Effect of glucocorticoid inhalation combined with oral montelukast on airway function and serum inflammatory cytokines in patients with bronchial asthma

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Objective: To study the effect of glucocorticoid inhalation combined with oral montelukast on airway function and serum inflammatory cytokines in patients with bronchial asthma.

Methods: 138 patients diagnosed with bronchial asthma in our hospital between August 2014 and February 2016 were selected and randomly divided into two groups (n=69), observation group received oral montelukast combined with symbicort inhalation treatment, and control group received symbicort inhalation treatment. 3 months and 6 months after treatment, spirometer was used to measure the airway function parameters, and enzyme-linked immunosorbent assay kits were used to determine Th1/Th2, Treg/Th17 and Th9/cTfh cytokine content.

Results: 3 months and 6 months after treatment, 1 second (FEV1)/forced vital capacity (FVC), tidal expiratory flow at 25%, 50% and 75% of tidal volume (TEF25%, TEF50% and TEF75%) of observation group were significantly higher than those of control group (P<0.05); serum interleukin-2 (IL-2), interferon-γ (IFN-γ), tumor necrosis factor (TNF-α), IL-10 and transforming growth factor (TGF-β) levels of observation group were significantly higher than those of control group (P<0.05) while IL-4, IL-6, IL-17, IL-22, IL-9 and IL-21 levels were significantly lower than those of control group (P<0.05).

Conclusions: Montelukast combined with conventional inhalation treatment of bronchial asthma can more effectively improve the airway function and inhibit the airway inflammatory response mediated by Th1/Th2, Treg/Th17 and Th9/cTfh imbalance.

1. Introduction

Bronchial asthma is a chronic inflammatory airway disease characterized by airway hyperresponsiveness and airway limitation, and glucocorticoid inhalation is the main clinical treatment for the disease[1,2]. Leukotriene is a new important inflammatory mediator discovered in recent years, and it can be combined with leukotriene receptor within the airway to recruit inflammatory cells and promote the release of various inflammatory cytokines, which aggravate the airway inflammation[3,4]. Although the conventional glucocorticoids aerosol inhalation can inhibit inflammation, it doesn’t have obvious inhibitory effect on the inflammation mediated by leukotriene and its receptor, so the airway inflammation in some patients with bronchial asthma fails to get control after clinical glucocorticoid inhalation therapy. Montelukast is a new selective leukotriene receptor antagonist developed in recent years, and it can inhibit the inflammatory response mediated by leukotriene[5]. In the following study, glucocorticoid inhalation combined with oral montelukast was used to treat patients with bronchial asthma, and the airway function indexes as well as serum inflammatory cytokine levels in patients with asthma were analyzed.

2. Materials and methods

2.1. Research subjects

138 patients diagnosed with bronchial asthma in our hospital between August 2014 and February 2016 were selected as the
research subjects, and all patients were clearly diagnosed with bronchial asthma for the first time and never received glucocorticoid, β2 agonists and histamine drug treatment. After the study obtained the informed consent from patients and the approval from hospital ethics committee, random number table was used to divide the included patients into two groups, 69 cases in each group. Observation group received oral montelukast combined with symbicort inhalation treatment, including 39 male cases and 30 female cases that were 31–72 years old; control group received symbicort inhalation treatment, including 41 male cases and 28 female cases that were 29–70 years old. The two groups of patients were not significantly different in general information ($P > 0.05$).

2.2. Treatment methods

Control group received glucocorticoid and β2 agonist inhalation treatment, and the method is as follows: symbicort inhalation, 1 or 2 times every day in the morning and evening, and each inhalation containing budesonide 160 μg and formoterol 4.5 μg. Observation group received oral montelukast combined with glucocorticoid and β2 agonist inhalation therapy, and the methods are as follows: symbicort inhalation, 1 or 2 times every day in the morning and evening as well as oral administration of montelukast 5 mg every day before sleep. Both groups of patients received continuous treatment for 6 months.

2.3. Airway function evaluation methods

3 months and 6 months after treatment, the lung function of both groups was inspected with spirometer by the same doctor, the measured parameters included the forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) as well as tidal expiratory flow at 25%, 50% and 75% of tidal volume (TEF25%, TEF50% and TEF75%), and the FEV1/FVC was calculate.

2.4. Serum cytokine level detection methods

3 months and 6 months after treatment, 5 mL of peripheral blood sample was collected from the two groups and centrifuged to get serum, and enzyme-linked immunosorbent assay kits were used to determine interleukin-2 (IL-2), IL-4, IL-6, IL-9, IL-10, IL-17, IL-21, IL-22, interferon-γ (IFN-γ), tumor necrosis factor (TNF-α) and transforming growth factor (TGF-β).

2.5. Statistical analysis

SPSS20.0 software was used to input and analyze data, measurement data analysis between two groups was by $t$ test and $P < 0.05$ meant statistical significance in differences.

