Montelukast and budesonide combination for children with chronic cough-variant asthma

Xiu-ping Wang, MB, Lin-dong Yang, MB, Jin-fang Zhou, MB*

Abstract
This study investigated the effectiveness and safety of montelukast combined budesonide (MCB) treatment for children with chronic cough-variant asthma (CCVA).

In total, 82 cases of children with CCVA, aged 4 to 11 years were included in this study. All cases received either MCB or budesonide alone between May 2015 and April 2017. The primary outcome was lung function, measured by the peak expiratory flow rates (PEFRs) and forced expiratory volume in 1 second (FEV1). The secondary outcome was measured by the clinical assessment score. Furthermore, adverse events (AEs) were also recorded in this study. All outcomes were measured after 8-week treatment.

By the end of 8-week treatment, MCB showed greater effectiveness than did budesonide alone in improving lung function, measured by PEFR V1 (P < .02), and FEV1 (P < .01). Similarly, the clinical assessment score also demonstrated significant difference between the 2 groups (P < .05). In addition, no serious AEs occurred in both groups.

The results of this study demonstrate that the effectiveness of MCB is superior to budesonide alone in the treatment of children with CCVA.

Abbreviations: CCVA = chronic cough-variant asthma, cysteinyl leukotriene; AE = adverse events, FEV1 = forced expiratory volume in 1 second, LTRA = leukotriene receptor antagonist, MCB = montelukast combined budesonide, PEFR = peak expiratory flow rate.

Keywords: budesonide, cough-variant asthma, effectiveness, montelukast

1. Introduction
Chronic cough-variant asthma (CCVA) is a very common subtype of bronchial asthma among children population.[1–3] This condition often manifests with acute cough, chronic cough, and intractable cough, especially at night.[4,5] It has been reported that CCVA contributed 24.0% to 33.3% of chronic cough cases, and children alone accounted for the incidence of 0.18% among the total CCVA population.[6]

Pharmacotherapy is predominantly used for the treatment of patients with CVA.[7–11] Such intervention includes glucocorticoids, antihistamine drugs, β2-agonists, and leukotriene receptor antagonists (LTRAs).[7–12] Of those medications, LTRAs have been used as the first-line treatment for such condition, and montelukast comprises the most commonly used type 1 cysteinyl leukotriene antagonist.

Previous studies have reported that montelukast can improve both the symptoms and lung function in patients with CCVA.[12–21] However, limit data are still available about montelukast and budesonide for the treatment of CCVA. In this retrospective study, we investigated the effectiveness and safety of montelukast and budesonide for the treatment of children with CCVA aged 4 to 11 years.

2. Methods
2.1. Design
This study was designed as a retrospective study. It included 82 eligible cases of Chinese children, aged 4 to 11 years with CCVA. Of those patients, 41 received montelukast combined budesonide (MCB) and were assigned to an intervention group, whereas the other 41 subjects underwent budesonide alone and were assigned to a control group. All the cases were collected at The People’s Hospital of Yan’an between May 2015 and April 2017.

This study was approved by the Medical Ethical Committee of Yan’an People’s Hospital. Legal guardians of all included children provided the informed written consent in this study.

2.2. Inclusion and exclusion criteria
The cases of both male and female Chinese children with CCVA aged from 4 to 11 years were included in this study. The cases were excluded if the children had prophylactic medications, budesonide, and montelukast 1-month before this study. In addition, the cases were excluded if the children had taken theophylline, inhaled corticosteroids, nasal steroid, and cromolyn during the period of this study. Furthermore, the cases were also excluded if they had insufficient information, and characteristic values, as well as the outcome data.
2.3. Intervention

All participants with CCVA in both groups received budesonide (1 mg, 3 times daily) for a total of 8 weeks. In addition, patients in the intervention group also underwent montelukast (4 mg daily) chewable tablet in the evening at bedtime for a total of 8 weeks.

