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Clinical Efficacy and Influencing Factors of Budesonide Inhalation in the Treatment of Cough Variant Asthma in Adults

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ABSTRACT

Budesonide inhalation therapy is effective for cough variant asthma (CVA), but the influencing factors are not well understood.

This retrospective study assessed the clinical efficacy and influencing factors of budesonide inhalation therapy in 223 adult patients with CVA treated between January 2022 and February 2024. All patients received standard symptomatic treatment along with budesonide inhalation. The primary outcomes included lung function, serum inflammatory markers, and immune function, along with adverse reactions. Patients were divided into effective and ineffective groups based on treatment outcomes, and logistic regression was used to identify factors influencing treatment effectiveness.

After treatment, lung function improved significantly, with increased forced expiratory volume, forced vital capacity, and peak expiratory flow. Additionally, serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-4, and immunoglobulin E decreased. Immune function showed an increase in $CD3^+$ and $CD4^+$ cells, while $CD8^+$ cells decreased. Adverse effects included nausea and indigestion in 5.83% of patients, drowsiness and fatigue in 4.04%, and throat discomfort in 3.14%. Based on the therapeutic efficacy evaluation after treatment, patients were divided into an effective group (n=188) and an ineffective group (n=35). Further multivariate logistic regression analysis revealed that older age (odds ratio [OR]=1.570), lower levels of 25-hydroxyvitamin D3 [25(OH)D3] (OR=0.798), and high levels of TNF-α (OR=1.850) increased the risk of reduced therapeutic efficacy.

Budesonide inhalation therapy is effective for CVA patients, as it can improve lung function, reduce inflammation, and enhance immune function. However, factors such as age, 25(OH)D3, and TNF-α may influence the treatment outcomes.

Keywords: Budesonide; Treatment outcome; Cough variant asthma; Immune system phenomena; Risk factor

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INTRODUCTION

Cough variant asthma (CVA) is a specific type of asthma characterized primarily by irritant cough and

nighttime cough, which can occur upon exposure to allergens, inhalation of cold air, or emotional excitement.[1] The treatment principles for CVA are similar to those for traditional asthma, emphasizing early diagnosis and standardized treatment, focusing on anti-inflammatory measures, and using bronchodilators as an adjunct.[2,3] Corticosteroids are the main medications for treating CVA, as they can inhibit inflammatory cells and mediators, alleviating symptoms. Considering safety and side effects, inhaled corticosteroids such as budesonide, beclomethasone dipropionate, and fluticasone propionate are widely used in clinical practice due to their strong local action and minimal systemic absorption.[4,5]

CVA is quite complex, involving airway inflammation, excessive contraction of airway smooth muscles, excessive mucus secretion, and remodeling of the airway wall.[1,6] These factors act together to cause narrowing and obstruction of the airways, leading to symptoms such as cough and wheezing. Budesonide, as a widely used inhaled corticosteroid, has been confirmed by multiple studies to improve the symptoms and lung function of CVA patients.[4,5] However, the therapeutic effect of CVA may be influenced by a variety of factors, such as the patient's baseline characteristics, comorbidities, treatment duration, cellular phenotype, and biochemical indicators.[7,8] The comprehensive consideration of these factors is of great significance for optimizing the treatment plan for CVA, improving therapeutic effects, and reducing the risk of complications.

The objective of this study was to evaluate the efficacy of budesonide inhalation therapy in adult patients with CVA through clinical data analysis and to explore in depth the factors that may influence the efficacy of treatment. Through this in-depth analysis, we hope to provide clinicians with more precise treatment guidance and decision support to optimize the treatment process for patients with CVA.

MATERIALS AND METHODS

Research Object

We conducted a retrospective study that included 223 CVA patients who visited the outpatient respiratory department of the hospital between January 2022 and February 2024.

Inclusion criteria included adult patients diagnosed with CVA for the first time, who received routine treatment combined with inhaled budesonide therapy, had complete medical records and clinical data and consented to the use of their data for this study.

