

Acupuncture Research

Efficacy of Chinese Medicine Acupoint Application Combined with Montelukast on Children with Perennial Allergic Rhinitis: A Randomized Controlled Trial*

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ABSTRACT **Objective:** To evaluate the efficacy of Chinese medicine acupoint application (CMAA) combined with Western medicine for perennial allergic rhinitis (PAR) in children. **Methods:** In this prospective, parallel, randomized, placebo-controlled and single-blind trial from August to September, 2017, 180 children with PAR were randomly assigned to an integrative group (CMAA and Montelukast), CMAA group (CMAA and placebo tablet), or Montelukast group (placebo CMAA and Montelukast). Participants were applied with CMAA for 6 sessions over 2 weeks, and/or Montelukast Chewable Tablet orally once daily for 12 weeks. The changes in severity of symptoms were measured by Visual Analog Scale (VAS) and rhinitis control assessment test (RCAT) at 0, 2, 4 and 12 weeks of treatment. Blood samples were collected for serum interleukin-4, interferon gamma γ and T helper type 1 (Th1)/Th2 flow cytometric analysis at the time points of 0, 4 and 12 weeks. **Results:** Eight cases dropped out from the trial, 3 in the integrative group, 2 in the CMAA group and 3 in the Montelukast group. The VAS scores decreased significantly while the RCAT scores increased significantly in all three groups at 4 and 12 weeks compared with baseline ($P < 0.01$ or $P < 0.05$). The VAS scores were significantly lower while the RCAT scores were significantly higher in the integrative and CMAA groups than the Montelukast group at 2 and 4 weeks ($P < 0.01$ or $P < 0.05$). At 2, 4 and 12 weeks, the scores of nasal congestion, sneezing, sleep problem, and rhinitis symptom control in the integrative and CMAA groups increased significantly compared with baseline ($P < 0.01$ or $P < 0.05$). The least percentages of Th2 and the most alleviated Th2 shift (highest Th1/Th2) were observed in the integrative group at 12 weeks compared with the other two groups ($P < 0.05$). **Conclusion:** The combination of CMAA with Montelukast might be more effective and appropriate than either option alone for children with PAR. (Registered at Chinese Clinical Trial Register, registration No. ChiCTR-IOR-17012434)

KEYWORDS allergic rhinitis, Chinese medicine, acupoint application, Montelukast, interferon gamma/interleukin-4, T helper type 1/T helper type 2

Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines reported that allergic rhinitis (AR) affected 10%–40% of the population in 2016.⁽¹⁾ The prevalence of allergic disease including AR in children over the past few decades has increased in China.⁽²⁾ Besides recognized classical symptoms of AR such as sneezing, rhinorrhea, nasal obstruction, and compromised respiratory function, children suffered from AR also have additional impairments such as decreased school performance, sleep disturbance, as well as emotional and other psychosocial problems.⁽³⁾ AR is classified into seasonal AR and perennial AR (PAR), based on the time and type of exposure and symptoms.⁽¹⁾ AR is typically an immunological disease caused by the interplay of genetic and environmental factors. T helper type 1 (Th1)/Th2 paradigm assumes that a dominance of Th2

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cell activation and an inadequate Th1 cell response are responsible for the development of allergies. The changes in the Th1 and Th2 signatory cytokines (interferon gamma (IFN- γ) and interleukin-4 (IL-4), respectively) highlight this biased immune response.⁽⁴⁾

Specific treatment options for AR include allergen avoidance, pharmacotherapy and immunotherapy. Current medication routines towards PAR in children are intranasal corticosteroids, antihistamines, anti-allergen and anti-leukotriene. These medicines can only alleviate allergic symptoms but fail to regulate the allergic reaction. Side-effects of these drugs include a bitter taste, nasal dryness and irritation of the nasal mucous membranes, epistaxis, drowsiness and fatigue, etc. However, a clinical trial showed that Montelukast was generally well tolerated in Japanese children with PAR.⁽⁵⁾ Chinese medicine (CM) used in AR patients has drawn the attention of allergy specialists and scientists, which is characterized by multi-target effects and allergic reaction regulating.⁽⁶⁾ Acupoint application has long been used as an complementary and alternative medicine (CAM) therapy for the treatment of asthma and AR in China. The most commonly reported adverse events (AEs) are local skin itching, stinging, redness and blisters.^(7,8) Sanfujiu is an effective method of applying herbal paste to acupoints during the hottest summer days, and its effect of alleviating allergic symptoms will be shown immediately after treatment.⁽⁸⁾ Integration of CM and Western medicine (WM) has been used in a diversity of dermatologic and immunologic diseases, including chronic non-infectious disease.⁽⁹⁻¹¹⁾

