Am J Transl Res 2023;15(12):6823-6831
www.ajtr.org /ISSN:1943-8141/AJTR0152254

Original Article

Effects of montelukast sodium combined with budesonide on pulmonary function, serum IgE levels, and EOS percentage in children with comorbid allergic rhinitis and asthma

Shasha Guo[1], Changxing Cao[2]

[1]*Department of Pediatric Medicine, Guizhou Provincial People's Hospital, Guiyang 550002, Guizhou, China;*
[2]*Department of Otorhinolaryngology, Guizhou Provincial People's Hospital, Guiyang 550002, Guizhou, China*

Received July 16, 2023; Accepted October 16, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Objective: This study was designed to determine the effects of montelukast sodium combined with budesonide on pulmonary function, serum immunoglobulin (Ig)E levels, and eosinophil (EOS) percentage in children comorbid with allergic rhinitis (AR) and asthma. Methods: The medical records of 114 children comorbid with AR and asthma treated in the Guizhou Provincial People's Hospital from February 2020 to September 2022 were collected and analyzed retrospectively. Among them, 54 children treated with budesonide were assigned to a control group, and the remaining 60 children treated with montelukast sodium combined with budesonide were assigned to an observation group. The efficacy was compared between the two groups. Additionally, the changes in pulmonary function, serum IgE levels, and EOS percentage were compared between the two groups before and after treatment (one month). The adverse reactions during the treatment and the recurrence of AR within 3 months were recorded. Logistics regression was conducted to analyze the risk factors affecting the efficacy in children. Results: The observation group showed a significantly higher overall response rate than the control group ($P<0.05$). After treatment, the observation group showed significantly higher levels of forced expiratory volume in 1 second (FEV1)%, FEV1/forced vital capacity (FVC), and peak expiratory flow (PEF) than the control group ($P<0.05$), and significantly lower IgE levels and EOS percentage than the control group ($P<0.05$). No significant difference was found between the two groups in terms of the total incidence of adverse reactions ($P>0.05$). According to the follow-up results of prognosis, the observation group presented a greatly lower recurrence rate of AR within 3 months than the control group ($P<0.05$). Multivariate logistics regression analysis showed that therapeutic regimen, IgE, and EOS were independent risk factors affecting the efficacy in the patients ($P<0.05$). Conclusion: Montelukast sodium combined with budesonide can substantially improve the pulmonary function in children with comorbid AR and asthma, alleviate their symptoms of asthma and rhinitis, and lower the IgE level and EOS percentage. In addition, therapeutic regimen, IgE and EOS are independent risk factors affecting the efficacy in patients.

Keywords: Montelukast sodium, budesonide, allergic rhinitis, asthma, pulmonary function

Introduction

Bronchial asthma is one of the most frequently diagnosed diseases of the respiratory system, with its pathophysiological process mainly involving eosinophils (EOSs), mast cells, T lymphocytes, and other cellular components that participate in chronic airway inflammation together [1]. Bronchial asthma mainly manifests as reversible expiratory airflow limitation, with recurrent symptoms such as wheezing, anhelation, and chest tightness [2]. Without timely effective treatment, bronchial asthma can trigger irreversible stenosis and structural changes of the airway, seriously compromising the quality of life and physical and mental health of the patients [3]. Additionally, allergic rhinitis (AR) is a chronic inflammatory disease of nasal mucosa due to atopic exposure to allergens [4], which often coexists with bronchial asthma. According to data survey results, more than 70% patients with bronchial asthma suffer different degrees of rhinitis, while approximately 50% patients with AR suffer allergic asthma [5].

Conventional drug therapy is usually not effective in the treatment of comorbid AR and bronchial asthma. Budesonide, a glucocorticoid drug, is often adopted for children with bronchial asthma, which can effectively control cough symptoms [6, 7]. Montelukast sodium is another drug frequently adopted for children with bronchial asthma. As a non-hormonal drug, it can meet the long-term treatment needs of children, with high safety profile [8]. However, whether the combination of montelukast sodium and budesonide can deliver high efficacy and improve the pulmonary function of children with comorbid AR and asthma still requires further investigation.

This study was designed to determine the effects of montelukast sodium combined with budesonide on pulmonary function, serum IgE levels, and EOS percentage in children with comorbid AR and asthma, aiming at providing reference for clinical treatment.