Exclusion criteria included patients with a history of autoimmune diseases, severe organic lesions, other respiratory diseases (e.g., tuberculosis or bronchiectasis), allergies to the medications used, or those who altered their medication dosage or used other drugs during the treatment period that could affect efficacy evaluation.

This study was conducted after obtaining review and approval from Zhaotong First People's Hospital's Ethics Committee. We communicated with all participants through telephone or instant messaging tools and obtained their verbal informed consent.

Diagnostic Criteria for Cough Variant Asthma

The diagnostic criteria for CVA were in line with the Guidelines for the Diagnosis and Management of Cough in China (2010).[9]

The diagnostic criteria for CVA include several key factors. First, patients experience a chronic cough that is either the only symptom or the most significant one, lasting for more than 8 weeks. Second, there must be evidence of airflow variability, which can be demonstrated through a positive bronchial challenge test, where there is a significant decrease in forced expiratory volume in one second (FEV1) by at least 20% from baseline following the administration of 12.8 μmol of methacholine or 7.8 μmol of histamine. Alternatively, a positive bronchodilator reversibility test can be used, showing a significant increase in FEV1 by at least 12% and 200 ml from baseline after the use of a bronchodilator. Lastly, the patient's response to anti-asthma treatment is considered, with improvement in cough symptoms upon the use of anti-asthmatic therapy during follow-up visits.

Treatment Methods

All patients received inhaled budesonide treatment on the basis of routine treatment. Routine treatment includes cough suppression and expectoration, as well as anti-infective therapy. Budesonide suspension (produced by AstraZeneca Pty Ltd, Australia) 1 mg was inhaled via nebulization, twice a day, for a continuous treatment period of 8 weeks. If the patient's symptoms disappear and the patient is clinically cured, medication should be discontinued.

Research Methods

By querying the electronic medical record system and related clinical treatment records, the following data were collected:

Lung function was assessed using the HI-801 spirometer (Chest Co Ltd, Japan), measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF). Serum factors were analyzed using the enzyme-linked immunosorbent assay (ELISA) method, in which serum samples were extracted and reacted with specific antibodies to quantitatively determine the levels of tumor necrosis factor-alpha (TNF-α), interleukin-4 (IL-4), and immunoglobulin E (IgE). Immune function was evaluated through flow cytometry of peripheral blood lymphocytes, marking CD3, CD4, and CD8 antigens. The percentages of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes were measured. Cough symptoms were scored by comparing daytime and nighttime symptoms between the 2 groups, with a scale ranging from 0 to 3. A lower score indicates less impact on the patient's daily life and a milder condition. Specifically, a score of 0 represents no cough symptoms, 1 indicates occasional coughing, 2 signifies more frequent coughing that slightly interferes with daily life and sleep, and 3 denotes severe coughing that significantly disrupts daily activities. Adverse reactions, including nausea, dyspepsia, drowsiness, fatigue, and throat discomfort, were also monitored.

Efficacy Evaluation and Grouping

The clinical efficacy evaluation criteria are defined as follows. Cured refers to patients whose symptoms completely disappear after treatment; for patients with mild or moderate cough, their symptoms should vanish entirely, while those with severe cough experience a reduction in symptoms to a mild level, with nocturnal cough symptoms disappearing or significantly decreasing. Improved indicates that after treatment, patients experience significant improvement or near-complete resolution of their nocturnal cough symptoms, leading to stable nocturnal sleep and the ability to carry out normal daytime activities. Ineffective is used when, after treatment, patients' cough symptoms persist without any sign of alleviation. The total effective rate is calculated as the sum of the Cured and Improved cases divided by the total number of cases, multiplied by 100%.

We divided the patients into effective and ineffective groups based on clinical efficacy, collected data on patients' baseline characteristics, cellular phenotype, and sputum cytology, and conducted logistic regression analysis to identify factors affecting efficacy.