Based on all the subjects with PAR who frequently need the steroid nasal spray and antihistamine orally, antileukotrienes (Montelukast) was selected as monotherapy according to the recommendation of ARIA (2016).⁽¹⁾ This trial aimed to evaluate the efficacy of CM acupoint application (CMAA) combined with Montelukast in treating symptomatic PAR.

METHODS

Study Design

A prospective, randomized, parallel, single-blind, and placebo-controlled study was performed. It has been registered at Chinese Clinical Trial Register in August 2017 (registration No. ChiCTR-IOR-17012434). This study was approved by the Ethics Committee of Shanghai Children's Medical

Center (No. SCMCIRB-K2015042) and conducted according to common guidelines for clinical trials (Declaration of Helsinki, ICH-GCP including certification by an external audit).

Diagnostic Criteria

The diagnostic criteria of PAR from ARIA⁽¹⁾ were used as follows: (1) occurrence of symptoms over 1 year; i.e., ≥ 2 persistent symptoms of water-like tears, nasal itching, congestion, or sneezing lasting for more than 1 h every day; (2) symptoms more than 4 days per week or more than 4 consecutive weeks; (3) ≥ 1 serum IgE species (SIgE) were found positive (≥ 0.35 IU/mL) for specific inhalant allergens, including indoor allergens such as house dust mite, cat/dog hair, molds, cockroaches. The patients who had one or more of the followings: poor sleep, poor academic performance, impaired daily activities such as entertainments and sports, or other troublesome symptoms were defined as moderate/severe cases. Otherwise, they were defined as mild cases.

Inclusion and Exclusion Criteria

Inclusion criteria included: (1) patients ≤ 16 years old; (2) patients diagnosed with PAR; (3) no use of oral corticosteroids in the previous 4 weeks; and (4) parents of the subjects were fully informed and signed consent forms. Exclusion criteria included: (1) patients with co-morbid asthma, eczema, or any other allergic diseases; (2) tumor in the nasal cavity or any other inflammatory nasal diseases or respiratory issues; (3) autoimmune disease, hematological disease, congenital heart disease or other chronic diseases; and (4) being unable to comply with the research protocol.

Patients and Randomization

Eligible children with PAR were recruited into this study from the Department of Otolaryngology and the Department of Chinese Medicine at Shanghai Children's Medical Center from August to September, 2017. Patients were randomly assigned to the integrative group, CMAA group and Montelukast group using a random number table.

Sample Size Estimation

The statistical power for the study was calculated using G*Power 3.1.9.2 software (<http://www.gpower.hhu.de/>). The statistical power ($1 - \beta$) for comparison of treatment groups was 95%, with the expected effect size of 0.25 and α of 0.05 (2-sided). Meanwhile,

about 10% lost rate of follow-up should be considered. Based on these assumptions, the sample size was set to 60 for each treatment group. Additionally, per-protocol analysis was only done to patients without major protocol violations by the end of 12 weeks.

Interventions

Patients in the integrative and CMAA groups were treated with Chinese herbal medicine (CHM) application on certain acupoints; while those in the Montelukast group were applied with non-effective dough, mixed with fresh ginger juice on the same acupoints instead. The CHM regimen were composed of *Herba Ephedrae*, *Herba Asari*, *Cortex Cinnamomi*, *Semen Sinapis Albae*, *Radix Scutellariae*, and *Borneolum Syntheticum* in ratio of 2:2:2:1:2:1, which were provided by Shanghai Hongqiao Traditional Chinese Herbal Medicine Co., Ltd., China. All CHMs were grounded into powder (mesh aperture number 100), and prepared with fresh ginger juice before the application (in ratio of 20 g herbal powder to 10 mL ginger juice). The herbal paste was smeared to the center of a nonwoven fabric of 1.5 cm × 1.5 cm, each contained 3 g of dry herbal powder. The patches were applied to the acupoints of Dazhui (DU 14), Tiantu (RN 22), Feishu (BL 13, bilateral), and Dingchuan (EX-B1, bilateral).^(12,13) CMAA or placebo application regimen was consisted of 6 sessions of 30-min treatment, and was administered over 2 weeks (3 sessions per week) from August to September, 2017.