Methods and data

Clinical data

The medical records of 114 children with AR and asthma treated in Guizhou Provincial People's Hospital from February 2020 and to September 2022 were collected and analyzed retrospectively. Among them, 54 children treated with budesonide were assigned to a control group, and the remaining 60 children treated with montelukast sodium combined with budesonide were assigned to an observation group. This study was approved by the Medical Ethics Committee of Guizhou Provincial People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients who met the criteria in the Guidelines for Diagnosis and Prevention of Bronchial Asthma in Children (2016 Edition) [9] and were confirmed with variable expiratory airflow restriction according to the respiratory symptoms, signs and pulmonary function tests; (2) patients younger than 12 years old; (3) children with detailed clinical data; (4) children who suffered bronchial asthma for the first time.

Exclusion criteria: (1) patients comorbid with other respiratory diseases or pulmonary infection diseases; (2) patients comorbid with autoimmune diseases or tumors; (3) patients who were allergic to drugs adopted in this study or had allergic constitution.

Therapeutic regimens

Both groups received basic routine treatments such as anti-inflammation, oxygen inhalation, and asthma relief, and were given oxygen inhalation according to their blood gas results. The control group received budesonide aerosol inhalation therapy, namely, budesonide inhalation aerosol produced by Lunan BETTER Pharmaceutical Co., Ltd. (State Food and Drug Administration (SFDA) approval number: H20030987), with a dose of 1.0-2.0 mg each time, twice a day.

The observation group was treated with additional montelukast sodium on the basis of the treatment in the control group. Montelukast sodium was administered through chewable tablets (Merck Sharp & Dohme B.V., SFDA approval number: H20181211), with a dose of 5-10 mg each time, twice a day. Both groups received continuous treatment for one month.

Outcome measures

The efficacy was compared between the two groups. To measure the serological indicators, venous blood (5 ml) was extracted from each patient before and after one month of treatment, followed by determining immunoglobulin (Ig)E through double antibody sandwich enzyme-linked immunosorbent assay and EOS percentage through hematoxylin-eosin staining under a high magnification microscope. The changes of pulmonary function in the two groups were compared before and after treatment. Additionally, the adverse reactions during the treatment and the recurrence of AR within 3 months were recorded.

Pulmonary function test

Pulmonary function indicators, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) were examined by a pulmonary function detector (Jaeger MasterScreen TM PAED) in the two groups before and after treatment.

Evaluation criteria of efficacy

The symptoms including runny nose, rhinocnesmus, sneezing, and nasal congestion in the two

Table 1. Baseline data

Factor	Control group (n = 54)	The observation group (n = 60)	χ^2 value	*P* value
Age				
≥6 years old	37	38	0.339	0.560
<6 years old	17	22		
Sex				
Male	34	30	1.940	0.164
Female	20	30		
Height				
≥120 cm	16	24	1.342	0.247
<120 cm	38	36		
Weight				
≥20 kg	24	32	0.899	0.343
<20 kg	30	28		
Family history of allergic rhinitis				
Yes	19	27	1.137	0.286
No	35	33		
Time of onset				
Morning	27	24	1.150	0.284
Night	27	36		
Hospitalization time				
≥12 d	22	33	2.314	0.128
<12 d	32	27		

groups were recorded. The symptoms were scored by 0-3 points: from normal state (0 points) to unbearable symptoms (3 points). With the score directly proportional to the severity of symptoms. According to the improvement degree of the score, the efficacy was classified into markedly effective, effective, and ineffective. Markedly effective: the symptom score was improved by more than 80%; Effective: the improvement of symptom score was between 30% and 80%; Ineffective: the improvement of symptom score was less than 30%. Total response rate = [(number of cases with markedly effective response) + that of cases of effective response]/total number of cases ×100%. The baseline data were compared between the two groups, and Logistics regression was conducted to analyze the risk factors affecting the efficacy in children.

Statistical analyses

This study adopted SPSS 22.0 statistical software for data processing. Measurement data were described by mean ± standard deviation, and analyzed using t test. Counting data were described as percentage (%), and analyzed using χ^2 test. Logistics regression was conducted to analyze the risk factors affecting the efficacy in children. P<0.05 suggests a statistically significant difference.

Results

Baseline data

The two groups were comparable in terms of age, sex, height, weight, family history of AR, onset time, and hospitalization time (P>0.05, **Table 1**).

