Influence of budesonide and salbutamol atomization inhalation on Th17/Treg balance in patients with bronchial asthma and its correlation with airway remodeling

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Abstract

Objective: To study the influence of budesonide and salbutamol atomization inhalation on Th17/Treg balance in patients with bronchial asthma and its correlation with airway remodeling. Methods: A total of 90 patients with bronchial asthma who received systemic treatment in our hospital between July 2013 and April 2016 were divided into control group (n=45) and observation group (n=45) according to random number table. Patients in the control group were treated with salbutamol atomization inhalation alone while those in observation group were treated with budesonide and salbutamol atomization inhalation. The Th17/Treg ratio in peripheral blood as well as serum contents of airway remodeling-related indicators was compared between two groups before and after treatment. The correlation between Th17/Treg balance and airway remodeling in patients with bronchial asthma was detected by Pearson test. Results: Before treatment, the differences in peripheral blood Th17/Treg ratio as well as serum contents of inflammatory mediators, growth factor indexes and collagen metabolism indexes were not statistically significant between two groups of patients. After treatment, peripheral blood Th17/Treg ratio in observation group was lower than that in control group, serum CRP, IL-8, IL-13 and TNF- contents in observation group were lower than those in control group, serum PDGF-BB, b-FGF and VEGF contents in observation group were lower than those in control group, and serum HA, PCⅢ and LN contents in observation group were lower than those in control group. The Th17/Treg ratio in patients with bronchial asthma after treatment was positively correlated with the levels of airway remodeling-related indexes. Conclusion: Budesonide combined with salbutamol atomization inhalation can optimize the Th17/Treg balance in patients with bronchial asthma, and Th17/Treg is directly correlated to the degree of airway remodeling.

1. Introduction

Bronchial asthma is a chronic inflammatory disease involving a variety of cells and factors, its main clinical symptoms include wheezing, chest tightness, cough and so on, sustained progress can cause airway remodeling and irreversible pulmonary dysfunction, and early positive intervention is needed[1,2]. Salbutamol belongs to selective β 2 agonist, which can effectively prevent anaphylactic material release and prevent bronchospasm, and is now the elementary drug for bronchial asthma treatment. Budesonide is a corticosteroid with local anti-inflammatory effects, it has multiple functions such as stabilizing smooth muscle cell and lysosome membrane stability and reducing the release of histamine and other anaphylactic media, and it is regarded as the effective adjuvant drug to control bronchial asthma[3]. Latest research shows that Th17/
Treg imbalance is directly involved in the development of bronchial asthma, so the effect of budesonide combined with salbutamol atomization inhalation therapy on Th17/Treg balance in patients with bronchial asthma was discussed in the study, and the inner link between Th17/Treg balance and airway remodeling was further analyzed.

2. Information and methods

2.1 General information

90 patients with bronchial asthma who received systemic treatment in our hospital between July 2013 and April 2016 were selected as the research subjects, those ≥18 years old signed the informed consent themselves, and for those < 18 years old, the guardians signed the informed consent. According to the random number table, the enrolled patients were divided into the control group (n=45) and the observation group (n=45). Control group included 23 male cases and 22 female cases, they were 12-51 years old, and the course of bronchial asthma was 1-12 years; observation group included 22 male cases and 23 female cases, they were 11-53 years old, and the course of bronchial asthma was 1-10 years. The two groups of patients were not significantly different in distribution of gender, age and course of bronchial asthma (P>.05), and the study was approved by hospital ethics committee.

2.2 Diagnostic criteria for bronchial asthma

(1) With recurrent wheezing and chest stuffiness, and the clinical symptoms might be alleviated or return to normal autonomously after treatment; (2) the pulmonary function indicators were significantly abnormal during asthma attacks and gradually recovered after treatment; (3) allergen skin test or serum IgE test confirmed the allergic reaction status; (4) there was no apparent abnormality in the chest X-ray examination during remission stage, and the transparency of two lungs increased during asthma attack.

2.3 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with the diagnostic criteria for bronchial asthma; (2) cooperating with clinical treatment and related examination, and with complete data. Exclusion criteria: (1) associated with budesonide/salbutamol allergy; (2) associated with pulmonary tumor disease; (3) associated with systemic infectious diseases; (4) pregnant or breastfeeding women.

2.4 Therapy

Control group of patients received salbutamol atomization inhalation treatment, specifically as follows: salbutamol sulfate (Shandong Jewim Pharmaceutical Co., Ltd., approved by H20113348) 1 mg in saline 2.5 mL, by atomization inhalation, for 10 min, atomization inhalation once every 3 d, for continuous 14 d of treatment.

