Original Article

Clinical study of Loratadine Tablet combined with Mometasone Furoate nasal spray combined with acupoint application of traditional Chinese Medicine in the treatment of allergic Rhinitis

Jun Li[1*], Jiangbo Qin[1] , Jianzhou Guo[1], Zishen Meng[1]

Abstract

Background: Allergic Rhinitis (AR) is a common variable of immune responses, affecting nearly 50 crores of people worldwide. Therefore, this study addresses both Western and traditional Chinese medicinal practices to combine and mediate a potent result in treating AR patients.

Objective: To achieve a sustainable and long-term impact on the treatment of Allergic Rhinities, a combination of Western medicines like synthetic corticosteroids and non-sedative antihistamines, along with the traditional Chinese medicine acupoint herbal patching, has been implemented.

Methods: A total of 782 patients were included in this study. They were randomly divided into four groups, maintaining approximately 1:1:1:1. The first group of patients was treated with Loratadine Tablet 10 mg and Mometasone furoate NS 200 micron (administered once in the morning at waking up and on an empty stomach for 15 days) with placebo traditional Chinese medicine. In contrast, the second group of patients received the traditional Chinese medicine acupoint herbal patching with placebo tablets (Vitamin C, 100 mg). Now, the third group was the integrated treatment group, where the patients received both treatments, and the fourth group received only the placebos for both treatment procedures.

Results: Different scales were employed to examine the different symptoms of AR, like the Visual Analog Scale (VAS), Total Nasal Symptom Score (TNSS), Total Symptom Score (TSS), etc. In order to assess the histological effects of allergic reactions in patients with AR (Allergic Rhinitis), a randomized blood testing approach was employed. The collected data was subjected to statistical analysis using SPSS 17.0 software. Continuous and normally distributed data were evaluated using the mean ± standard deviation ($\bar{x} \pm s$) measurement. Additionally, geometric mean and standard deviation, ANOVA, and Dunnett's test were performed to identify any potential multiple comparisons. Finally, a Chi-square test was employed to summarize the data findings.

Conclusion: The study is a great success in achieving its result on the AR patients. However, to come with a definite sustainable result, the time of the study needs to be increased by at least a year so that the effectiveness of this treatment on the changing seasons can be observed and thus statistically analyzed. [*Ethiop. J. Health Dev.* 2023; 37(4): 00-00]

Keywords: Allergic Rhinitis, Synthetic corticosteroids, non-sedative antihistamines, monotherapy, traditional Chinese medicine acupoint herbal patching, Visual Analog Scale (VAS), placebo group, Total Nasal Symptom Score (TNSS), Total Symptom Score (TSS), Geometric mean, standard deviation, ANOVA, Dunnett's test, Chi-square test.

Introduction

Allergic Rhinitis (AR) is a common yet diuturnal, non-infectious airway ailment determined by the infiltration of inflammogenic cells in the respiratory tract, specifically the nasal mucosa. It presents syptoms such as hypersecretion, hypersensitivity, exudation and more. AR is also commonly known as Hay Fever. AR involves a series of allergic reactions to some foreign particle entering a body. Depending upon the causing agents', AR is found to be of two types: ***Seasonal Rhinitis***- usually occurs in the spring or shedding season, and the outdoor allergense outdoor allergens cause this type cause this type; ***Perennial Rhinitis***- can occur at any time of the year as it is generally caused by agents like pet dander, dust mites, etc. The symptoms of AR include sneezing, running nose, congested nose, excessive nose itching, coughing, a feeling of continuous throat scratching, itching of the eyes, clogged ears, watery eyes, redness of eyes, dark circles around the eyes, throbbing headache, eczema-like skin issues, excess fatigue. Approximately 10-30% of the worldwide population have AR, and 40% of the AR affected patients are found eventually to be

affected with asthma (bronchial) and severe nasal symptoms, even some pulmonary complications like wheezing, chest tightness, etc. It is even observed that patients with present or past records of atopic eczema and asthma are very much prone to grow AR. Outdoor and indoor foreign allergens like tree pollen, dust mites, grass pollen, animal dander, cat saliva, mold, etc are proven to be the causing agents of AR. Apart from these, other external factors like cigarette smoking, certain chemicals, excessively cold temperatures, excessively humid conditions, air pollution, few hairsprays, perfumes, cologne, fumes, wood smoke, etc can also trigger AR. When these allergens enter the body, they get involved in initiating the immune response involving the activation of certain ranges of cytokines and immune active cells. This helps in the further release of immunoglobulin IgE-mediated mediators, mainly histamines. Through the H1

