Effects of pidotimod combined with dermatophagoides farinae drops on the immune inflammatory response of children with allergic rhinitis complicated by asthma

Jin-Song Luo 1,2, Xiao-Ping Yang 2, Chun-Hua Ma 2, Xiao-Ling Zhang 2, Li-Ya Ma 2, Jin-Mei Yao 2

1. Department of Pediatrics, Renmin Hospital of Wuhan University, 430060, China
2. Department of Pediatrics, the Fifth Division Hospital of Xinjiang Production and Construction Corps, 833400, China

ARTICLE INFO

Article history:
Received 16 Jan 2018
Received in revised form 26 Jan 2018
Accepted 4 Feb 2018
Available online 14 Feb 2018

Keywords:
Allergic rhinitis
Asthma
Pidotimod
Dermatophagoides farinae drops
Immune response
Inflammatory response

ABSTRACT

Objective: To investigate the effects of pidotimod combined with dermatophagoides farinae drops on the immune inflammatory response of children with allergic rhinitis complicated by asthma. Methods: A total of 142 children with allergic rhinitis complicated by asthma were treated in this hospital between March 2014 and January 2017 were selected and divided into the control group (n=71) and study group (n=71) by random number table method. Control group were treated with dermatophagoides farinae drops, and study group received pidotimod combined with dermatophagoides farinae drops therapy. The differences in serum contents of immunoglobulin and inflammatory cytokines were compared between two groups of children before treatment and after 1 month of treatment. Results: There was no statistically significant difference in serum contents of immunoglobulin, Th1/Th2 cytokines and Th17/Treg cytokines between the two groups before treatment. After 1 month of treatment, serum sIgE content was lower than that of control group whereas sIgG4 content was higher than that of control group; serum Th1 cytokines IFN-γ and IL-2 contents were higher than those of control group whereas Th2 cytokines IL-4 and IL-5 contents were lower than those of control group; serum Th17 cytokine IL-17 content was lower than that of control group whereas Treg cytokine IL-10 content was higher than that of control group. Conclusion: Pidotimod combined with dermatophagoides farinae drops can effectively optimize the immune function and suppress the systemic inflammatory response in children with allergic rhinitis complicated by asthma.

1. Introduction

Both allergic rhinitis and asthma are clinical common respiratory diseases, their repeated attacks can significantly affect the patients' physical and mental health, and the two diseases easily occur in the same patients and are directly related to the patients' allergic constitution[1,2]. Due to the aggravation of environmental pollution and other factors, the incidence of allergic rhinitis and asthma is increasing rapidly in children, which not only affects their normal life, but also negatively affects their growth and development.

Dermatophagoides farinae drops is a common drug for allergic rhinitis, it is mostly swallowed after sublingual administration and generates similar immune response towards allergens to subcutaneous injection, and it has been successfully applied in the treatment of allergic rhinitis and others[3,4]. Pidotimod is a new type of immunostimulant, which can enhance both non-specific immune and specific immune system function of the body and enhance the immune function to inhibit the incidence of disease[5,6]. In this study, pidotimod combined with dermatophagoides farinae drops was used for the treatment of children with allergic rhinitis complicated by asthma, and the effect was described from immune response and inflammatory response.
2. Materials and methods

2.1. General information

A total of 142 children with allergic rhinitis complicated by asthma who were treated in this hospital between March 2014 and January 2017 were divided into the control group (n=71) and study group (n=71) by random number table method. There were 39 males and 32 females in the control group, and they were 2-11 years old; there were 38 males and 33 females in the study group, and they were 3-10 years old. There was no significant difference in the basic data distribution between the two groups, and the follow-up study plan was approved by the hospital ethics committee.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) in line with the diagnostic criteria for allergic rhinitis and asthma respectively; (2) diagnosed for the first time, and receiving no systematic treatment before; (3) whose parents signed the informed consent. Exclusion criteria: (1) combined with systemic inflammatory diseases such as pneumonia and nephrotic syndrome; (2) combined with severe congenital diseases such as congenital heart disease; (3) combined with tumor diseases.

2.3. Therapy

Both groups received conventional symptomatic treatment, and control group also received sublingual dermatophagoides farinae drops therapy, which was as follows: Changdi No. 1, 2 mL in the 1st week, Changdi No. 2 in the 2nd week and Changdi No. 3 in the 3rd week, and sublingual administration of 1, 2, 3, 4, 6, 8 and 10 drops in turn from d1-d7 every week according to the instructions. From the 4th week Changdi No. 4 was adopted, 3 drops each time, sublingual administration for 1-3 min, once a day. From the 6th week, Changdi No. 5 was adopted, 2 drops each time, once a day, for 1 year.