Comparison of clinical efficacy

The control group showed a notably lower overall response rate than the observation group (P<0.05, **Table 2**).

Comparison of serological indexes

The IgE levels and EOS percentage in the two groups were not greatly different before treatment (P>0.05, **Figure 1**), whereas after treatment, the IgE levels and EOS percentage in both groups decreased significantly (P<0.05, **Figure 1**), and the observation group showed more significant decreases than the control group (P<0.05, **Figure 1**).

Table 2. Clinical efficacy evaluation

Group	Markedly effective	Effective	Ineffective	Total response rate
Control group (n = 54)	15	27	12	42 (77.78%)
Observation group (n = 60)	22	33	5	55 (91.67%)
χ^2 value				4.321
P value				0.037

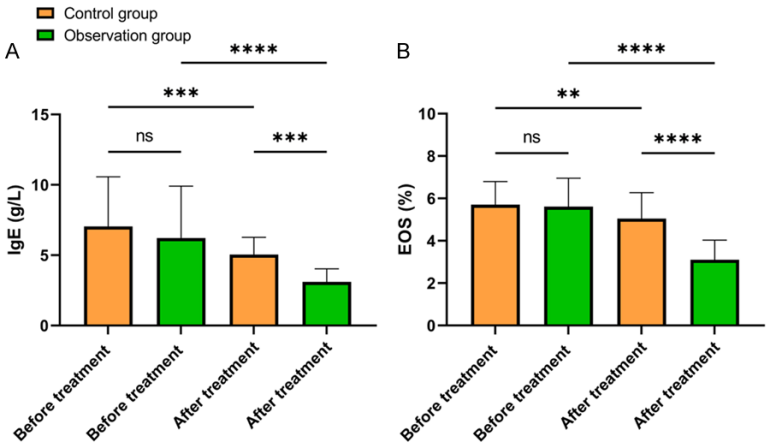

Figure 1. Change in serological indexes before and after treatment. A: Comparison of IgE levels before and after treatment; B: Comparison of EOS percentage before and after treatment. Note: IgE: Serum immunoglobulin E; EOS: Eosinophil; nsP>0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Changes of pulmonary function

Before treatment, the two groups were comparable in terms of FEV1, FVC, and PEF (P>0.05, **Figure 2**), whereas after treatment, the FEV1, FVC, and PEF increased significantly in both groups (P<0.05, **Figure 2**), with more notable increases in the observation group than those in the control group (P<0.05, **Figure 2**).

Comparison of adverse reactions and recurrence

There were no significant differences between the two groups in the incidence of adverse reactions and recurrence rate within 3 months (P>0.05, **Table 3**).

Efficacy assessment

According to the clinical efficacy after treatment, the children were further divided into an effective group and an ineffective group. The risk factors affecting the clinical efficacy in the two groups were analyzed, and therapeutic regimen, IgE, and EOS were found to be strongly associated with the efficacy (P<0.05, **Table 4**). These significant indicators were then assigned (**Table 5**). According to multivariate logistics regression analysis, therapeutic regimen, IgE, and EOS were found to be independent risk factors affecting the efficacy in patients (P< 0.05, **Table 6**).

Discussion

Reportedly, AR is a chronic inflammatory disease of nasal mucosa involving various immunocompetent cells and cytokines [10]. Its main symptoms include nasal discharge, sneezing, nasal obstruction, and rhinocnesmus. T lymphocytes play a crucial part in the development and progression of bronchial asthma, a special chronic airway inflammatory allergy [11]. Prior research has revealed that T lymphocytes can trigger the increase of airway hyperresponsiveness and extensive reversible airflow restriction, which is one of the main causes of bronchial asthma [12]. The AR-induced immune inflammatory reaction may be the main reason for the recurrence of these two diseases. Accordingly, actively alleviating the inflammatory response, improving the immune function of patients, and restoring the normal airway response mechanism are the key points of comprehensive treatment of comorbid AR and asthma [13].