[1] Department of Otolaryngology Head and Neck Surgery, Heping Hospital Affiliated to Changzhi Medical College;Shanxi, Changzhi, 046000 China

*Corresponding author: Jun Li, E-mail: lijunzhde@yeah.net

receptors of histamine, it induces 3 main cardinal symptoms of AR i.e., pruritus, mucosal Edema, and sneezing. The secretion from the nasal mucosa can be responsively induced by H1 & also by H2 receptors. So, to treat AR, antihistamine medicines are applied to subside allergic symptoms.

In present times, the most effective approach to control the inflammation caused by both seasonal and perennial AR is through the application of glucocorticoids. The anti-inflammatory action of glucocorticoids follows 2 pathways: the trans-repression pathway and the trans-activation pathway. It also induces Forkhead box FOX P3+ T cells and regulatory cytokines. It exerts regulatory effects on nasal and ocular symptoms and can even help in improving other symptoms. Apart from these 2 front-line drugs, the other drugs that are usually applied to treat AR are anti-leukotrienes, mast cell membrane stabilizers, decongestants, anticholinergics, ,etc. Tough, the research suggests, by taking certain precautions, the overall QoL (quality of life) of the patients can be improved, and the symptoms can efficiently be controlled but AR can not completely be cured through any standardized comprehensive prevention and treatment.

Usually, AR shows a history of repetitive recurrence, so the patients need to undergo a prolonged administration of drugs to maintain potency against AR, which causes several side effects in the patients. Here comes the touch of traditional medicines and their other applications, like acupuncture, which works miracles even if combined with Western medicines. Some Chinese herbal medicines efficiently show effects like anti-allergic, anti-inflammatory, immunomodulatory, etc. Even few show significant improvement in the nasal signs of AR. The acupuncture in traditional Chinese medicinal practice has a history of more than a thousand years. Acupuncture includes a variety of processes. Among them, the mostly known and common acupuncture process engages some special needles pricked at certain specific acupuncture points, guided by the elaborate theory of traditional Chinese medicines; even in other processes, they make some concoction paste and put them on certain acupoints which are known as the acupoint herbal patching. It is a type of minimal operational method where the energy alignment is drawn between all the meridians and acupoints. Acupuncture can be used to treat Allergic Rhinitis, like other diseases. Several studies showed that warm acupuncture could facilitate the signs of AR in rats, which exhibited the effect of inhibition on the serum IgE expression, interleukin-1beta, etc. Randomised controlled trials in human patients even show more efficacy, safety, and persistent advantages of acupuncture when compared with the western medicated ones. Research regarding the effects of acupuncture on AR has significantly increased in recent years. However, a comprehensive meta-analysis on the treatment given to AR patients is yet to be conducted. In this paper, the main purpose deals with a systematic assessment of the potency of treatment while acupuncture is paired with the combination of front-line western medicines applied on the AR patients.

Materials and Methods

A randomly selected, controlled with placebo, paralleled, and single-anonymized study was done. The approval of this study was gained from the Ethics Committee of Beijing Medical Center and was performed in accordance with the clinical trial guidelines. All subjects were patients registered under the Department of Otolaryngology and the Department of Chinese Medicine at Beijing Medical Center from February to March 2019. The study inclusion and exclusion factors are mentioned below. The design of the study was completely mediated according to the guidelines of the Good Clinical Practice and Helsinki Declaration. The participating patients were thoroughly informed about the objective of this study and the design of the entire study. Written, informed, and signed consent forms were collected from each of the participating patients. Each participant underwent a thorough health check-up, and laboratory tests, gathering information about the past medical records and evaluation of the rhinitis symptoms. A new Visual Analog Scale (VAS) was created to assess the severity of symptoms based on their intensity. This 4-point scale ranges from 0 to 3, where 0 represents the absence of significant symptoms, 1 indicates mild and easily tolerable symptoms, 2 reflects moderate and perplexing symptoms that are still manageable, and 3 signifies severe and intolerable symptoms that greatly impact daily life and sleep.