At the same time of dermatophagoides farinae drops therapy, study group were treated with pidotimod, which was as follows: pidotimod oral solution, 0.4 g/time, 2 times /d, for continuous 1 month of treatment.

2.4. Observation indexes

Before treatment and after 1 month of treatment, fasting peripheral blood samples were extracted from two groups of children, and the upper serum was separated and cryopreserved. Enzyme-linked immunosorbent assay was used to detect serum contents of immunoglobulins specific immunoglobulin E (slgE) and specific immunoglobulin G4 (slgG4), Th1 cytokines interferon γ (IFN-γ) and interleukin-2 (IL-2), Th2 cytokines interleukin-4 (IL-4) and interleukin-5 (IL-5), Th17 cytokine interleukin-17 (IL-17) and Treg cytokine interleukin-10 (IL-10).

2.5. Statistical methods

The contents of immunoglobulins, Th1/Th2 cytokines and Th17/Treg cytokines all belonged to measurement data and were input in SPSS 25.0, and \( P<0.05 \) was set as the standard of statistical significance in differences.

3. Results

3.1. Immunoglobulins

Comparison of serum slgE and slgG4 contents between two groups of children was as follows: before treatment, the differences in serum slgE and slgG4 contents were not statistically significant between the two groups (\( P>0.05 \)). After 1 month of treatment, serum slgE contents of both groups were lower than those before treatment whereas slgG4 contents were higher than those before treatment; serum slgE content of study group was lower than that of control group whereas slgG4 content was higher than that of control group at the same point in time (\( P<0.05 \)), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>slgE Before treatment (mg/L)</th>
<th>slgE After 1 month of treatment (mg/L)</th>
<th>slgG4 Before treatment (mg/L)</th>
<th>slgG4 After 1 month of treatment (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>71</td>
<td>54.28±5.91</td>
<td>50.17±5.49</td>
<td>0.45±0.06</td>
<td>0.71±0.09</td>
</tr>
<tr>
<td>Study group</td>
<td>71</td>
<td>54.32±5.87</td>
<td>46.35±5.12</td>
<td>0.46±0.07</td>
<td>0.98±0.12</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, \( P<0.05 \).

3.2. Th1/Th2 cytokines

Comparison of serum contents of Th1 cytokines IFN-γ and IL-2 as well as Th2 cytokines IL-4 and IL-5 between two groups of children was as follows: before treatment, the differences in serum IFN-γ, IL-2, IL-4 and IL-5 contents were not statistically significant between the two groups (\( P>0.05 \)). After 1 month of treatment, serum IFN-γ and IL-2 contents of both groups were higher than those before treatment whereas IL-4 and IL-5 contents were lower
than those before treatment; serum IFN-γ and IL-2 contents of study group were higher than those of control group whereas IL-4 and IL-5 contents were lower than those of control group at the same point in time ($P<0.05$), shown in Table 2.

### 3.3. Th17/Treg cytokines

Comparison of serum contents of Th17 cytokine IL-17 and Treg cytokine IL-10 between two groups of children was as follows: before treatment, the differences in serum IL-17 and IL-10 contents were not statistically significant between the two groups ($P>0.05$). After 1 month of treatment, serum IL-17 contents of both groups were lower than those before treatment whereas IL-10 contents were higher than those before treatment; serum IL-17 content of study group was lower than that of control group whereas IL-10 content was higher than that of control group at the same point in time ($P<0.05$), shown in Table 3.

### 4. Discussion

Allergic rhinitis is similar to asthma in pathogenesis, and they have synergistic effect when they occur together, which can aggravate the patient's condition and the difficulty of treatment. At present, sublingual or subcutaneous immunization is clinically adopted to control the symptoms of allergic diseases, but the children's immune system is not fully mature, dermatophagoides farinae drops and other routine immune preparations are with long onset time and fluctuant curative effect, and immune regulation should still be paid attention to during the treatment. Pidotimod is a new synthetic high-purity dipeptide and broad-spectrum immunostimulant, and can activate natural killer cells, increase the phagocyte function, promote the lymphocyte proliferation and complement activation, and also strengthen the nonspecific immune and specific immune function[7–9]. In this study, pidotimod was added to the clinical treatment of children with allergic rhinitis combined with asthma, and the optimization effect of the combined therapy on the children's condition was explored.