Currently, drug therapy is one of the main treatment measures for comorbid AR and asthma [14]. Therapeutic drugs are mainly classified into control drugs and relief drugs. Control drugs, such as glucocorticoid, long-acting β2 receptor agonist, and leukotriene regulator, usually require long-term administration to control asthma symptoms through anti-inflammatory mechanisms [15]. Relief drugs, such as

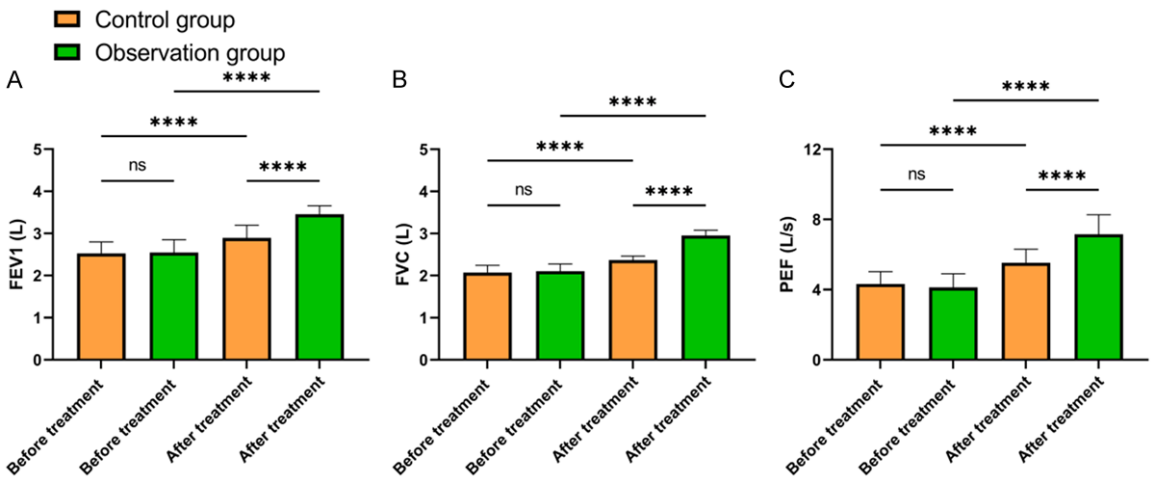

Figure 2. Changes in pulmonary function indexes before and after treatment. A: Comparison of FEV1 before and after treatment; B: Comparison of FVC before and after treatment; C: Comparison of PEF before and after treatment. Note: FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PEF: Peak expiratory flow; nsP>0.05; ****P<0.0001.

Table 3. Adverse reactions

Group	Nasal mucosa stimulation	Somnolence	Gastrointestinal reaction	Mental disorder	Recurrence
Control group (n = 54)	3	2	2	1	8
Observation group (n = 60)	4	3	2	2	11
χ^2 value	0.060	0.113	0.011	0.243	0.253
P value	0.805	0.735	0.914	0.621	0.614

short-acting theophylline, quick-acting inhaled β2 receptor agonist, and systemic hormone, are mainly adopted to quickly relieve symptoms of bronchospasm and asthma [16].

Budesonide, a novel glucocorticoid, is adept at inhibiting inflammatory exudation, curtailing airway inflammation, and profoundly relaxing bronchi. Administered via aerosol inhalation, it offers a convenient and rapid delivery mechanism, ensuring a high local blood concentration and excellent drug safety. This allows for swift inflammation inhibition and bronchial dilation [17]. Over recent years, budesonide has solidified its position as a first-line treatment for bronchial asthma across all age groups. Nevertheless, while employing such medications, it's pivotal to meticulously monitor the application duration and abstain from prolonged use to avert adverse reactions like allergies and psychological symptoms [18].

Montelukast sodium, a newly-introduced specific leukotriene receptor antagonist [19], works by directly inhibiting leukotriene polypeptide activity through its unique receptor antagonism, thereby cutting down on the release of leukotriene-mediated inflammatory agents. As a result, it substantially enhances vascular permeability, mitigates bronchospasms and EOS infiltration associated with AR, and reduces the airway hyperresponsiveness in patients with AR-induced bronchial asthma [20].

In our study, the observation group demonstrated a remarkably superior overall response rate compared to the control group. Additionally, after treatment, the observation group experienced more significant decline in serum IgE levels and EOS percentage, as well as more pronounced elevations in FEV1, FVC, and PEF than the control group. No significant differences were observed between the two groups concerning the incidence of adverse reactions and the recurrence rate of AR. These findings suggest that the combination of montelukast sodium and budesonide offers augmented efficacy for children with coexisting AR and asthma, enhancing their immune and pulmonary functions without amplifying the adverse reactions