3. Results

3.1. Airway function parameters

3 months and 6 months after treatment, analysis of airway function parameters FEV1/FVC, TEF25%, TEF50% and TEF75% between two groups of patients is as follows: FEV1/FVC, TEF25%, TEF50% and TEF75% of observation group were significantly higher than those of control group ($P < 0.05$) (Table 1).

3.2. Serum Th1/Th2 cytokine levels

3 months and 6 months after treatment, analysis of serum Th1 cytokines IL-2, IFN-γ and TNF-α as well as Th2 cytokines IL-4 and IL-6 between two groups of patients is as follows: serum IL-2, IFN-γ and TNF-α levels of observation group were significantly higher than those of control group ($P < 0.05$) while IL-4 and IL-6 levels were significantly lower than those of control group ($P < 0.05$) (Table 2).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time after treatment</th>
<th>FEV1/FVC</th>
<th>TEF25% (mL/s)</th>
<th>TEF50% (mL/s)</th>
<th>TEF75% (mL/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>92.16±10.37</td>
<td>90.16±10.32</td>
<td>128.97±16.14</td>
<td>164.42±17.89</td>
</tr>
<tr>
<td>Control</td>
<td>3 months</td>
<td>80.15±9.15</td>
<td>83.76±9.42</td>
<td>115.16±12.93</td>
<td>132.16±16.21</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>83.42±9.37</td>
<td>85.14±10.25</td>
<td>119.36±13.26</td>
<td>140.29±16.84</td>
</tr>
</tbody>
</table>

*: compared with control group at the same point in time, $P < 0.05$.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time after treatment</th>
<th>IL-2 (pg/mL)</th>
<th>IFN-γ (μg/mL)</th>
<th>TNF-α (pg/mL)</th>
<th>IL-4 (ng/mL)</th>
<th>IL-6 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>3 months</td>
<td>8.93±0.91</td>
<td>9.45±1.16</td>
<td>23.58±3.63</td>
<td>1.02±0.15</td>
<td>10.44±1.76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>11.47±1.27</td>
<td>13.07±1.69</td>
<td>32.77±4.16</td>
<td>0.83±0.10</td>
<td>8.61±0.89</td>
</tr>
<tr>
<td>Control</td>
<td>3 months</td>
<td>6.25±0.77</td>
<td>7.16±0.93</td>
<td>15.65±1.92</td>
<td>1.42±0.18</td>
<td>15.28±1.82</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>8.93±1.04</td>
<td>9.26±1.09</td>
<td>19.37±2.07</td>
<td>1.25±0.15</td>
<td>13.04±1.36</td>
</tr>
</tbody>
</table>

*: compared with control group at the same point in time, $P < 0.05$. 

Table 1

Comparison of airway function parameters between two groups of patients after treatment ($n=69$, $\bar{x} \pm s$).

Table 2

Comparison of serum Th1/Th2 cytokine levels between two groups of patients after treatment ($n=69$, $\bar{x} \pm s$).
3.3. Serum Th17/Treg cytokine levels

3 months and 6 months after treatment, analysis of serum Th17 cytokines IL-17 and IL-22 as well as Treg cytokines IL-10 and TGF-β between two groups of patients is as follows: serum IL-17 and IL-22 levels of observation group were significantly lower than those of control group \(^{p<0.05}\) while IL-10 and TGF-β levels were significantly higher than those of control group \(^{p<0.05}\) (Table 3).

3.4. Serum Th9/cTfh cytokine levels

3 months and 6 months after treatment, analysis of serum Th9/cTfh cytokines IL-9 and IL-21 between two groups of patients is as follows: serum IL-9 and IL-21 levels of observation group were significantly lower than those of control group \(^{p<0.05}\) (Table 4).

4. Discussion

Montelukast is a newly developed selective leukotriene receptor antagonist that can antagonize the biological effect of leukotriene receptor, reduce airway inflammation caused by leukotriene and inhibit the release of inflammatory media\(^{[5-6]}\). In the study, conventional inhalation combined with leukotriene receptor antagonist montelukast was used in the treatment of bronchial asthma, and in order to define the curative effect of montelukast combined with conventional inhalation in the treatment of bronchial asthma, the airway function of two groups of patients was analyzed at first after treatment in the study. The airway spasm and airway limitation are the most prominent features of asthma, FEV1/FVC can accurately reflect the degree of airway limitation, TEF25%, TEF50% and TEF75% can accurately reflect the degree of small airway spasm, and analysis of the airway function parameters in the study showed that FEV1/FVC, TEF25%, TEF50% and TEF75% of observation group were significantly higher than those of control group after treatment \(^{p<0.05}\). It illustrates that montelukast combined with conventional inhalation therapy has better improving effect on the airway spasm and airway limitation in patients with bronchial asthma than conventional inhalation therapy alone, and the effect may be associated with the restrained inflammatory response after montelukast antagonizes leukotriene receptor.