Patients in the Montelukast and integrative groups were treated with Montelukast Chewable Tablet (lot No.12773/15175, Merck&Co, Inc., Whitehouse Station, NJ, USA) once daily at bedtime (4 mg for 3–6 years old and 5 mg for 7–12 years old), while patients in the CMAA group were allocated with placebo tablets (Vitamin C, 100 mg, lot No. 10150801, Xinyi Pharmaceutical Factory, Shanghai, China). The duration of Montelukast or placebo tablet treatment was a total of 12 weeks. All the patients and statisticians were masked to the treatment allocations.

In all treatment groups, intranasal corticosteroids (a spray/each nostril, daily in the morning; Nasonex®, MSD, Merck & Co., Inc., Whitehouse Station, NJ, USA) and/or H1-antagonist (5 mg orally for 3–6 years old, 10 mg orally for 7–12 years old, daily at bedtime; Cetirizine, UCB FARCHIM S.A., Brussels, Belgium) were prepared as rescue medications in the entire

course of study. All patients with acute attacks would be treated with rescue medications recommended above. Rescue medication usage was asked to be recorded by the patients daily. And at the admission and each follow-up time point, total number of days of rescue medication usage and details of the rescue medication during the past 2 weeks would be documented by the doctors. The usage of a new or changing dosage of the medication resulted in case withdrawal.

Primary Outcomes

Visual Analog Scale (VAS) and rhinitis control assessment test (RCAT) were employed to assess the severity of disease at admission (0), 2, 4 and 12 weeks.

Parents or guardians of the patients were asked about the influence of nasal discomfort caused by AR on their children during the previous week and were required to indicate it on the VAS ruler, ranging from 0 (nasal symptoms, not at all bothersome) to 10 cm (nasal symptoms, extremely bothersome).⁽¹⁴⁾

RCAT was used to detect the variation of rhinitis symptoms. RCAT has 6 items, including nasal congestion, sneezing, watery eyes, sleep problems caused by rhinitis, activity avoidance, and rhinitis symptom control. Responses were measured on 5-point Likert-type scales by 2 experienced physicians. RCAT scores ranged from 6 to 30, with higher scores indicating better rhinitis control.⁽¹⁵⁾

Secondary Outcomes

Serum levels of IL-4, IFN- γ , and Th1/Th2 were tested and counted at the time points of 0, 4 and 12 weeks for all the patients.

Blood Sampling

The blood samples were collected in siliconized tubes for serum cytokines, and potassium-EDTA preparation tubes for flow cytometry. Clotting was allowed at room temperature. The serum was separated from whole blood by centrifugation at 3,000 r/min for 10 min and was preserved at –80 °C until being assayed.

Serological Cytokines Analysis

Serum Th2 response (IL-4) and Th1 response (IFN- γ) were measured using high-sensitivity enzyme linked immunosorbent assay (ELISA, kits BMS225HS, BMS228HS, Thermo-Fisher Scientific, USA). The

minimum detectable levels of human IL-4 and IFN- γ were <0.10, 0.06 pg/mL, respectively.