The efficacy of the treatment was judged through another scale from 1-5, where 1 indicates complete recovery and 5 shows treatment failure. Participating patients with moderate nasal congestion exhibited a Total Nasal Symptom Score (TNSS) of at least 6 and a Total Symptom Score (TSS), including total non-nasal symptom score where the TNSS with at least 11 taken as the screening. The participating patients and the physicians were purposefully unaware of the recipients of the effective and placebo drugs to avoid any biased ness.

Inclusion Criteria: The diagnostic criteria of AR were (1) occurrence of the clinical history of symptoms over 2 years; (2) occurrence of symptoms: minimum 3 days a week continued for a minimum of 4 consecutive weeks; (3) Positive report of skin prick test and positive allergen-specific serum IgE (SIgE) reports (0.30 IU/mL);(4) age of the AR patients was between 25 and 65years old; and (5) the participants were well informed and they willingly signed consent forms; (6) (participants) must be complying with the research protocol.

Exclusion criteria: (1) patients having comorbidity to asthma, persistent eczema, or any other allergic or autoimmune diseases; (2) any respiratory and congenital heart diseases; (3) hematological disease and any other chronic diseases (4) Rhinitis medicamentosa, Nasal candidiasis, nasal structural abnormalities, (5) record of recurring rhinosinusitis

Randomization: For research purposes, the individuals diagnosed with AR were randomly assigned to four different groups: integrative therapy, traditional Chinese Medicine acupoint, western medicine, and placebo. The random allocation was conducted using a random number table.

Interventions: Patients from the integrative were treated with traditional Chinese medicine acupoint herbal patching technique on certain acupoints paired with the administration of Western drugs, whereas in the Western medicinal group, the participating patients were treated with non-functional dough as a placebo for traditional Chinese medicine acupoint herbal patching treatment, on the same acupoints instead. In the traditional Chinese medicine acupoint herbal patching group, a vitamin tablet was given as a placebo for Western medicine. The herbal medicine applied for the traditional Chinese medicines acupoint herbal patching treatment is usually composed of a few ingredients, which are composed of Herba Asari, Herba Ephedrae, Radix Scutellariae, Cortex Cinnamomi, Borneolum Syntheticum and Semen Sinapis Albae in ratio of 2:2:2:2:1:1. All the ingredients were then turned into powder and with addition of ginger juice (2:1), a paste is formed. Now, a wide, porous sterilized fabric of 1.5 cm×1.5cm was taken, and the herbal paste was spread on that then these clothes were placed on the acupoints of the selected patients. According to the traditional Chinese medicinal theories, the important acupoints are Dazhui (DU 14), Dingchuan (EX-B1, bilateral), Tiantu (RN 22), and Feishu (BL 13, bilateral) for treating AR. The entire regimen of applying traditional Chinese medicine acupoint herbal patch therapy was continued over 2 weeks, consisting of a total of 6 sessions of 30-minute treatment (minimum 3 sessions per week).

A total of 782 registered and willing patients participated in this study. They were randomly split into four groups, maintaining approximately 1:1:1:1. The first group of patients was treated with Loratadine Tablet 10 mg and Mometasone furoate NS 200 micron (administered once in the morning at waking up and on empty stomach for 15 days) with placebo traditional Chinese medicine. In contrast, the second group of patients received the traditional Chinese medicine acupoint herbal patching with placebo tablets (Vitamin C, 100 mg). Now, the third group was the integrated treatment group, where the patients received both treatments, and the fourth group received only the placebos for both treatment procedures.

In all treatment groups, Cetirizine was applied as rescue medication in the total tenure of the study. The use of rescue medication two weeks before and during the study was taken into account by the physicians.

