteroids have been proven to effectively decrease the symptoms of CVA and to improve the quality of life of patients with CVA, and are recommended as the first-line treatment for asthma including CVA [18,19]. Recent studies reported that CVA patients exhibited more improvements in airway inflammation and airway

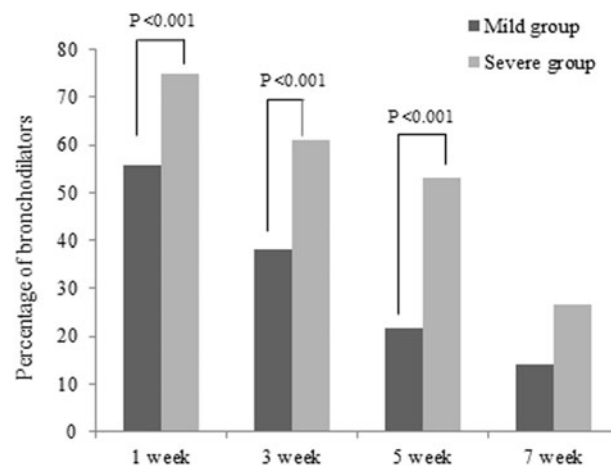


Figure 2. Use of bronchodilators and symptom control at 1, 3 5 and 7 weeks.

hyper-responsiveness compared to those with classic asthma, when treated by inhaled corticosteroids [20]. Furthermore, nebulized corticosteroids are more effective than metered-dose inhaler or dry powder inhaler in increasing drug deposition in the airways and changing the distribution of drug particles [21]. The present study suggests that both mild and severe patients could benefit from BIS treatment; however, patients with severe symptoms and higher symptom scores at baseline could achieve more reductions in symptom score after a relatively-longer treatment compared with patients with mild symptoms, who achieve an efficacy plateau by five weeks. Thus, patients in the severe group may need more than seven weeks of treatment to achieve overall control. To the best of our knowledge, this is the first study that classified patients with CVA according to the severity of symptoms. The previous FENotype trial performed in patients with classical asthma suggests that corticosteroid treatment should be personalized [13].

The present study is not without limitations. First, since CVA and classical asthma are closely associated, some patients with asthma may have been enrolled in our study, but there were no signs of wheezing during the whole periods of observation for the enrolled patients, and they may have been diagnosed with asthma only after the study. Second, the definitions of controlled, partially controlled, and uncontrolled CVA were relatively subjective, which may have caused biases. Third, if more precise indicators were available for CVA, more accurate conclusions could be drawn. Fourth, since most patients achieved control of their symptoms, multivariate analysis could not be carried out. Finally, the patients were not followed up further.

In conclusion, CVA patients with higher cough symptom scores at baseline could achieve more benefits from BIS treatment and may require treatment for a longer duration of time until control is expected. Therefore, individualized BIS treatment should be formulated according to the severity of symptoms in CVA patients.

Acknowledgements

The study was funded by AstraZeneca. The authors would like to thank Dr Ramu Periyasamy (Indegene Lifesystems Pvt

Ltd, Bangalore, India) for assisting the authors in revising this manuscript, funded by AstraZeneca. We thank the investigators of the 39 sites for their substantial support (sorted alphabetically): AN Su-ying (The Second Hospital of Hebei Medical University); CHEN Qiang (Children's Hospital of Jiangxi Province); CHEN Zhi-min (The Children's Hospital, Zhejiang University School of Medicine.); CHENG Bao-jin (Changzhou No.2 People's Hospital); CHENG Huan-ji (The First Affiliated Hospital of Jilin University); FANG Hong (Tongji Hospital, Tongji Medical College of Tongji Medical College Huazhong University of Science and Technology); HAN Yu-ling (Jinan Children's Hospital); HAN Zhi-ying (Shanxi Maternal & Child Healthcare Hospital); HE Shao-ru (Guangdong People's Hospital); HONG Jian-guo (The First Affiliated People's Hospital of Shanghai Jiaotong University); HU Ying-hui (Beijing Children's Hospital); HU Yue (Shenyang Children's Hospital); HUANG Xian-mei (Hangzhou First People's Hospital); HUANG Ying (Children's Hospital of Chongqing Medical University); LI Chang-chong (The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University); LI Guo-rong (Ningbo Women & Children's Hospital); LI Li (First People's Hospital of Yunnan Province); LI Min (Sichuan Provincial People's Hospital); LI Xin-min (First Teaching Hospital of Tianjin University of TCM); LI Yun (Hunan Provincial People's Hospital); LIANG Kun (First Affiliated Hospital of Kunming Medical University); LIN Rong-jun (The Affiliated Hospital of Qingdao University); LIU Xiao-hong (The First Affiliated Hospital of Xi'an Jiaotong University); LIU Yu-ling (Boai Hospital of Zhongshan); PAN Jia-hua (Anhui Provincial Hospital); SHENG Jin-yun (Soochow University Affiliated Children's Hospital.); SUN Guang-rong (Qingdao Women and Children Medical Healthcare Center); TAN Wei-ping (Second Affiliated Hospital of Sun Yat-Sen University); WANG Li-bo (Children's Hospital of Fudan University); WANG Xiu-fang (Third Affiliated Hospital of Zhengzhou University); WU Jin-zhun (The First Affiliated Hospital of Xiamen); XIE Juan-juan (Wuxi People's Hospital); YANG Jian-zhi (Quanzhou Women's and Children's Hospital); YAO Li (The Second Affiliated Hospital of Harbin Medical University); ZHANG Guo-zhong (Ruian People's Hospital); ZHAO De-yu (Nanjing Children's Hospital); ZHEN Yue-jie (Shenzhen Children's Hospital); ZHOU Wei (Peking University Third Hospital); ZHOU Xiao-qin (Hubei Women & Children's Health Hospital).