Data Analysis

In this study, all data were analyzed using GraphPad Prism 9.5.0. Categorical data were expressed as percentages and analyzed using the χ^2 test; continuous data were expressed as mean ± standard deviation and a pairwise *t* test was used to analyze the differences from baseline to the 8th weeks. Factors affecting the efficacy in adult CVA patients were analyzed using univariate and multivariate logistic regression. A p value of <0.05 was considered statistically significant.

RESULTS

Technical Route

As shown in Figure 1, we included 223 patients with CVA who received budesonide inhalation treatment, assessing the clinical effects before and after treatment, including lung function, serum inflammatory factor levels, and immune function. Based on the treatment outcomes, patients were divided into ineffective and effective groups, and clinical factors related to efficacy were collected. Logistic regression analysis was used to explore the factors influencing treatment efficacy.

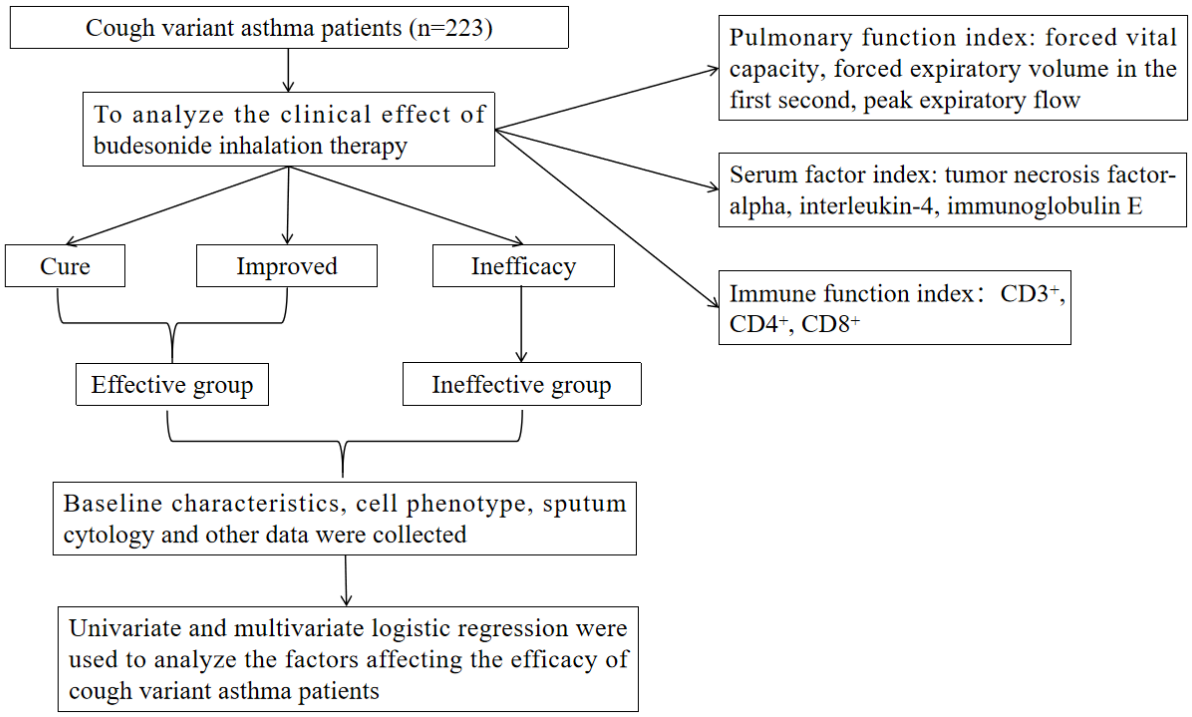

Figure 1. Study flow chart. We included 223 patients with cough variant asthma who received conventional treatment combined with inhaled budesonide. To analyze clinical outcomes, improvements in lung function index, serum factor index, and immune function index before and after treatment. Based on the treatment outcomes, patients were classified into the ineffective group and the effective group. We collected baseline characteristics, cell phenotypes, sputum cytology, and other data, and used logistic regression analysis to explore the factors influencing treatment efficacy.

