To the Editor,

Cough variant asthma (CVA) is the most common cause of chronic cough, accounting for 41.95% of the causes of chronic cough among Chinese children, which greatly affects their learning, sleep, and quality of life[1,2]. About 40%–50% of CVA patients may eventually develop wheezing symptoms and progress to typical asthma if no appropriate and timely treatment is given[3]. However, the treatment plan and duration of children with CVA remain unclear. To this end, we performed retrospective longitudinal cohort study to explore the best therapeutic regimen and treatment duration of CVA in children.

The study was approved by the Ethics Committee of Children’s Hospital Affiliated to Shandong University (The ethics protocol number is SDFE–IRB/T–2022075), which absolved the need for written informed consent. A total of 314 children with CVA were assigned to receive inhaled corticosteroid (ICS) combined with long-acting β2-agonist (LABA) group (group 1, n = 63), ICS combined with leukotriene receptor antagonist (LTRA) group (group 2, n = 186), ICS monotherapy group (group 3, n = 30), and LTRA monotherapy group (group 4, n = 35). Based on the causal diagram (Figure S1) model assumption, the marginal structure model and the Cox proportional hazard regression model were fitted to estimate the direct causal effect of the first medication on the efficacy and safety outcomes based on inverse probability weighting. Additional details on the methods are presented in the online supplementary.

General Information of Children with CVA is shown in Table S1. Distribution of the number of patients changed from 0 weeks to 60 weeks with four treatment regimens is plotted in Figure S2. Results of superiority analysis with group 1 as the control (Table 1): ICS + LABA had the best effect within 8 weeks, followed by ICS + LTRA, whereas ICS alone and LTRA alone had the worst efficacy. With the extension of medication time, the efficacy of the ICS + LABA group was gradually lower than other groups in the same period. ICS alone was predominant at 8 weeks and beyond, followed by LTRA alone, whereas ICS + LABA and ICS + LTRA had the worst efficacy. Due to most of the guidelines recommend that the CVA treatment is for at least 8 weeks, we divided it into two parts with 8 weeks as the boundary[4-6]. There was no significant difference in therapeutic effects of the four treatment regimens within 8 weeks of diagnosis of CVA (Table S2). And the efficacy of ICS or LTRA alone was better than that of combination therapy after 8 weeks of diagnosis (Table S3).

Table 1. Comparison of four medication regimens for CVA children at different courses.
<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>Efficacy Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>ICS+LABA, ICS+LTRA, ICS, LTRA</td>
</tr>
<tr>
<td>4 weeks</td>
<td>ICS+LABA, LTRA, ICS+LTRA, ICS</td>
</tr>
<tr>
<td>8 weeks</td>
<td>ICS, ICS+LABA, ICS+LTRA, LTRA</td>
</tr>
<tr>
<td>12 weeks</td>
<td>ICS, LTRA, ICS+LTRA, ICS+LABA</td>
</tr>
<tr>
<td>16 weeks</td>
<td>ICS, LTRA, ICS+LABA, ICS+LTRA</td>
</tr>
<tr>
<td>20 weeks</td>
<td>ICS, LTRA, ICS+LABA, ICS+LTRA</td>
</tr>
<tr>
<td>28 weeks</td>
<td>ICS, LTRA, ICS+LABA, ICS+LTRA</td>
</tr>
<tr>
<td>36 weeks</td>
<td>ICS, LTRA, ICS+LABA, ICS+LTRA</td>
</tr>
</tbody>
</table>

Notes: ICS: inhaled corticosteroids; LABA: ICS + long-acting bete2-agonist; LTRA: Leukotriene receptor antagonists.

Results of optimal course comparison with other groups not using the drug as controls are plotted in Figure 1, the ICS + LABA group showed a significant improvement in cough at an early stage, particularly in the 4th week, the symptoms significantly improved; meanwhile, the symptoms of ICS+LTRA and ICS groups were significantly improved at 36 weeks. LTRA alone showed a significant improvement at 20 weeks. The safety analysis results with group 1 as the control are shown in Table S4, all four treatment regimens could reduce the risk of CVA recurrence and progression to typical asthma. The effect of the LTRA group was the most significant, followed by ICS and ICS+LABA groups, and then the ICS+LTRA group.
Figure 1. Effective changed from 2 weeks to 36 weeks of ICS+LABA group (A), ICS+LTRA group (B),
ICS alone (C), and LTRA alone (D). ICS: inhaled corticosteroids; LABA: ICS+ long-acting beta2-agonist;
LTRA: Leukotriene receptor antagonists.

In conclusion, our results suggest that the four treatment regimens for CVA children are effective. This
article believes that ICS+LABA is the first choice within 8 weeks of diagnosis, and ICS+LATR treatment
can be selected if the child cannot master the drug absorption technology well. After 8 weeks, it can be
reduced to ICS alone to control CVA for at least 36 weeks based on the remission of symptoms in children.

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Conflict of interest
All authors declare no conflict of interests

Nannan Lou1, Xiang Ma1, 2*, Qingxin Luo3, 4, Xiaoling Wei1, 2, Yun Zhang1, 2, Jing Guo1, 2, Jing Wang1, 2,
Zhongtao Gai1, 2*
1. Department of Respiratory Diseases, Children’s Hospital Affiliated to Shandong University (Jinan Chil-
dren’s Hospital), Jinan, Shandong, 250022, China.
2. Jinan Key Laboratory of Pediatric Respiratory diseases, Jinan Children’s Hospital, Jinan, Shandong,
250022, China.
3. Department of Biostatistics, School of Public Health, Cheeloo College of Medicine, Shandong University,
Jinan, 250000, People’s Republic of China.
4. Institute for Medical Dataology, Cheeloo College of Medicine, Shandong University, Jinan, 250000, Peo-
ple’s Republic of China.
* They are co-corresponding authors.

Correspondence
Xiang Ma, M.D, associate professor, Department of Respiratory Disease, Children’s Hospital affiliated to
Shandong University (Jinan Children’s Hospital), Jinan, Shandong University, Key Laboratory of Pediatric Respiratory Disease, Children’s Hospital affiliated to Shandong University (Jinan Children’s Hospital), Jinan, Shandong 250022,
China, email:maxiang0176@163.com, ORCID: https://orcid.org/0000-0001-6139-4355
Zhongtao Gai, professor, Department of Respiratory Disease, Children’s Hospital affiliated to Shandong
University (Jinan Children’s Hospital), Key Laboratory of Pediatric Respiratory Disease, Children’s Hos-
pital affiliated to Shandong University (Jinan Children’s Hospital), Jinan, Shandong 250022, China,
email:gaizhongtao@sina.com.

They are co-corresponding authors.

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combined with loratadine in treating children with cough variant asthma and influence on inflammatory


**Supporting information**

Additional supporting information can be found online in the Supporting Information section at the end of this article.