Observation group received budesonide combined with salbutamol atomization inhalation, which was as follows: budesonide (Shanghai Sine Promod Pharmaceutical Co., Ltd., approved by H20080316) 2 mL in saline 2.5 mL, by atomization inhalation, for 10 min, atomization inhalation once every 3 d. Salbutamol atomization inhalation dosage was the same as that of control group, and the treatment lasted for 14 d.

2.5 Th17/Treg balance

Before and after treatment, 2.0 mL fasting cubital venous blood was extracted from two groups of patients, flow cytometer was used to measure the percentage of Th17 cells and Treg cells, and the Th17/Treg ratio was further calculated.

2.6 Airway remodeling indexes

Before and after treatment, 2.0 mL fasting cubital venous blood was extracted from two groups of patients, anti-coagulated and then centrifuged at low speed to separate supernatant, which was stored in the profound hypothermia environment for test. ELISA kit instructions were referred to detect serum contents of inflammatory mediators C-reactive protein (CRP), interleukin-8 (IL-8) and interleukin-13 (IL-13), tumor necrosis factor alpha (TNF-α) content. RIA kit instructions were referred to determine serum contents of growth factor indexes platelet-derived growth factor-BB (PDGF-BB), basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF). Radioimmunoassay was used to determine serum contents of collagen metabolism indexes hyaluronic acid (HA), procollagen type [Ⅲ] (PC[Ⅲ]) and laminin (LN).

2.7 Statistical methods

Data in the study were recorded and calculated by specially-assigned person, and statistical software was SPSS 20.0. Th17/Treg ratio, inflammatory mediators, growth factor indexes, collagen metabolism indexes and other measurement data were in terms of mean ± standard deviation and comparison between groups was by t test. Correlation analysis was by Pearson test. P<0.05 was set as the standard of statistical significance in differences.
3. Results

3.1 Th17/Treg balance

Before treatment, peripheral blood Th17/Treg ratio in control group was (0.45±0.06), peripheral blood Th17/Treg ratio in observation group was (0.43±0.05), and the differences in peripheral blood Th17/Treg ratio were not statistically significant between the two groups (P>0.05). After treatment, peripheral blood Th17/Treg ratio in control group was (0.33±0.04), peripheral blood Th17/Treg ratio in observation group was (0.28±0.03), peripheral blood Th17/Treg ratio in observation group was lower than that in control group, and differences were statistically significant (P<0.05).

3.2 Inflammatory mediators

Comparison of serum inflammatory mediators CRP (mg/L), IL-8 (ng/mL), IL-13 (pg/mL) and TNF-α (ng/mL) contents between two groups of patients was as follows: before treatment, the differences in serum CRP, IL-8, IL-13 and TNF-α contents were not statistically significant between two groups of patients (P>0.05); after treatment, serum CRP, IL-8, IL-13 and TNF-α contents in both groups were significantly lower than those before treatment, serum CRP, IL-8, IL-13 and TNF-α contents in observation group were lower than those in control group, and differences were statistically significant (P<0.05), shown in Table 1.

3.3 Growth factor indexes

Comparison of serum growth factor indexes PDGF-BB (pg/mL), b-FGF (μg/L) and VEGF (ng/L) contents between two groups of patients was as follows: before treatment, the differences in serum PDGF-BB, b-FGF and VEGF contents were not statistically significant between two groups of patients (P>0.05); after treatment, serum PDGF-BB, b-FGF and VEGF contents in both groups were significantly lower than those before treatment, serum PDGF-BB, b-FGF and VEGF contents in observation group were lower than those in control group, and differences were statistically significant (P<0.05), shown in Table 2.

3.4 Collagen metabolism indexes

Comparison of serum collagen metabolism indexes HA (ng/mL), PC[III] (pg/mL) and LN (ng/mL) contents between two groups of patients was as follows: before treatment, the differences in serum HA, PC[III] and LN contents were not statistically significant between two groups of patients (P>0.05); after treatment, serum HA, PC[III] and LN contents in both groups were lower than those before treatment, serum HA, PC[III] and LN contents in observation group were lower than those in control group, and differences were statistically significant (P<0.05), shown in Table 3.
3.5 Correlation of Th17/Treg balance with inflammatory mediators, growth factors and collagen metabolism indexes

Pearson test showed that after treatment, the peripheral blood Th17/Treg ratio in patients with bronchial asthma was positively correlated with the serum contents of inflammatory mediators CRP, IL-8, IL-13 and TNF-α, growth factor indexes PDGF-BB, b-FGF and VEGF as well as collagen metabolism indexes HA, PC[III] and LN.