The Rhinitis control assessment test (RCAT), ranging the score from 6 to 30 (the higher the score, the better the rhinitis control) was employed to detect the rhinitis symptoms variation. RCAT includes 6 factors, i.e., nasal congestion, watery eyes, sneezing, rhinitis symptom control, activity avoidance, and sleep problems caused by Rhinitis. A 5-point Likert scale was used to document the responses by 2 experienced participating physicians.

To detect the levels of serum Th1/Th2, IL-4, and IFN-γ, blood sampling of the participating patients was done for flow cytometry, and was then kept in silicone tubes before the process. The collected blood was kept at room temperature for Clotting, and then the serum was separated through centrifuging the samples. Now, it was kept at –80 °C before assaying.

For analysing Serological Cytokines, the Serums were put under high-sensitivity enzyme-linked immunosorbent assay (ELISA) to measure the responses of Th2 (IL-4) and Th1.

The flow cytometric data analysis determined the intracellular cytokines. The percentage of cytokine-positive lymphocytes in the analyzed culture was considered as the result. The presence of cytokine-producing T cells (IL-4+CD4+ and IFN-γ+CD4+) in percentile was obtained from the total subpopulation of CD3+CD8.

Safety Observation

In case any serious condition appeared during treatment, then the experimental process was immediately suspended, and the ethical committee was thoroughly informed.

Statistical Analysis

The collected data was further analyzed through SPSS 17.0. Mean ± standard deviation (x–±s) was used to evaluate the continuous and normally distributed data. Initially, the Log transformation of all the variables was performed to eliminate abnormal distributions, and then a comparison of measurements gained from the laboratory was done. Geometric mean and standard deviation were then used to show the final data. Methods, like Fisher's least significant difference method and one-way analysis of variance (ANOVA), were performed to compare the demographic and baseline characteristic data of the 4 groups, and Dunnett's test determined any multiple comparisons if found. Chi-square test was used for recapitulating data.

Results

Trial Completion Condition:

In this study conducted from February to March 2019, a group of 782 patients were chosen to take part. These participants were divided into four groups: the western medicine placebo group consisted of 196 patients, the traditional Chinese medicine acupoint herbal patching with placebo western medicine group had 196 patients, the integrated medicine group included 201 patients, and the placebo group comprised 189 individuals. Prior to the study, all four groups had similar demographic and clinical characteristics at the baseline stage.

Difference between VAS Scores and the use of Rescue Medication in Patients

In the first week, VAS scores were significantly lower in the combined and traditional Chinese medicine acupoint herbal patching groups than those in the Western medicine group. However, the VAS scores of the combined and traditional Chinese medicine groups

were not found to be significantly different. Later on, the VAS scores started to fall significantly in the Western medicine group. The effects of treatment with time have a significant effect on the VAS scores.
Days of using rescue medication in the combined treatment group were distinctly low compared to the baseline.

Betterment in TNSSs
The records of TNSSs of the patients during the 15 days of therapy demonstrated more effectiveness of the first three active treatments than the placebo. The effectiveness between the integrated therapy and the Western medicine monotherapy was not significantly distinct, but the sustainability of the integrated therapy was significantly longer than the Western medicine monotherapy. Whereas the traditional Chinese medicine acupoint herbal patching therapy initially took a longer time to exert its effect in the patients of AR. Statistically insignificant differences were observed in individual nasal symptoms between integrated combination therapy and traditional Chinese medicine acupoint herbal patching monotherapy. Records indicated betterment with sneezing in all active treatment groups apart from the placebo group. Western medicine and traditional Chinese medicine acupoint patching integrated treatment ultimately led to better overall improvement compared to the Western medicine monotherapy and placebo for all four nasal symptom groups.