Table 4. Univariate analysis

Factor	Effective group (n = 97)	Ineffective group (n = 17)	χ^2 value	*P* value
Age				
≥6 years old	63	12	0.204	0.651
<6 years old	34	5		
Sex				
Male	53	11	0.595	0.440
Female	44	6		
Height				
≥120 cm	31	9	2.796	0.094
<120 cm	66	8		
Weight				
≥20 kg	48	8	0.034	0.854
<20 kg	49	9		
Family history of allergic rhinitis				
Yes	39	7	0.006	0.940
No	58	10		
Time of onset				
Morning	44	7	0.102	0.749
Night	53	10		
Hospitalization time				
≥12 d	48	7	0.400	0.527
<12 d	49	10		
IgE (g/L)	8.84±3.12	6.22±3.57	2.843	0.005
EOS (%)	6.49±0.98	5.51±1.21	3.180	0.002
FEV1 (L)	2.52±0.29	2.54±0.29	0.230	0.818
FVC (L)	2.09±0.19	2.09±0.17	0.069	0.945
PEF (L/s)	4.00±0.56	4.26±0.77	1.341	0.182

Note: IgE: Serum immunoglobulin E; EOS: Eosinophil; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PEF: Peak expiratory flow.

Table 5. Assignment

Factor	Assignment
Therapeutic regimen	Control group = 1, Observation group = 0
IgE (g/L)	≥6 = 1, <6 = 0
EOS (%)	≥5.67 = 1, <5.67 = 0
Efficacy	Ineffective = 1, Markedly effective + Effective = 0

Note: IgE: Serum immunoglobulin E; EOS: Eosinophil.

or recurrence rate of AR. This heightened effectiveness is likely attributed to montelukast sodium's ability, as a leukotriene receptor antagonist, to specifically obstruct human airway smooth muscle, macrophages, and cysteinyl leukotriene receptors. This action minimizes biological effects, halts vascular permeability and EOS aggregation, and diminishes immunoglobulin E synthesis. Consequently, it reduces the functional impairment of nasal mucosa and regulates disease progression. In synergy, the budesonide nasal spray and montelukast sodium can address various clinical symptoms, facilitating patient recovery. In the previous study of Wei et al. [21], montelukast sodium combined with loratadine significantly improved the clinical efficacy in children with cough variant asthma, and as well as the levels of FEV1, FEV1/FVC, PEF, TNF-α, IL-4, EOS and IgE. In addition, another study found that montelukast sodium combined with budesonide aerosol effectively promoted the improvement of airway function, regulated the level of T lymphocytes, reduced inflammatory reaction, and improved the total clinical efficacy [22]. This suggests that the combination of montelukast and budesonide is effective in treating children with both AR and asthma.

Table 6. Logistics regression analysis of risk factors affecting patient efficacy

Factor	β	Standard error	Chi square value	*P*-value	OR value	95% CI	
						Lower limit	Upper limit
Therapeutic regimen	1.316	0.633	4.317	0.038	3.727	1.077	12.893
IgE (g/L)	-1.841	0.716	6.612	0.01	0.159	0.039	0.645
EOS (%)	-2.248	0.722	9.702	0.002	0.106	0.026	0.435

Note: IgE: Serum immunoglobulin E; EOS: Eosinophil.

At the end of the study, the risk factors affecting the efficacy in patients were analyzed. Montelukast sodium is a specific leukotriene receptor antagonist, which can inhibit leukotrienes-induced airway inflammation and allergic reactions [23]. Budesonide is a corticosteroid, which can inhibit the release of inflammatory mediators, thus alleviating inflammation [24]. The combination use of the two drugs may produce superimposed or enhanced effects on different inflammatory pathways, inhibiting allergic reactions and inflammation more effectively. IgE is an antibody closely related to allergic diseases. It binds with specific allergens in the body and then triggers allergic reactions, such as asthma and AR [25]. EOS are a kind of white blood cells related to allergic reaction and inflammation, which plays a central role in allergic diseases, especially in asthma [26]. Higher IgE and EOS levels usually mean more severe allergic reactions, and may increase the difficulty of treatment. Therefore, the IgE and EOS levels may affect the efficacy.

However, this study still has some limitations. First of all, the study is a retrospective study with a small number of sample size. Secondly, only the recurrence data within 3 months have been acquired, so the long-term effect of the two drugs on children still requires further investigation. Therefore, we hope to conduct more clinical experiments in the future to improve the research conclusions.