Improvement of Lung Function

Table 1 shows the changes in lung function indicators in 223 patients from baseline (before treatment) to the 8th week. The data indicate that whether it is FVC, FEV1, or PEF, patients showed significant improvement in the 8th week after treatment ($p < 0.05$), which may suggest that the treatment has a positive impact on the patients' respiratory function.

Changes in Serum Factors

Table 1 shows the changes in serum factors in 223 patients from baseline to week 8. TNF-α, IL-4, and IgE significantly decreased after the treatment ($p<0.05$), which may be related to the treatment's effects in reducing inflammatory responses and allergic symptoms.

Improvement of Immune Function

Table 1 demonstrates the improvement of immune function in 223 patients from baseline to the 8th week. Budesonide inhalation treatment significantly increased the percentage of $CD3^+$ and $CD4^+$ lymphocytes, enhancing the patients' immune function, while reducing the percentage of $CD8^+$ lymphocytes, indicating that the treatment helps to regulate the overactive immune response.

Cough Symptom

Table 1 shows the cough symptom scores of 223 patients from baseline to the 8th week. In conclusion, after budesonide inhalation treatment, the patients' cough symptoms were reduced ($p<0.05$).

Table 1. Improvement of lung function, serum factors, immune function and cough symptoms from baseline to week 8

Pulmonary function index	Baseline	Week 8	*t*	*p* value
FVC (L)	2.79±0.34	3.56±0.35	−22.831	＜0.001
FEV1 (L)	1.62±0.23	2.51±0.43	−27.326	＜0.001
PEF (L/s)	2.15±0.47	3.16±0.41	−24.152	＜0.001
TNF-α (ng/L)	26.35±6.54	20.78±5.96	9.697	＜0.001
IL-4 (ng/L)	69.85±9.54	60.35±10.57	10.044	＜0.001
IgE (U/L)	1.53±0.33	1.22±0.17	11.744	＜0.001
$CD3^+$%	44.52±4.32	50.32±5.17	−12.788	＜0.001
$CD4^+$%	35.37±5.14	40.12±5.32	−21.441	＜0.001
$CD8^+$%	22.51±5.01	17.85±3.25	11.668	＜0.001
Daytime cough scores	2.65±0.62	0.99±1.07	23.237	＜0.001
Evening cough score	2.66±0.58	1.11±1.11	19.568	＜0.001

FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; PEF: peak expiratory flow; TNF-α: tumor necrosis factor-alpha; IL-4: interleukin-4; IgE: immunoglobulin E.

Clinical Effects

After 8 weeks of treatment, out of 223 patients treated, 86 were cured, 102 showed improvement, and 35 were ineffective, with a total effective rate of 84.31%, indicating that the majority of patients experienced an improvement in their condition after receiving treatment.

Adverse Reaction Situation

During the treatment, 13 patients (5.83%) experienced nausea and dyspepsia, 9 patients (4.04%) experienced drowsiness and fatigue, and 7 patients (3.14%) reported throat discomfort. The adverse reaction symptoms were all mild, and no serious adverse reactions were observed, which did not affect the treatment process.

Univariate Analysis

Among the 223 patients, 35 were included in the ineffective group, and the other 188 were included in the effective group. In the univariate logistic regression analysis, we found that factors such as age, smoking, small airway dysfunction, duration of cough, 25-hydroxyvitamin D3 [25(OH)D3], percentage of eosinophils in sputum (Eos%), $CD4^+$%, and TNF-α levels all had significant effects on the efficacy. Patients who were younger had no smoking history or had quit smoking, had no small airway dysfunction, had a shorter duration of cough, had high levels of 25(OH)D3, had low levels of Eos%, had high levels of CD4+%, and had low levels of TNF-α had better therapeutic outcomes. See Table 2.

Multivariate Analysis

In the multivariate logistic regression analysis, we further verified the impact of factors such as age, smoking, small airway dysfunction, duration of cough, 25(OH)D3, Eos%, $CD4^+$%, and TNF-α levels on the efficacy. The results showed that after controlling for other variables, age, 25(OH)D3, and TNF-α levels remained significant factors affecting the efficacy. See Table 3.