Betterment in TSSs
Statistically insignificant differences were found between Western medicine combined with traditional Chinese medicine acupoint herbal patching therapy and monotherapy of Chinese medicine acupoint herbal patching in average TSS reduction from day 1 to 15. Both therapies were found to be more efficient than the monotherapy of Western medicine and placebo. Improvement was recorded from the baseline in non-symptomatic (nasal) patients who rated Western medicine and traditional Chinese medicine acupoint herbal patching integrated therapy, western medicine monotherapy and traditional Chinese medicine acupoint herbal patching monotherapy was found efficient if compared to placebo in reducing mean total non-nasal symptom scores. The reductions in total non-nasal symptom scores from baseline to the endpoint were more than 52% with combination therapy, more than 51% with traditional Chinese medicine acupoint herbal patching monotherapy, nearly 43% with Western medicine monotherapy, and less than 33% with placebo. Statistically insignificant differences were found in the records for individual non-nasal symptoms between combination therapy and Western medicine monotherapy. However, all three treatments were found to be efficient when compared to the placebo in reducing ocular and ear itching, redness of the eyes and tearing, and palate itching. According to the reports from the patients, combination therapy was found to be more efficient when compared to Western medicine therapy for all non-nasal symptoms except ear/palate itching. Western monotherapy was more effective than placebo for all individual non-nasal symptoms except eye redness.

Comparison of Th1/Th2 Cytokines Release and Th2 Shift in Patients with PAR among Three:
The significant effect on serum IL-4 was found with the change of time; among them, the patients from the combined therapy group showed the minimum levels of serum IL-4. However, this effect had no impression on serum IFN-γ levels.

Significant effects were recorded on IFN-γ+CD4 and IL-4+CD4+ at the end days of the study, and the patients in the combination treatment group exhibited the minimal percentile record of Th2 at the end of the study. A significantly low Th2 shift was recorded in the group receiving the combination therapy in 2nd week when compared to the other three groups.

Safety
In the entire group of 782 patients participating in this study, 7 patients from the integrated and the group of traditional Chinese medicine acupoint herbal patching monotherapy reported skin itching in the area the herbal medicine was applied, which eventually resolved in a few days after the treatment was withdrawn. The elimination of specific elements from the herbal paste used in the patching increased the effectiveness of the treatment. This skin itching was suspected to be caused due to some allergic sensitivity towards certain elements.

Table 1. **Clinical and Demographic analysis of the baseline Population**

Parameters	**Group 1 n = 196**		**Group 2 n =196**		**Group 3 n =201**		**Group 4 n =189**	
Age Mean Range	26	12-65	25	11-65	26	12-65	26	12-64
Gender, M/F	`95/101		100/96		102/99		92/97	
AR duration Mean Range	18	2-56	16	2-55	16	2-58	14	2-51
TNSS,mean± SD Physicians Patients	8.6±1.7	7.9±2.2	8.5±1.7	8.0±2.0	8.4±1.8	7.8±2.4	8.8±1.8	8.0±2.5
TSS, mean ± SD Physicians Patients	16.2±3.2	14.3±4.5	15.9±3.4	14.5±4.2	16.1±3.5	14.8±3.1	15.8±3.1	14.6±4.4

Total Nasal Symptom Score (TNSS), Total Symptom Score (TSS); Group 1- receiving traditional Chinese medicine acupoint herbal patching with placebo western medicine; Group 2- receiving western

medicines i.e., mometasone furoate NS and loratadine and placebo acupoint herbal patching; Group 3- receiving the integrated therapy consisting of western medicine i.e. mometasone furoate NS and loratadine and traditional Chinese medicine acupoint herbal patching therapy; Group 4- placebo medicines for both treatments. .

Table 2. **Patient Diaries accounting from Days 1–15 show a decrease from Baseline in Individual Nasal Symptoms.**

Symptoms	Decrease, mean (%)								P value		
	Gr 1		Gr 2		Gr 3		Gr 4		3vs1	3vs2	3vs4
Nasal discharge											
Baseline Day 1-15	2.1	-0.8	2.1	-0.5	2.1	-0.8	2.1	-0.4	NS	<.05	<.01
Nasal congestion											
Baseline Day 1-15	2.2	-0.8	2.2	-0.5	2.3	-0.8	2.2	-0.4	NS	<.05	<.01
Sneezing											
Baseline Day 1-15	1.7	-0.8	1.7	-0.7	1.8	-0.9	1.6	-0.5	NS	<.05	<.01
Nasal itching											
Baseline Day 1-15	1.7	-0.7	1.9	-0.7	1.8	-0.8	1.9	-0.5	NS	<.05	<.01