2.4. Effectiveness evaluation

The primary outcome measurement of lung function was measured by the peak expiratory flow rate (PEFR) \(^{24}\) and forced expiratory volume in one second (FEV\(_1\)). The secondary outcome was measured by the clinical assessment score. PEFR was measured by a bedside spirometry using PiKo-1 (ATS and EU electronic peak flow monitor, Ferraris Respiratory Europe Ltd, Westford, UK) software. It was performed between 08:30 AM and 10:30 AM each morning by the experienced physicians at Yan’an People’s Hospital, who were trained strictly before this study by 3 times. Moreover, adverse events (AEs) were recorded in this study. All outcomes were measured before and 8 weeks after the treatment.

2.5. Statistical analysis

All the data of this study were analyzed by using IBM SPSS Statistics 19.0 (IBM Corp, Armonk, NY). The categorical data were performed by using Chi-squared test. The continuous data were applied by \(t\) test or Mann-Whitney \(U\) test to analyze the differences between 2 groups. The statistical significance was set as \(P < .05\).

3. Results

The patient characteristics are summarized in Table 1. The 2 groups did not differ significantly in all characteristics and clinical variables in this study.

After 8-week treatment, patients received MCB exerted better outcome in lung function, measured by the PEFR (\(P = .02\), Table 2) and FEV\(_1\) (\(P < .01\), Table 3); and clinical assessment score (wheeze, \(P < .01\); activity, \(P = .04\); cough, \(P = .03\); sleep, \(P < .01\), Table 4) compared with patients who underwent budesonide alone.

All AEs were mild in both groups (Table 5). No serious AEs occurred in either group. No patient withdrew from the study due to the AEs in both groups. In addition, no significant differences were found regarding the AEs between 2 groups (Table 5).

4. Discussion

Cys-LTs play a very important role in the pathogenesis of asthma.\(^{26,27}\) Generally speaking, although the anti-inflammatory

### Table 2

| Characteristics | Intervention (n=41) | Control (n=41) | \(P\) |
|-----------------|--------------------|---------------|------|
| PEFR | | | |
| At baseline | 118.9 (14.6) | 121.3 (15.1) | .46 |
| After treatment | 133.4 (16.3) | 126.1 (16.5) | .38 |
| Difference from baseline | 14.4 (9.9–17.7) | 4.9 (1.5–9.3) | .03 |
| Difference between groups | 9.5 (6.2–12.1) | | .02 |

Data are present as mean ± standard deviation. PEFR = peak expiratory flow rates.

### Table 3

| Characteristics | Intervention (n=41) | Control (n=41) | \(P\) |
|-----------------|--------------------|---------------|------|
| NRS score | | | |
| At baseline | 70.8 (1.6) | 71.1 (1.5) | .38 |
| After treatment | 83.2 (5.9) | 77.4 (5.8) | .19 |
| Difference from baseline | 12.4 (8.1, 16.3) | 6.3 (3.5, 9.2) | .04 |
| Difference between groups | 6.1 (4.0, 8.8) | | <.01 |

Data are present as mean ± standard deviation. FEV\(_1\)= forced expiratory volume in 1 second.

### Table 4

| Characteristics | Intervention (n=41) | Control (n=41) | \(P\) |
|-----------------|--------------------|---------------|------|
| Wheeze | 0.91 (0.57) | 1.26 (0.64) | .03 (0.14, 0.49) | <.01 |
| Activity | 1.04 (0.65) | 1.34 (0.69) | .03 (0.11, 0.47) | .04 |
| Cough | 0.97 (0.68) | 1.30 (0.71) | .03 (0.14, 0.49) | .03 |
| Sleep | 0.93 (0.60) | 1.28 (0.62) | .03 (0.21, 0.54) | <.01 |

Data are present as mean ± standard deviation.

### Table 5

| Characteristics | Intervention (n=41) | Control (n=41) | \(P\) |
|-----------------|--------------------|---------------|------|
| Anxiety | 5 (12.1) | 3 (7.3) | .46 |
| Depression | 5 (12.1) | 4 (9.8) | .16 |
| Headache | 7 (17.1) | 5 (12.1) | .53 |
| Nausea | 5 (12.1) | 4 (9.8) | .69 |
| Skin rash | 3 (7.3) | 4 (9.8) | .19 |
| Insomnia | 4 (9.8) | 3 (7.3) | .69 |

Data are present as mean ± standard deviation.