At present, the positive effect of montelukast for the treatment of bronchial asthma has received more and more recognition, but there is no exact report about the influence of montelukast on the inflammatory response in patients with asthma. The balance of Th1/Th2 cells is an important factor in regulating airway inflammation\(^{[7]}\). Th1 cells mainly secrete IL-2, IFN-γ, TNF-α and other immunoregulatory media, and mediate the cellular immune response in local tissue\(^{[8]}\); Th2 cells mainly secrete IL-4, IL-6 and other media, have inhibitory effect on Th1 cell differentiation, and can also mediate humoral immune response, increase the IgE synthesis and make the airway in sensitization state and hyperresponsiveness state\(^{[9,10]}\). In the pathogenesis of bronchial asthma, Th1/Th2 balance shifts significantly to Th2, and the enhanced Th2 cells can aggravate airway inflammatory response, increases airway sensitivity and induce asthma attacks. In the study, analysis of the levels of Th1 and Th2 cytokines showed that serum IL-2, IFN-γ and TNF-α levels of observation group were significantly higher than those of control group \(^{p<0.05}\) while IL-4 and IL-6 levels were significantly lower than those of control group after treatment \(^{p<0.05}\). This means that montelukast combined with conventional inhalation therapy can more effectively regulate Th1/Th2 balance, strengthen the Th1 cell function and inhibit Th2 cell function in patients with bronchial asthma.

Th1 and Th2 cells were the first discovered T lymphocyte subsets, Treg and Th17 are the newly discovered T lymphocyte subsets involved in the regulation of immune response and inflammatory response, and the Treg and Th17 maintain relative balance and regulate airway inflammation. Th17 cells specifically secrete IL-17, can also secrete IL-22, and can not only activate the airway inflammatory response in patients with asthma.

Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time after treatment</th>
<th>Th17 cytokines</th>
<th>Treg cytokines</th>
<th>IL-17</th>
<th>IL-22</th>
<th>IL-10</th>
<th>TGF-β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>3 months</td>
<td>14.5±1.78¹</td>
<td>29.7±3.56¹</td>
<td>9.3±1.03¹</td>
<td>5.6±1.78¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6 months</td>
<td>11.0±1.47¹</td>
<td>20.3±2.89¹</td>
<td>14.2±1.84¹</td>
<td>8.9±1.04¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>22.1±3.06¹</td>
<td>42.3±5.68¹</td>
<td>6.7±0.93¹</td>
<td>3.3±0.52¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>15.6±1.78¹</td>
<td>29.5±3.62¹</td>
<td>8.4±0.91¹</td>
<td>5.6±0.71¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹: compared with control group at the same point in time, \(^{p<0.05}\).

Table 4

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time after treatment</th>
<th>IL-9</th>
<th>IL-21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>3 months</td>
<td>122.3±15.36¹</td>
<td>16.2±1.95¹</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>98.1±10.25¹</td>
<td>12.9±1.37¹</td>
</tr>
<tr>
<td>Control</td>
<td>3 months</td>
<td>219.4±28.33</td>
<td>27.2±3.15</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>153.8±18.31</td>
<td>19.2±2.27</td>
</tr>
</tbody>
</table>

²: compared with control group at the same point in time, \(^{p<0.05}\).
smooth muscle cell activation and aggravate the airway spasm[11,12]; Treg specifically expresses Foxp3 on surface and can inhibit the activation of Th17 through cell-cell contact, and Treg cells can also secrete IL-10, TGF-β and other inhibitory media and reduce airway inflammation[13,14]. In the study, analysis of the levels of Treg and Th17 cytokines showed that serum IL-17 and IL-22 levels of observation group were significantly lower than those of control group while IL-10 and TGF-β levels were significantly higher than those of control group. This means that montelukast combined with conventional inhalation therapy can more effectively regulate the balance of Th17/Treg, inhibit the Th17 cell function and strengthen the Treg cell function in patients with bronchial asthma.

In recent years, more and more studies have found that the changes in the levels and function of Th1/Th2 and Th17/Treg cannot fully explain all pathological changes in the progression of bronchial asthma. The discovery of Th9 and cTfh cells has provided a new idea for the pathogenesis of bronchial asthma. IL-9 is the cytokine specifically secreted by Th9 cells, and it can on the one hand, directly promote the Th2 activation and strengthen the sensitization effect of Th2 on the pathogenesis of asthma, and on the other hand, act on B cells, promote the IgE synthesis and aggravate the condition of asthma[15,16]. IL-21 is the main medium for cTfh cells to exert biological effect, and IL-21 can induce B lymphocyte differentiation into plasma cells and secrete antibodies, participates in the regulation of local airway inflammation and immune response in the process of bronchial asthma, and can promote the development of asthma[17].

In the study, analysis of the levels of Th9 and cTfh cytokines showed that serum IL-9 and IL-21 levels of observation group were significantly lower than those of control group (P<0.05). This means that montelukast combined with conventional inhalation therapy can more effectively inhibit the Th9/cTfh function in patients with bronchial asthma.

To sum up, it is believed that montelukast combined with conventional inhalation treatment of bronchial asthma has better improving effect on the airway function and better regulating effect on the inflammatory response mediated by Th1/Th2, Treg/Th17 and Th9/cTfh than conventional inhalation treatment.

References