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Table 2. Univariate logistic analysis of the effect of budesonide inhalation therapy on adult cough variant asthma patients

Variable	Effective group (n=188)	Ineffective group (n=35)	Odds ratio	95% CI	*p* value
Gender					
Male	103 (54.79)	24 (68.57)	Ref.		
Female	85 (45.21)	11 (31.43)	0.555	0.249–1.170	0.130
Age. y	42.56±5.89	52.46±6.30	1.300	1.210–1.430	<0.001
Smoke					
Never/quit smoking	142 (75.53)	18 (51.43)	Ref.		
Present	46 (24.47)	17 (48.57)	2.920	1.380–6.150	0.005
Family history of asthma					
No	111 (59.04)	26 (74.29)	Ref.		
Yes	77 (40.96)	9 (25.71)	0.570	0.241–1.250	0.180
Small airway dysfunction					
No	124 (65.96)	16 (45.71)	Ref.		
Yes	64 (34.04)	19 (54.27)	3.190	1.530–6.750	0.002
Asthma duration, y	2.69±0.36	2.97±0.42	9.440	3.130–31.900	<0.001
Cough quality					
Have phlegm	124 (65.96)	21 (60.00)	Ref.		
Dry cough	64 (34.04)	14 (40.00)	0.774	0.372–1.650	0.500
Trigger					
Other	28 (14.89)	9 (25.71)	Ref.		
Catch a cold	58 (30.85)	10 (28.57)	0.897	0.389–1.940	0.790
Allergy	67 (35.64)	8 (22.86)	0.535	0.217–1.200	0.150
Pungent smell	21 (11.17)	4 (11.43)	1.030	0.285–2.930	0.960
Eat/drink	14 (7.45)	4 (11.43)	1.600	0.433–4.820	0.430
25(OH)D3	69.52±15.36	41.33±10.74	0.863	0.821–0.900	<0.001
Eos%	13.69±3.21	16.25±3.45	1.270	1.130–1.430	<0.001
$CD3^+$%	44.38±4.42	45.25±3.73	1.100	1.05–0.965	0.270
$CD4^+$%	35.69±5.14	33.65±4.85	0.922	0.855–0.992	0.030
$CD8^+$%	22.27±5.17	23.80±3.87	1.060	0.987–1.130	0.100
FVC (L)	2.79±0.34	2.83±0.35	1.360	0.476–3.860	0.560
FEV1 (L)	1.63±0.23	1.56±0.25	0.311	0.061–1.490	0.150
PEF (L/s)	2.13±0.48	2.20±0.40	1.370	0.631–3.020	0.430
TNF-α (ng/L)	25.03±6.00	33.46±4.56	1.420	1.270–1.600	<0.001
IL-4 (ng/L)	70.02±9.20	68.97±11.26	0.988	0.951–1.030	0.550
IgE (U/L)	1.53±0.33	1.51±0.36	0.865	0.291–2.560	0.790

25(OH)D3: 25-hydroxyvitamin D3; Eos%: percentage of eosinophils in sputum; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; IgE: immunoglobulin E; IL-4: interleukin-4; PEF: peak expiratory flow; TNF-α: tumor necrosis factor-alpha.

Table 3. Multivariate logistic regression analysis of risk factors affecting the efficacy of budesonide inhalation therapy in cough variant asthma patients

Variable	β	$\|Z\|$	Odds ratio	95% CI		*p* value
				Lower	Upper	
Age	0.450	2.690	1.570	1.220	2.410	0.007
Asthma duration	−0.370	0.213	0.690	0.018	23.100	0.830
Smoke	−0.872	0.613	0.418	0.022	7.090	0.540
Small airway dysfunction	1.790	1.330	6.010	0.541	146.00	0.180
25(OH)D3	−0.226	2.970	0.798	0.656	0.893	0.003
Eos%	0.357	1.830	1.430	1.030	2.300	0.070
$CD4^+$%	−0.215	1.680	0.807	0.602	1.010	0.090
TNF-α	0.615	2.860	1.850	1.340	3.240	0.004