In summary, budesonide nasal spray combined with montelukast sodium can effectively improve the pulmonary function, serum IgE levels, and EOS percentage of children with comorbid AR and asthma, without increasing the adverse reactions and recurrence rate. These results are benefical to the immune function and pulmonary function of children.

Disclosure of conflict of interest

None.

Address correspondence to: Changxing Cao, Department of Otorhinolaryngology, Guizhou Provincial People's Hospital, No. 83, Zhongshan East Road, Nanming District, Guiyang 550002, Guizhou, China. Tel: +86-15685118799; E-mail: 319468ccc@sina.com

References

[1] Kunc P, Fabry J, Lucanska M and Pecova R. Biomarkers of bronchial asthma. Physiol Res 2020; 69 Suppl 1: S29-S34.

[2] Chetta A and Calzetta L. Bronchial asthma: an update. Minerva Med 2022; 113: 1-3.

[3] Comite Nacional de Neumonología; Comite Nacional de Alergia; Comite Nacional de Emergencia y Cuidados Críticos; Comite Nacional de Familia y Salud Mental. Guideline on diagnosis and treatment: bronchial asthma in children ≥6 years old. Update 2021. Arch Argent Pediatr 2021; 119: S123-S158.

[4] Siddiqui ZA, Walker A, Pirwani MM, Tahiri M and Syed I. Allergic rhinitis: diagnosis and management. Br J Hosp Med (Lond) 2022; 83: 1-9.

[5] Bousquet J, Schunemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, Klimek L, Pfaar O, Wallace D, Ansotegui I, Agache I, Bedbrook A, Bergmann KC, Bewick M, Bonniaud P, Bosnic-Anticevich S, Bosse I, Bouchard J, Boulet LP, Brozek J, Brusselle G, Calderon MA, Canonica WG, Caraballo L, Cardona V, Casale T, Cecchi L, Chu DK, Costa EM, Cruz AA, Czarlewski W, D'Amato G, Devillier P, Dykewicz M, Ebisawa M, Fauquert JL, Fokkens WJ, Fonseca JA, Fontaine JF, Gemicioglu B, van Wijk RG, Haahtela T, Halken S, Ierodiakonou D, Iinuma T, Ivancevich JC, Jutel M, Kaidashev I, Khaitov M, Kalayci O, Kleine Tebbe J, Kowalski ML, Kuna P, Kvedariene V, La Grutta S, Larenas-Linnemann D, Lau S, Laune D, Le L, Lieberman P, Lodrup Carlsen KC, Lourenco O, Marien G, Carreiro-Martins P, Melen E, Menditto E, Neffen H, Mercier G, Mosgues R, Mullol J, Muraro A, Namazova L, Novellino E, O'Hehir R, Okamoto Y, Ohta K, Park HS, Panzner P, Passalacqua G, Pham-Thi N, Price D, Roberts G, Roche N, Rolland C, Rosario N, Ryan D, Samolinski B, Sanchez-Borges M, Scadding GK, Shamji MH, Sheikh A, Bom AT, Toppila-Salmi S, Tsiligianni I, Valentin-Rostan M, Valiulis A, Valovirta E, Ven-

tura MT, Walker S, Waserman S, Yorgancioglu A and Zuberbier T; Allergic Rhinitis and Its Impact on Asthma Working Group. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol 2020; 145: 70-80, e3.

[6] Papi A, Chipps BE, Beasley R, Panettieri RA Jr, Israel E, Cooper M, Dunsire L, Jeynes-Ellis A, Johnsson E, Rees R, Cappelletti C and Albers FC. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. N Engl J Med 2022; 386: 2071-2083.

[7] Heo YA. Budesonide/glycopyrronium/formoterol: a review in COPD. Drugs 2021; 81: 1411-1422.

[8] Murphy KR, Hong JG, Wandalsen G, Larenas-Linnemann D, El Beleidy A, Zaytseva OV and Pedersen SE. Nebulized inhaled corticosteroids in asthma treatment in children 5 years or younger: a systematic review and global expert analysis. J Allergy Clin Immunol Pract 2020; 8: 1815-1827.

[9] Subspecialty Group of Respiratory Diseases, Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Guideline for the diagnosis and optimal management of asthma in children (2016). Zhonghua Er Ke Za Zhi 2016; 54: 167-181.

[10] Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, Melen E, Palomares O, Scadding GK, Togias A and Toppila-Salmi S. Allergic rhinitis. Nat Rev Dis Primers 2020; 6: 95.