Flow Cytometric Analysis of CD3⁺CD8⁻ T Lymphocytes and Intracellular Cytokines

Peripheral blood mononuclear cells (PBMCs) were isolated by centrifugation on a Ficoll gradient and resuspended in RPMI medium supplemented with 10% heat-inactivated fetal calf serum and 2% penicillin-streptomycin (Sigma, USA). After 5-h stimulation (cell stimulation, eBioscience, USA), PBMCs were mixed with the appropriate volume of fluorescence dye-conjugated monoclonal antibodies (5 μ L: 1×10^6 cells/mL) and stained for 15 min at room temperature in the dark. Then the reaction mixtures were centrifuged at 1,500 r/min, followed by the addition of 100 μ L fixation and permeabilization reagent (Intraprep; Beckman Coulter, USA). Next, cells were stained with anti-human CD3-PerCP (PerCP; eBioscience), anti-human CD8-fluorescein isothiocyanate (FITC; eBioscience), anti-human IL-4-APC (eBioscience, 0.2 μ g/ 10^6 cells) and anti-human IFN- γ -phycoerythrin (PE; eBioscience, 0.5 μ g/ 10^6 cells). IgG isotype controls were utilized for each antibody and patient. The cell pellets were resuspended in 400 μ L phosphate-buffered saline (PBS) containing 0.2% w/v paraformaldehyde (Sigma) for flow cytometric analysis after washing and centrifugation.

Intracellular cytokines were determined by acquisition and analysis of flow cytometric data. The stained and fixed samples were injected into a FACSCalibur flow cytometer (Becton Dickinson, San Jose, CA, USA), and the data were analyzed using the FlowJo software (Tree Star, Inc., Ashland, OR, USA) according to the manufacturer's instructions. Totally 10,000 events in CD3⁺CD8⁻ lymphocyte gates were typically acquired for analysis of the frequency of intracellular cytokine staining. Cytokine production was affirmed based on the staining of isotype-matched negative controls. The results were expressed as the percentage of cytokine-positive lymphocytes in stimulated culture. The percentage of cytokine-producing Th cells (IL-4⁺CD4⁺ and IFN- γ ⁺CD4⁺) was calculated within the total CD3⁺CD8⁻ subpopulation. There was no difference in mean fluorescence intensity for each sample or across time points.

Safety Observation

AEs were assessed and documented by physician at each follow-up. Treatment would be

suspended immediately if serious AEs occurred, and the event would be reported to the ethical committee.

Statistical Analysis

Data were collected and analyzed using SPSS 17.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). The values of normally distributed continuous data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$). Comparisons of laboratory measurement were performed after log transformation of variables in case of abnormal distribution and data was shown as geometric mean and standard deviation. One-way analysis of variance (ANOVA) and Fisher's least significant difference method were used to compare the demographics and baseline characteristic data among three groups; differences among different time points and groups were assessed with the repeated measure ANOVA and multivariate tests, and Dunnett's test was used for further multiple comparisons; χ^2 test was used for enumeration data. *P*-value <0.05 was considered statistically significant.

RESULTS

Trial Completion Condition

Totally 180 patients (106 boys and 74 girls, aged 3–12 years) were recruited in this trial from August 1 to September 26, 2017. Among them, 172 patients completed the trial according to protocol (57 in the integrative group, 58 in the CMAA group and 57 in Montelukast group). Eight patients (4.4%) withdrew the study prior to study completion. None of these patients dropped out of the study due to AEs except for 1 patient with skin itching (Figure 1). There were no significant differences among the three groups in related demographic and clinical features in the baseline stage (*P*>0.05, Table 1).

Comparison of VAS Scores and Rescue Medication Usage in Patients with PAR among Three Groups

All of these three treatments had significant effects on reducing VAS scores at 4 and 12 weeks compared with baseline (*P*<0.01 or *P*<0.05). At 2 and 4 weeks, VAS scores were significantly lower in the integrative and CMAA groups than those in the Montelukast group (*P*<0.01 or *P*<0.05). However, VAS scores did not differ between integrative group and CMAA group (*P*>0.05). At 12 weeks, VAS scores decreased significantly in the Montelukast group

Table 1. Comparison of Demographic and Clinical Features of Patients among Three Groups