25(OH)D3: 25-hydroxyvitamin D3; Eos%: percentage of eosinophils in sputum; TNF-α: tumor necrosis factor-alpha

DISCUSSION

Data show that CVA is the second most common cause of chronic cough,[2] accounting for as much as 32.6% of cases of chronic cough.[6] We have observed that most patients often perceive the severity of CVA to be low, leading to insufficient attention and systematic treatment in the early stages of the disease. This results in further deterioration and can ultimately develop into more severe respiratory diseases like asthma. Coughing is the only or main clinical manifestation in patients with CVA, who primarily present with intense, dry coughs that are often triggered by inhaling cold air, dust, smoke, and other irritants. Notably, coughing frequently occurs at night and in the early morning, without significant symptoms like wheezing or shortness of breath.[1,2,3,6,10] Currently, the pathogenesis of CVA remains unclear, and its treatment is generally consistent with typical asthma management.

Through clinical data analysis, we evaluated the efficacy of budesonide inhalation treatment in patients with CVA, and the results showed that budesonide inhalation treatment can significantly improve the lung function indicators of CVA patients, reduce inflammatory responses, and improve cough symptoms. This is consistent with previous research results.[11,12] As a local anti-inflammatory drug, budesonide can inhibit the activity and number of eosinophils involved in the inflammatory response, reduce the airway's response to direct and indirect stimuli, alleviate cough caused by immediate and late allergic reactions, effectively prevent and suppress related diseases, and promote the recovery of lung function.[5] In addition, after nebulization inhalation, budesonide has an inhibitory effect on mucus, improves tracheal ciliary movement, improves vascular fragility, reduces the incidence of airway adverse reactions, smooths the airway, relieves bronchial spasms, and significantly improves the respiratory function of patients.[13]

The etiology of CVA is diverse, including genetic, environmental, and immune response factors. An imbalance of T lymphocytes and abnormal secretion play a key role in the occurrence and development of the disease. Under normal circumstances, T lymphocytes maintain the body's immune balance through mutual cooperation and regulation, with $CD4^+$ and $CD8^+$ T lymphocytes playing important roles in immune regulation. This study observed that after treatment with budesonide nebulization, the levels of $CD3^+$ and $CD4^+$ T lymphocytes in CVA patients increased, while the levels of $CD8^+$ T lymphocytes decreased, indicating that budesonide nebulization may improve immune function by regulating the balance of T lymphocytes. This is consistent with previous research findings.[14] $CD4^+$ T lymphocytes are the precursors of type 1 and 2 helper T cells (T_H1 and T_H2). Budesonide may increase the levels of $CD4^+$ T lymphocytes and decrease the levels of $CD8^+$ T lymphocytes by promoting T_H1 immune responses or inhibiting T_H2 immune responses. In the study by Pace E et al[15] budesonide was able to increase the expression of Toll-like receptor 4 (TLR4) and TLR2 in regulatory T (Treg) cells, which helps to enhance the activity of Treg cells, reducing the release of IL-6 and TNF-α in asthma patients by increasing the expression of TLR4, TLR2, and IL-10. Additionally, another study by Dai et al[16] pointed out that budesonide, through sustained

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release treatment for allergic rhinitis, not only effectively controlled allergic symptoms but also significantly downregulated T_H2 cells and T_H2-type inflammatory factors, while increasing the ratio of T_H1 to T_H2 cells. Pace et al[17] also explored the multiple in vitro and in vivo regulatory effects of budesonide on $CD4^+$ T lymphocyte subsets in patients with allergic asthma. The study results showed that budesonide can regulate T cell survival, inducible costimulatory molecules on T cells, forkhead box P3, and IL-10 molecules in different ways, thereby affecting T lymphocyte subsets. These studies indicate that budesonide has a regulatory effect on the T_H1/T_H2 balance by affecting the secretion and function of T lymphocytes.