Declaration of interest

The authors declare that they have no any conflict of interests.

References

- Pender ES, Pollack Jr. CV. Cough-variant asthma in children and adults: case reports and review. *J Emerg Med* 1990;8:727–731.
- Antoniou SA, Mihaescu T, Donner CF. Pharmacotherapy of cough-variant asthma. *Expert Opin Pharmacother* 2007;8:3021–3028.
- Lu Q. Clinical research coordination group of the causes constituents ratio of chronic cough in Chinese children. [Prospective multicenter clinical study on the causes constituents ratio of chronic cough in Chinese children]. *Chin J Pediatr* 2012;50:83–92.
- Hong JG. Chronic cough and asthma in children: intensive reading of the Guideline for diagnosis and treatment of chronic cough in pediatrics (II). *Zhonghua Er Ke Za Zhi* 2008;46:819–821.
- Niimi A, Matsumoto H, Minakuchi M, Kitaichi M, Amitani R. Airway remodelling in cough-variant asthma. *Lancet* 2000;356:564–565.
- Matsumoto H, Niimi A, Takemura M, Ueda T, Tabuena R, Yamaguchi M, Matsuoka H, et al. Prognosis of cough variant asthma: a retrospective analysis. *J Asthma* 2006;43:131–135.
- Fujimura M, Hara J, Myou S. Change in bronchial responsiveness and cough reflex sensitivity in patients with cough variant asthma: effect of inhaled corticosteroids. *Cough* 2005;1:5.
- Koh YY, Jeong JH, Park Y, Kim CK. Development of wheezing in patients with cough variant asthma during an increase in airway responsiveness. *Eur Respir J* 1999;14:302–308.
- Drugs@FDA - FDA Approved Drug Products. Budesonide. FDA. 2015. 12-12-2014. (Ref Type: Electronic Citation).
- Szefer SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol* 2002;109:730–742.
- Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;120:S94–S138.
- Kohno S, Ishida T, Uchida Y, Kishimoto H, Sasaki H, Shioya T, Tokuyama K, et al. The Japanese Respiratory Society guidelines for management of cough. *Respirology* 2006;11:S135–S186.
- Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENO-type trial. *Chest* 2012;142:1553–1561.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2006. Available from: www.ginasthma.org [last accessed 10 Aug 2015].
- Hong JG, Cheng HJ, Xie JJ, Yang JZ, Chen Q, He SR, Li Y, et al. A study of cough variant asthma treated with budesonide suspension nebulization in childhood. *Chin J Pract Pediatr* 2012;27:270–274.
- Bao W, Chen Q, Lin Y, Liu H, Zhao G, Chen Z, Zhou X, et al. Efficacy of procaterol combined with inhaled budesonide for treatment of cough-variant asthma. *Respirology* 2013;18: 53–61.
- Tagaya E, Kondo M, Kirishi S, Kawagoe M, Kubota N, Tamaoki J. Effects of regular treatment with combination of salmeterol/fluticasone propionate and salmeterol alone in cough variant asthma. *J Asthma* 2015;52:512–518.
- Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143–178.
- Pedersen SE, Hurd SS, Lemanske Jr. RF, Becker A, Zar HJ, Sly PD, Soto-Quiroz M, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol* 2011. doi: 10.1002/ppul.21321.
- Liu M, Liu K, Zhu N, Xia J, Chen X. Inflammatory mediators in induced sputum and airway hyperresponsiveness in cough variant asthma during long-term inhaled corticosteroid treatment. *Mediators Inflamm* 2012;2012:403868.
- Kamimura M, Izumi S, Hamamoto Y, Morita A, Toyota E, Kobayashi N, Kudo K, et al. Superiority of nebulized corticosteroids over dry powder inhalers in certain patients with cough variant asthma or cough-predominant asthma. *Allergol Int* 2012;61: 411–417.