4. Discussion

Both budesonide and salbutamol are the common drugs for bronchial asthma treatment at present, the two drugs were used together in the study, and the illness change was judged. Many studies have confirmed that Th17 and its representative cytokine IL-17 play an important role in the occurrence and development of immune system diseases such as rheumatoid arthritis and systemic lupus erythematosus, which induce neutrophil aggregation to mediate airway inflammation, also act on the eosinophils, and prompt them to release chemical mediators and enhance local inflammatory response[4,5]. Latest research shows that the proportion of Th17 in peripheral blood of adult patients is higher than that of normal population during acute attack of bronchial asthma, but the proportion of Treg cells decreases significantly. Treg cells can negatively regulate T cell activation to avoid the immune damage caused by its overactivation[6,7]. Th17/Treg balance state is closely related to the severity of bronchial asthma, and it was found in the study that peripheral blood Th17/Treg ratio after treatment was lower than that in control group, showing that budesonide combined with salbutamol atomization inhalation can effectively balance the patient’s immune function, and avoid the excessive activation of Th17 cells and the excessive suppression of Treg cells. There is not much research on the internal link between the balance of Th17/Treg and the airway remodeling in bronchial asthma patients, which is to be confirmed in following study.

The bronchial asthma is essentially chronic airway inflammation, and the levels of the inflammatory mediators mostly increase in patients with acute disease attack, and are directly involved in the airway remodeling process[8,9]. CRP and TNF-α participate in the concentration and activation of neutrophils in local inflammatory processes, accelerate the division and proliferation of respiratory cells, and aggravate airway remodeling and pulmonary fibrosis[10]. IL-8 and IL-13 can synthesize and excessively start the inflammatory response, which causes inflammatory local lymphocyte infiltration and exacerbates asthma[11]. In the study, comparison of inflammatory medium contents between two groups of patients showed that serum CRP, IL-8, IL-13 and TNF-α contents in observation group were lower than those in control group after treatment, and the Th17/Treg ratio was positively correlated with CRP, IL-8, IL-13 and TNF-α levels. It shows that budesonide combined with salbutamol atomization inhalation can effectively inhibit the systemic and local inflammation reaction in bronchial asthma patients, and the ratio of Th17/Treg can intuitively reflect the degree of inflammation, and indirectly judge airway remodeling process.

A variety of growth factors are directly involved in airway remodeling in patients with asthma, PDGF-BB is recognized as the growth factor that promotes cell division, and its release increases after airway damage, which helps myofibroblast proliferation and airway epithelial fibrosis[12]. b-FGF plays an important role in regulating cell differentiation and proliferation, and the mast cells, macrophages, etc., can continue to proliferate under the action of b-FGF and participate in airway remodeling. VEGF can cause endothelial cell proliferation and angiogenesis, and epithelial cell proliferation, activation of neutrophils and other inflammatory cells, and so on are all closely associated with VEGF[13]. In the study, comparison of serum growth factor levels between two groups of patients showed that serum PDGF-BB, b-FGF and VEGF contents in observation group were lower than those in control group, confirming that budesonide combined with salbutamol atomization inhalation can reduce the levels of growth factor indexes in patients with bronchial asthma. Further Pearson test showed that Th17/Treg ratio in patients with bronchial asthma was positively correlated with PDGF-BB, b-FGF and VEGF levels, showing that Th17/Treg ratio after treatment is directly correlated with the degree of airway remodeling.

The airway wall structure abnormality may appear in the early stage of asthma, and progress over time. Increased extracellular matrix (ECM) deposition in airway wall is one of the core mechanisms of airway remodeling, HA, PC[III] and LN are the major components of ECM, and the increase in their contents indicates the airway wall thickening and airway remodeling in patients with asthma[14–16]. It was found in the study that serum HA, PC[III] and LN contents in observation group were lower than those in control group after treatment, explaining that combination inhalation therapy can effectively inhibit airway wall thickening process. Further Pearson test showed that the peripheral blood Th17/Treg ratio in patients with bronchial asthma after treatment was consistent with the airway remodeling process.

To sum up, it can be concluded that budesonide combined with salbutamol atomization inhalation can effectively reduce the
peripheral blood Th17/Treg ratio and restore Th17/Treg cell balance in patients with bronchial asthma. The ratio of Th17/Treg is directly correlated with the degree of airway remodeling in patients with bronchial asthma, and can be used as a reliable indicator to judge the disease severity and therapeutic effect of such patients.

References