Nebulized inhalation therapy is a method of treatment that uses high-speed oxygen to convert the drug solution into fine mist droplets, which enter the body through the respiratory tract. Compared with oral administration, nebulized inhalation is not affected by the digestive system, thus requiring a smaller dose of medication. Moreover, by avoiding the first-pass effect of the blood circulation and liver, it reduces the side effects of the drug. At the same time, nebulized inhalation allows the drug to act directly on the respiratory tract and lungs, increasing the local drug concentration and accelerating the onset of therapeutic effects. In this study, the overall efficacy of budesonide inhalation treatment in patients with CVA was 84.31%, which is consistent with the high efficacy rates of inhaled corticosteroids reported in previous studies on asthma treatment.[18] We further analyzed and found that age, 25(OH)D3 levels, and TNF-α are associated with an increased risk of reduced therapeutic efficacy.

Older patients may experience poorer treatment efficacy, which may be related to age-related physiological changes, such as slowed drug metabolism, alterations in airway structure, or the cumulative effects of chronic inflammation. Jin et al[19] conducted a prospective cohort study on elderly patients with asthma and chronic cough and found that older chronic cough asthma patients had worse asthma control and quality of life, more severe airway obstruction, and a higher frequency of moderate to severe asthma exacerbations during a 12-month follow-up period. Additionally, McGeachie et al[20] found that the *SMARCD1* gene (SWI/SNF related BAF chromatin remodeling complex subunit D1) may influence the response of asthma patients to inhaled corticosteroid treatment and that the expression of the *SMARCD1* gene interacts with age, with asthma control deteriorating as age increases. Low levels of 25(OH)D3 increase the risk of reduced efficacy of budesonide inhalation therapy for CVA, possibly because vitamin D has roles in regulating immune responses and exerting anti-inflammatory effects. Low vitamin D levels are associated with chronic inflammatory states, which can affect the control of airway inflammation and the improvement of lung function, ultimately impacting overall treatment efficacy.[21,22]

Research has found that in patients with mild to moderate asthma, low levels of 25(OH)D3 are associated with an increased risk of severe asthma exacerbations requiring systemic corticosteroid treatment, and supplementing vitamin D can reduce the occurrence of such events, with some studies showing a 30% reduction in risk.[23] However, the study by Jolliffe et al[24] points out that there is a disorder in vitamin D metabolism in asthma patients, indicating that these patients may have a weakened response to vitamin D supplementation. This implies that in the treatment of asthma, it is necessary to consider the status and metabolism of vitamin D, and personalized treatment methods may be needed to optimize the patient's response. These findings suggest that in the clinical management of asthma and CVA patients, assessing and maintaining an appropriate level of vitamin D may be an important aspect. In addition, our study also found that high expression of TNF-α is associated with an increased risk of reduced efficacy of budesonide inhalation treatment in CVA patients, consistent with the results of the study by Chen et al.[25] TNF-α is a major proinflammatory cytokine, and high expression of TNF-α may lead to the persistence and exacerbation of airway inflammation, offsetting the anti-inflammatory effects of budesonide, especially in cases where airway inflammation is more stubborn, thus affecting the efficacy.[26]

Overall, our study confirms that budesonide inhalation therapy has a certain efficacy for patients with CVA, demonstrating the ability to improve lung function, reduce inflammatory responses, and enhance immune function. Additionally, we found that older age, low levels of 25(OH)D3, and high expression of TNF-α may decrease the efficacy of budesonide inhalation therapy for CVA. However, there is still room for improvement in this study, such as conducting long-term follow-up research to assess the impact of vitamin D

supplementation and TNF-α control on the long-term efficacy and quality of life of asthma patients. In the future, we will progressively refine our research from the aforementioned perspectives, enhancing our understanding and approach to the study of cough variant asthma and its treatment.

STATEMENT OF ETHICS

This study was conducted after obtaining review and approval from Zhaotong First People's Hospital's Ethics Committee (Grant No.20240355). We communicated with all participants through telephone or instant messaging tools and obtained their verbal informed consent.

FUNDING

There were no supporting sources for the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

Data Availability

(The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.)

AI Assistance Disclosure

Not applicable.

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