Characteristic	Integrative (57 cases)	CMAA (58 cases)	Montelukast (57 cases)
Gender (Male/female, case)	34/23	36/22	32/25
Age (Year, $\bar{x} \pm s$)	7.16 $\pm$ 2.23	7.10 $\pm$ 2.09	7.14 $\pm$ 2.69
Weight (kg, $\bar{x} \pm s$)	27.11 $\pm$ 8.68	27.71 $\pm$ 9.90	26.93 $\pm$ 7.84
Height (cm, $\bar{x} \pm s$)	124.93 $\pm$ 14.60	125.69 $\pm$ 15.44	124.55 $\pm$ 14.84
Severity of symptom [Case (%)]			
Moderate/severe	52 (91.23)	52 (89.66)	53 (92.98)
Mild	5 (8.77)	6 (10.34)	4 (7.02)
Allergen category [Case (%)]			
House dust mite	41 (71.93)	42 (72.41)	40 (70.18)
Cat/dog hair	22 (38.60)	18 (31.03)	20 (35.09)
Molds	14 (24.56)	11 (18.97)	12 (21.05)
Seasonal grass/tree pollens	6 (10.53)	5 (8.62)	5 (8.78)
Cockroaches	4 (7.02)	4 (6.90)	4 (7.02)
Ragweed	4 (7.02)	4 (6.90)	4 (7.02)
<i>Artemisia argyi</i>	3 (5.23)	3 (5.17)	3 (5.26)
<i>Penicillium notatum</i>	3 (5.26)	4 (6.90)	3 (5.26)
<i>Aspergillus fumigatus</i>	3 (5.26)	3 (2.58)	2 (3.51)

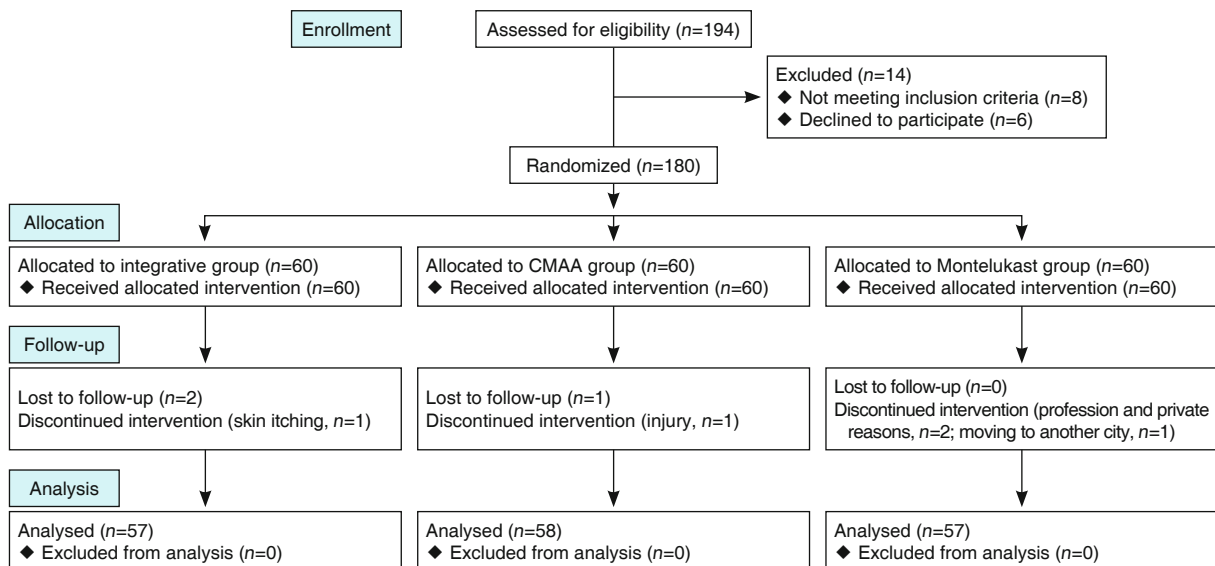
Note: CMAA: Chinese medicine acupoint application

($P < 0.01$), and there was no significant difference in VAS scores among three groups ($P > 0.05$). VAS scores were significantly affected by main effect of time and group among three groups ($P < 0.01$ or $P < 0.05$, Figure 2).

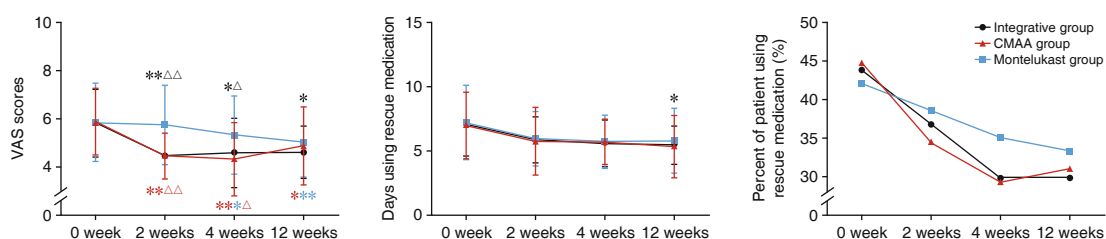
Days using rescue medication at 12 weeks in the integrative group were significantly lower than baseline ($P < 0.05$). Differences in percent of patient using rescue medication were not statistically significant among three groups ($P > 0.05$, Figure 2).