[11] Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, Suzaki H, Fujieda S and Masuyama K; Japanese Society of Allergology. Japanese guidelines for allergic rhinitis 2020. Allergol Int 2020; 69: 331-345.

[12] Iinuma T, Kiuchi M, Hirahara K, Kurita J, Kokubo K, Yagyu H, Yoneda R, Arai T, Sonobe Y, Fukuyo M, Kaneda A, Yonekura S, Nakayama T, Okamoto Y and Hanazawa T. Single-cell immunoprofiling after immunotherapy for allergic rhinitis reveals functional suppression of pathogenic T(H)2 cells and clonal conversion. J Allergy Clin Immunol 2022; 150: 850-860, e5.

[13] Kaminuma O, Nishimura T, Saeki M, Mori A and Hiroi T. T cell-mediated nasal hyperresponsiveness in allergic rhinitis. Biol Pharm Bull 2020; 43: 36-40.

[14] Breiteneder H, Peng YQ, Agache I, Diamant Z, Eiwegger T, Fokkens WJ, Traidl-Hoffmann C, Nadeau K, O'Hehir RE, O'Mahony L, Pfaar O, Torres MJ, Wang DY, Zhang L and Akdis CA. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. Allergy 2020; 75: 3039-3068.

[15] Eguiluz-Gracia I, Mathioudakis AG, Bartel S, Vijverberg SJH, Fuertes E, Comberiati P, Cai YS, Tomazic PV, Diamant Z, Vestbo J, Galan C and Hoffmann B. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. Allergy 2020; 75: 2170-2184.

[16] Nappi E, Paoletti G, Malvezzi L, Ferri S, Racca F, Messina MR, Puggioni F, Heffler E and Canonica GW. Comorbid allergic rhinitis and asthma: important clinical considerations. Expert Rev Clin Immunol 2022; 18: 747-758.

[17] Zhang Y, Shan C, Liu W, Han Y, Shi G, Ma Y, Wagner K, Tian X, Zhang L, Larona AJ, Sacavage S, Franklin K, Wang C and Zhang L. Intranasal budesonide for rhinitis during a high airborne pollution period: a randomized controlled trial. Allergy Asthma Clin Immunol 2022; 18: 56.

[18] Bagherinia E, Falahi S, Mortazavi SH, Salari F, Rezaiemanesh A and Karaji AG. Co-treatment with fexofenadine and budesonide increases FoxP3 gene expression in patients with allergic rhinitis. Am J Rhinol Allergy 2023; 37: 623-629.

[19] Paljarvi T, Forton J, Luciano S, Herttua K and Fazel S. Analysis of neuropsychiatric diagnoses after montelukast initiation. JAMA Netw Open 2022; 5: e2213643.

[20] Menku Ozdemir FD, Ustun GG, Kosemehmetoglu K, Ispirli M, Boynuyogun E and Uzun H. Comparison of cromolyn sodium, montelukast, and zafirlukast prophylaxis for capsular contracture. Plast Reconstr Surg 2022; 150: 1005e-1014e.

[21] Wei H, Li W, Jiang Z, Xi X and Qi G. Clinical efficacy of montelukast sodium combined with budesonide or combined with loratadine in treating children with cough variant asthma and influence on inflammatory factors in the serum. Exp Ther Med 2019; 18: 411-417.

[22] Jin W, Zhao Z and Zhou D. Effect of Montelukast sodium combined with Budesonide aerosol on airway function and T lymphocytes in asthmatic children. Pak J Med Sci 2022; 38: 1265-1270.

[23] Yi F, Zhan C, Liu B, Li H, Zhou J, Tang J, Peng W, Luo W, Chen Q and Lai K. Effects of treatment with montelukast alone, budesonide/formoterol alone and a combination of both in cough variant asthma. Respir Res 2022; 23: 279.

[24] Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group; Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R and Hawthorne AB. British Society of Gastroenterology consen-

sus guidelines on the management of inflammatory bowel disease in adults. Gut 2019; 68: s1-s106.

[25] Fang S, Song Y, Zhang S and Li C. Retrospective study of budesonide in children with eosinophilic gastroenteritis. Pediatr Res 2019; 86: 505-509.

[26] Dedaj R and Unsel L. Case study: a combination of mepolizumab and omaluzimab injections for severe asthma. J Asthma 2019; 56: 473-474.