\(P < .01\), Table 4) compared with patients who underwent budesonide alone.
effects of montelukast are regarded to be milder as compared to inhaled corticosteroids in the management of asthma, most studies used it as an add-on therapy to budesonide.\(^{[18,30]}\) It has been reported that the combination of MCB may help to better manage the symptom control, lung function improvement, and also against the airway narrow protection compared with inhaled corticosteroids alone.\(^{[28-30]}\)

This retrospective study firstly investigated the effectiveness of MCB for treating CCVA in children aged 4 to 11 years in China. The results showed that significant differences were found in the pulmonary function tests by FEV\(_1\) and PEFR, as well as the clinical assessment score after 8-week treatment. In addition, no serious AEs occurred in this study. Our results are partly consistent with data published of related study by Ghosh et al.\(^{[31]}\)

They included 50 children and found that clinical outcomes showed significant improvement after 4 and 12 weeks of treatment.\(^{[31]}\)

To the best of our knowledge, this study specifically focused on the pediatric population in China, and provided significant clinical benefit in children with CCVA. The results of this study demonstrated that MCB can either improve lung function, measured by the PEFR and FEV\(_1\), or enhance the clinical symptoms for children with CCVA.

This study has several following limitations. First, the sample size was quite small in this study, which may affect the results of this study. Second, the cases of this retrospective were selected from a single center, and thus, it may be not generalized to other pediatric population. Third, this study is a retrospective study with its own limitation, which may increase the selection bias.

5. Conclusion

The results of this study found that MCB may be benefit for treating CCVA in children aged 4 to 11 years. However, larger sample size with longer treatment duration would still be required for further evaluation of the role of MCB in the treatment of CCVA.

Author contributions

Conceptualization: Jinfang Zhou, Xiu-ping Wang, Lin-dong Yang.

Data curation: Jinfang Zhou, Xiu-ping Wang, Lin-dong Yang.

Formal analysis: Lin-dong Yang.

Investigation: Jinfang Zhou.

Methodology: Xiu-ping Wang, Lin-dong Yang.

Project administration: Jinfang Zhou.

Resources: Jinfang Zhou, Xiu-ping Wang.

Software: Xiu-ping Wang.

Supervision: Jinfang Zhou.

Validation: Xiu-ping Wang, Lin-dong Yang.

Visualization: Xiu-ping Wang, Lin-dong Yang.

Writing – original draft: Jinfang Zhou, Xiu-ping Wang, Lin-dong Yang.

Writing – review and editing: Jinfang Zhou, Xiu-ping Wang, Lin-dong Yang.

References

[1] Wang X, Liu B, Lu B, et al. Micro-invasive embedding combined with montelukast sodium for children cough variant asthma: a randomized controlled trial. Zhongguo Zhen Jiu 2017;37:259-64.

[2] Zhang YX, Liu Y, Xue Y, et al. Correlative study on atmospheric concentrations of fine particulate matter and children cough variant asthma. Eur Rev Med Pharmacol Sci 2016;20:2650–4.

[3] Li W, Ban C, Zhang J, et al. Correlation study of cough variant asthma and mycoplasma pneumonia infection in children. Pak J Pharm Sci 2017;30:1099–102.

[4] Fujimura M. Pathophysiology, diagnosis and treatment of cough variant asthma. Rinsho Byori 2014;62:464–70.

[5] Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. J Allergy Clin Immunol Pract 2014;2:671–80.

[6] Liu CH, Shao MJ, Wang Q, et al. Epidemiological survey of children asthma prevalence in Beijing urban area. Chin J Pediatr 2013;93:574–8.

[7] Tagaya E, Kondo M, Kirishi S, et al. Effects of regular treatment with combination of salmeterol/budesonide propionate and salmeterol alone in cough variant asthma. J Asthma 2015;52:512–8.