Comparison of RCAT Scores in Patients with PAR among Three Groups

As shown in Figure 3, the RCAT scores increased significantly from 2 weeks to 12 weeks in the integrative and CMAA groups, and from 4 weeks to 12 weeks in the Montelukast group ($P < 0.01$ or $P < 0.05$). At 2, 4 and 12 weeks, the scores of nasal congestion, sneezing, sleep problem, and rhinitis symptom control in the integrative and CMAA groups increased significantly

**Figure 1. Flow Chart of the Study of CMAA Combined with Montelukast on Patients with PAR**

Note: CMAA: Chinese medicine acupoint application

**Figure 2. Comparison of VAS Scores and Rescue Medication Usage in Patients with PAR among Three Groups ($\bar{x} \pm s$)**

Notes: * $P < 0.05$, ** $P < 0.01$ vs. 0 week in the same group; $\triangle P < 0.05$, $\triangle\triangle P < 0.01$ vs. Montelukast group at the same time point. VAS: Visual Analog Scale; CMAA: Chinese medicine acupoint application

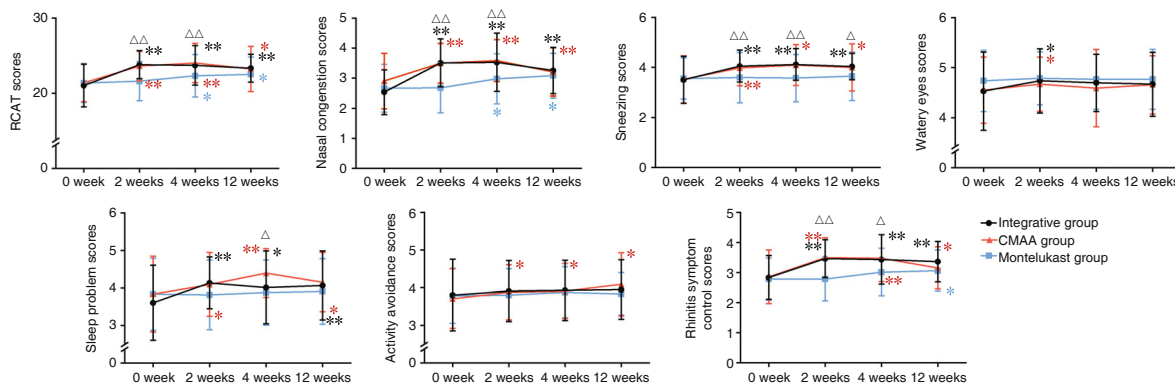


Figure 3. Comparison of RCAT Scores in Patients with PAR among Three Groups ($\bar{x} \pm s$)

Notes: * $P < 0.05$, ** $P < 0.01$ vs. 0 week in the same group; $\Delta P < 0.05$, $\Delta\Delta P < 0.01$ among three groups at the same time point. RCAT: rhinitis control assessment test; CMAA: Chinese medicine acupoint application

compared with baseline ($P < 0.01$ or $P < 0.05$). However, scores of nasal congestion in the Montelukast group started to increase from 4 weeks ($P < 0.05$), at 12 weeks there was no significant difference among the three groups ($P > 0.05$).

Comparison of Th1/Th2 Cytokines Release and Th2 Shift in Patients with PAR among Three Groups

As shown in Figure 4, the main effect of time on serum IL-4 within groups was significant ($P < 0.05$ or $P < 0.01$), with the patients in the integrative group having the lowest levels of IL-4 at 12 weeks ($P < 0.01$); the main effect of group on serum IL-4 was significant too ($P < 0.01$). However, neither the main effect of group nor of time was shown on serum IFN- γ levels ($P > 0.05$).