Children are at a critical stage of growth and development, and the expression of protective immune factors such as respiratory IgG is relatively low, which leads to immunocompromise in children and makes them vulnerable to pathogen infection[10,11]. Both allergic rhinitis and asthma belong to type I allergic diseases, IgE is the main medium of allergy, and many studies have confirmed that there is high IgE expression in airway secretions of children with allergic rhinitis and those with asthma, which is not only the main pathological characteristic of disease, but also the important medium leading to disease progression[12,13]. In this study, the differences in serum levels of above immunoglobulin were compared between the two groups, and the results showed that compared with those before treatment, serum sIgE contents of both groups decreased whereas sIgG4 contents increased after treatment; further compared with those of control group, serum sIgE content of study group was lower whereas sIgG4 content was higher after treatment, proving that pidotimod combined with dermatophagoides farinae drops therapy can be more effective to regulate the immune function, increase the secretion of protective IgG and inhibit the synthesis of IgE.

Th1/Th2 cell dysfunction is involved in the occurrence and development of allergic rhinitis and asthma, Th1 cells mainly enhance anti-infection immunity mediated by phagocytes, they produce IFN-γ and IL-2, they can strengthen the phagocytosis and killing ability of phagocytes and also actively promote the synthesis of IgG, and IFN-γ can inhibit IgE synthesis[14,15]. Th2 cells are mainly responsible for the immune response caused by extracellular multicellular parasites, and the inflammatory cytokines IL-4 and IL-5 secreted by them are involved in the occurrence of allergic diseases. IL-4 is the specific IgE synthesis irritant, which can promote the IgG to transform into IgE, and also enhance the B lymphocyte to synthesize IgE[16,17]. In this study, the differences in serum levels of above Th1/Th2 cytokines were compared between the two groups of children, and the results showed that compared with those before treatment, serum Th1 cytokines IFN-γ and IL-2 levels increased whereas Th2 cytokines IL-4 and IL-5 levels decreased after treatment; further compared with those of control group, serum Th1 cytokines IFN-γ and IL-2 contents of study group

### Table 2

Comparison of serum Th1/Th2 cytokine contents between the two groups before and after treatment (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>71</td>
<td>5.39±0.57</td>
<td>6.11±0.64</td>
<td>1.37±0.19</td>
<td>1.79±0.23</td>
<td>11.38±1.76</td>
<td>9.21±0.98</td>
<td>23.17±3.21</td>
<td>18.26±2.15</td>
</tr>
<tr>
<td>Study group</td>
<td>71</td>
<td>5.34±0.61</td>
<td>7.05±0.78</td>
<td>1.41±0.18</td>
<td>2.16±0.25</td>
<td>11.41±1.69</td>
<td>6.53±0.78</td>
<td>23.42±3.09</td>
<td>19.73±1.88</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, $P<0.05$.

### Table 3

Comparison of serum Th17/Treg cytokine contents between the two groups before and after treatment (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
<th>Before treatment</th>
<th>After 1 month of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>71</td>
<td>45.19±5.18</td>
<td>37.25±4.18</td>
<td>18.34±2.11</td>
<td>20.18±2.64</td>
<td>23.17±3.21</td>
<td>18.26±2.15</td>
</tr>
<tr>
<td>Study group</td>
<td>71</td>
<td>45.23±5.04</td>
<td>21.79±3.52</td>
<td>18.37±2.09</td>
<td>24.57±3.11</td>
<td>23.17±3.21</td>
<td>18.26±2.15</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, *$P<0.05$.*
were higher than whereas Th2 cytokines IL-4 and IL-5 contents were lower after treatment, confirming that pidotimod combined with dermatophagoides farinae drops therapy can effectively adjust the balance of Th1/Th2 cell function in children with allergic rhinitis combined with asthma, and indirectly inhibit the disease progression. Th17 cells are unique Th cell subset and mainly secrete cytokine IL-17, and IL-17 has strong pro-inflammatory effect, further stimulates the synthesis of other inflammatory cytokines and chemokines, causes tissue cell infiltration and sabotage, and plays a key role in the progression of allergic rhinitis, asthma and other allergic diseases[18,19]. Treg cells are T-lymphocytes that play a negative regulatory role, which secretes IL-10 and others to induce immune tolerance, and can inhibit T cell activation, reduce IgE synthesis and also increase IgG4 production[20,21]. In this study, the differences in serum levels of above Th17/Treg cytokines were compared between the two groups of children, and the results showed that compared with those before treatment, serum Th17 cytokine IL-17 contents of both groups decreased whereas Treg cytokine IL-10 contents decreased after treatment; further compared with those of control group, serum Th17 cytokine IL-17 content of study group was lower whereas Treg cytokine IL-10 content was higher after treatment, confirming that the pidotimod combined with dermatophagoides farinae drops therapy can be more effective to balance the expression of Th17/Treg cells and inhibit the disease progression.