[8] Ge ZY, Tong J, Lu FG. The meta-analysis of effects of traditional Chinese medicine on cough variant asthma in children. J Tradit Chin Med Univ Hunan 2013;33:194–8.

[9] Zhang TH, Li XJ, Zhang S, et al. The systematic review of Chinese herbal medicine on childhood coughing variant asthma of randomized controlled trials. J Inform Tradit Chin Med 2009;16:97–100.

[10] Chen XW, Zhou Y, Zhong D, et al. Evaluation of literature quality of traditional Chinese medicine for cough asthma variant in children. J Emerg Tradit Chin Med 2013;32:1291–2.

[11] Antoniu SA, Mihaescu T, Donner CF. Pharmacotherapy of cough-variant asthma. Expert Opin Pharmacother 2007;8:3021–8.

[12] Kamimura M, Izumi S, Hamamoto Y, et al. Superiority of nebulized inhaled corticosteroids in the management of asthma, most studies effects of montelukast are regarded to be milder as compared to inhaled corticosteroids over dry powder inhalers in certain patients with cough variant asthma or cough-predominant asthma. Allergol Int 2016;65:320–6.

[13] Bao W, Chen Q, Lin Y, et al. Efficacy of procaterol combined with inhaled budesonide for treatment of cough-variant asthma. Respirology 2013;18(suppl 3):53–61.

[14] Miao Q, Wei PC, Fan MR, et al. Clinical study on treatment of cough variant asthma by Chinese medicine. Chin J Integ Med 2013;19:539–45.

[15] Kamimura M, Izumi S, Hamamoto Y, et al. Superiority of nebulized corticosteroids over dry powder inhalers in certain patients with cough variant asthma or cough-predominant asthma. Allergol Int 2012;61:411–7.

[16] Stanković I, Pejić T, Ranić M, et al. The impact of inhaled corticosteroids on cough and bronchial hyperreactivity in cough variant asthma. Med Pregl 2010;67:170–4.

[17] Tamaoki J, Yokohori N, Tagaya E, et al. Comparable effect of a leukotriene receptor antagonist and long-acting beta₂-adrenergic agonist in cough variant asthma. Allergy Asthma Proc 2010;31:78–84.

[18] Takemura M, Niimi A, Matsumoto H, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. Respiration 2012;83:108–15.

[19] Kita T, Fujimura M, Ogawa H, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. Allergol Int 2010;59:185–92.

[20] Sun LH, Chen AH, Zhang Y. Therapeutic efficacy and follow-up study of inhaled corticosteroids vs. oral montelukast in treatment of cough variant asthma. Zhonghua Er Ke Za Zhi 2008;46:85–8.

[21] Kawai S, Baba K, Matsubara A, et al. The efficacy of montelukast and inhaled corticosteroids in allergic asthma in children. Bronchial asthma 2008;21:142–5.

[22] Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. Ann Allergy Asthma Immunol 2004;93:232–6.

[23] Guilla KM, Kahra SK. Peak expiratory flow rate as a monitoring tool in asthma. Indian J Pediatr 2017;84:173–4.

[24] Dockery DW, Berekly CS, Ware JH, et al. Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. Am Rev Respir Dis 1983;128:405–12.

[25] Buusse W, Kraft M. Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy. Chest 2005;127:1312–26.

[26] Birring SS, Parker D, Brightling CE, et al. Induced sputum inflammatory mediator concentrations in chronic cough. Am J Respir Crit Care Med 2004;169:15–9.
[28] Jat GC, Mathew JL, Singh M. Treatment with 400 microg of inhaled budesonide vs 200 microg of inhaled budesonide and oral montelukast in children with moderate persistent asthma: randomized controlled trial. Ann Allergy Asthma Immunol 2006;97:397–401.

[29] Barnes N, Laviolette M, Allen D, et al. Effects of montelukast compared to double dose budesonide on airway inflammation and asthma control. Respir Med 2007;101:1652–8.

[30] Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003; 58:211–6.

[31] Ghosh G, Manglik AK, Roy S. Efficacy and safety of montelukast as monotherapy in children with mild persistent asthma. Indian Pediatr 2006;43:780–5.