The significant main effects of group were shown on IFN- γ ⁺CD4⁺ at 4 weeks ($P < 0.05$), IL-4⁺CD4⁺ at 12 weeks ($P < 0.05$), and the patients in the integrative group had the least percentages of Th2 at 12 weeks ($P < 0.05$). The most alleviated Th2 shift (highest Th1/Th2) were observed in the integrative group at 12 weeks compared with the other two groups ($P < 0.05$).

Safety

Among the 172 patients treated in this study, 1 patient in the integrative group reported skin itching attributing to herbal patch, which resolved a few days after stopping the treatment. During the trial, none of the patients experienced serious AEs.

DISCUSSION

Using of CAM therapy is gaining momentum in recent decades. Research results from the 2007

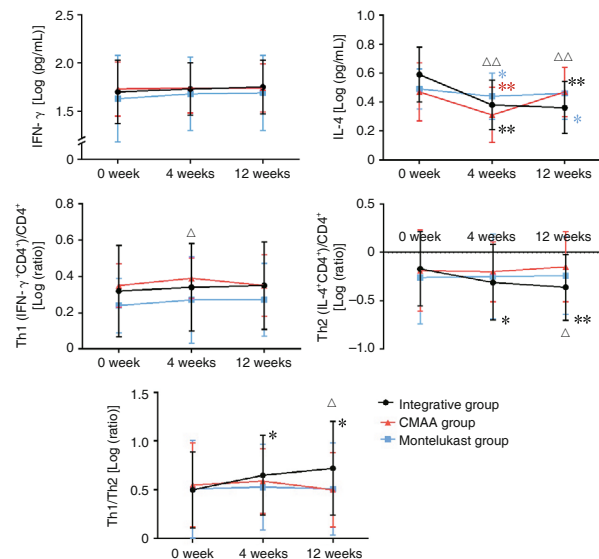


Figure 4. Comparison of Th1/Th2 Cytokines Release and Th2 Shift in Patients with PAR among Three Groups

Notes: Data are shown as geometric mean and standard deviation. * $P < 0.05$, ** $P < 0.01$ vs. 0 week in the same group; $\Delta P < 0.05$, $\Delta\Delta P < 0.01$ among three groups at the same time point. IFN- γ : interferon gamma γ ; IL-4: interleukin-4; Th1: T helper type 1; CMAA: Chinese medicine acupoint application

National Health Interview Survey (NHIS) found that almost 4 out of 10 adults had used CAM therapy in the past 12 months, and approximately 1 in 9 children (11.8%) used CAM therapy.⁽¹⁶⁾ In CM, herbs,⁽¹⁷⁾ acupuncture,⁽¹⁸⁾ and external application of drug paste⁽¹⁹⁾ are commonly used therapies in AR patients. CMAA, the external application of CHM powder-made preparation on specific acupoints, has been proved to be effective in treating AR.⁽¹²⁾ Moreover, CMAA is well accepted in children, because of its non-invasive and convenient application, mild side effects and well noted efficacy in treating allergic disease. Yang, et al⁽²⁰⁾ reported that the effect CMAA for children with AR was especially better than adults.

When applied to acupoints, CHM exerts its pharmacological effects through transdermal absorption. At the same time, the application of the herbs stimulates the acupoints, thus acupuncture-like effects can be achieved too. Based on this theory, selection of herbs and acupoints is critical to CMAA. In this study, our prescription is made up of 3 different kinds of herbs: (1) pungent and aromatic herbs, like *Semen Sinapis Albae* and *Borneolum Syntheticum*, who prone to stimulate and penetrate the skin; (2) herbs expelling coldness and dispersing Fei (Lung) qi, like *Herba Ephedrae*, *Herba Asari* and *Cortex Cinnamomi*; (3) herbs clearing Fei heat, like *Radix Scutellariae*. In composition, they help to regulate the function of respiratory system and strengthen the resilience to disease. The acupoints we selected are all commonly used in clinical practice to treat respiratory disease, which help to relieve the symptoms like coughing, asthma and nasal congestion.^(13,21) All these acupoints are located on the upper part of body, which are easy to be exposed and are especially suitable to be adopted in CMAA. Other acupoints around nose, like Yingxiang (LI 20) and Sibai (ST 2), are widely used in acupuncture to treat rhinitis,⁽²¹⁾ but generally they will not be used in CMAA, because most patients cannot tolerate the unavoidable irritation to the skin of herbal application on face.

We selected summer vacation to treat the children for 2 reasons. Firstly, according to CM theory, in the hottest days during the year, yang qi inside body also reaches to the peak amount. So, it is the best chance to replenish yang qi, and expel coldness from the body. Secondly, in the summer vacation, most children are not so busy coping with their studying, thus the compliance of the patient then is much better. As a result, almost all the children had finished the CMAA regime in our study.

Montelukast is regarded undoubtedly as a viable alternative for the treatment of AR. Its benefits are equivalent to antihistamines, when used as monotherapy.⁽²²⁾ The leukotriene-receptor type I inhibitor, to which Montelukast belongs, is recommended for treatment of moderate-to-severe AR and may be considered to be a well-tolerated therapeutic option for children with AR with minor side effects through long-term results.⁽²³⁾ Montelukast can help these patients when used prophylactically or as long-term controller.⁽²⁴⁾ These agents have been shown to reduce IL-4 and IL-13 levels and increase IFN- γ level. Leukotriene receptor antagonists also

reduce peripheral eosinophilia in patients with AR.^(24,25)

This trial investigated the efficacy of CMAA combined with Montelukast for PAR children comparing to CMAA or Montelukast alone. Results of this study showed that CMAA had a better short-term (up to 2 weeks) effects, while the combined treatment were better in both short- and long-term (12 weeks) effects, especially the long-term effect. Patients who received the combined treatment had a less AR severity and better improvement of symptoms at 12 weeks than patients who received CMAA or Montelukast alone. Based on these results, we recommended the combination of CMAA and Montelukast in treating PAR children rather than CMAA or Montelukast alone.

Further analyzed each item of RCAT, we found that CMAA, used alone or combined with Montelukast, contributed to relieving sneezing, nasal congestion, sleep problem and improving rhinitis symptoms control. So, if the child's symptom is specialized in sneeze, or in case nasal congestion needs to be alleviated quickly, we prioritize CMAA. In spite of the poor short-term effects, Montelukast were especially good in items of nasal congestion 12 weeks later. The quantification of the concurrent use of conventional relief medication has also been taken into consideration in our study. As expected, days using rescue medication were observed to be significantly shorter at 12 weeks when compared to the baseline.

Balance of Th1/Th2 plays a crucial role in allergic reaction in AR.^(26,27) IL-4 is produced by the antigen activated Th2 cell, which afterwards increases the production of IgE from B lymphocytes. While Th1-derived cytokine IFN- γ is associated with the suppression of IgE synthesis.⁽²⁸⁾ Our data showed that serum IL-4 level of the integrative group significantly decreased and the ratio of Th1/Th2 increased at 12-week treatment. And the trends of the cytokines were consistent with the changes of AR severity from clinical observation. These results suggested that CMAA might exert its anti-allergic effect by regulating the balance of Th1/Th2 ratio in AR.

Strengths of this study included interventions based on expert consensus and practiced by qualified and experienced medical staffs, using measurement of symptom scores and laboratory measures as recommended in guidelines for trials on rhinosinusitis,⁽²⁹⁾

and prominently good compliance of patients and high follow-up rates. However, there are several limitations in it. Firstly, the follow-up time was not long enough to balance the seasonal variation of the onset of AR, and follow-up for a whole year would be better. Secondly, we did not introduce recurrence indicators and quality of life assessment of the children, which could help us evaluate CMAA more comprehensively. Therefore, future trials on the optimal treatment course conducted with a high-quality design are needed.

In conclusion, the results of this study showed that the combination of CMAA and Montelukast was more effective than either treatment alone at long follow-up supported by reducing Th1/Th2 ratios mechanically.

Conflict of Interest

None.

Author Contributions

Li YJ and Qin LP were responsible for design of the study and data analysis, and drafted manuscript. Li YJ, Zong M, Ding LF, Rui XQ, Ma BY and Qin LP performed the experiments and contributed reagents/materials/analysis tools. Li YJ and Qin LP participated in critical revision and final approval of the manuscript.

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