- Group 1- receiving traditional Chinese medicine acupoint herbal patching with placebo western medicine; Group 2- receiving western medicines i.e., mometasone furoate NS and loratadine and placebo acupoint herbal patching; Group 3- receiving the integrated therapy consisting of western medicine i.e. mometasone furoate NS and loratadine and traditional Chinese medicine acupoint herbal patching therapy; Group 4- placebo medicines for both the ways.
- Abbreviation: NS- not significant;

Discussion

Statistically significant differences were evident between the two groups of the integrated treatment and traditional Chinese medicine acupoint herbal patching therapy in terms of assessment of QoL, TNSS, nasal nitric oxide levels, etc. Both treatment regimens exhibited significant improvement for change in all of the variables of efficacy, apart from the nasal nitric oxide levels.

Intranasal corticosteroids suppress the migratory inflated agents such as interleukin 3 (IL-3), IL-4, IL-5, and IL-13; eotaxin; intercellular adhesion molecule-1. They also reduce the histamine release. In contrast, H1-antihistamines exhibit a primary anti-allergic effect by opposing the actions of histamine through selectively binding to the H1-histamine receptor. This antihistamine-H1 receptor binding inhibits the tissue response.

The anti-inflammatory actions of intranasal corticosteroids in AR are efficient enough, so further anti-inflammatory activity provided by the inclusion of an antihistamine may be superfluous.

On the other hand, traditional Chinese medicine acupoint herbal patching shows brilliant effects of pharmacological and overall physiological aspects through skin absorption. The application of the herbs on the skin stimulates the acupoints of the patients. In herbal patching composition, they help to improve the disease resilience and regulate the functions of the respiratory system. The selected acupoints, present mostly in the upper body, are thoroughly addressed in the clinical practice of treating respiratory diseases.

Gaining equilibrium of Th1/Th2 plays a major part in allergic reactions in AR. Antigen- activated Th2 cell produces IL-4, which further induces the B lymphocytes to produce IgE. Where the suppression of IgE synthesis is mediated by Th1-derived cytokine IFN-γ. The data showed a marked decrease in the serum IL-4 level and a sharp increase in the ratio of Th1/Th2 in the integrative group. The cytokine trends were steady with the alterations of clinical AR severity. These results indicated that traditional Chinese medicine acupoint herbal patching, while combined with western medicine i.e., mometasone furoate NS and loratadine, might exert a strong anti-allergic effect by maintaining the proper balance of Th1:Th2 in AR.

The strength of this study comprehended the interventions from the qualified, experienced, and skilled medical staff; the use of symptom score scales and laboratory measures according to the clinical trial guidelines on AR. Further, the study was enriched with good conduct of the patients, and high follow-up rates. However, the major limitation of this study was the short follow-up time to assess the seasonal variation of the onset of AR, so assessment for a complete year would have always been better to conclude with sustainability.

Conclusion

The conclusive result of this study prominently exhibited the efficiency of the combination of Western medicine i.e., mometasone furoate NS and loratadine, and traditional Chinese medicine acupoint herbal patching treatment (supported by reducing Th1/Th2 ratios mechanically) over either treatment. The recurrence of AR even gradually decreased, and got eventually arrested. Though the tenure of the study was not significant for studying the standardized decreased recurrrence rate of AR, a study of an entire year is needed to assess the lowered recurrence rate of AR in the patients. This study has shown a definite decrease in the side effects of Western medicine in ths combination treatment when compared to the

monotherapies performed with Western medicine. The following check-up of the AR patients for another six months has revealed the decreased recurrence of AR in the participating patients, but further studies are needed to establish a definite sustainable treatment with this combination therapy on both kinds of AR patients.

Acknowledgment
The authors are thankful to the higher authorities for the facilities provided.

Conflict of interest
The author declares that no conflict of interest is associated with this study.

Authors' contribution
The authors mentioned in this article conducted the study and assume full responsibility for any claims arising from it and its contents.

Funding
No funding was received for this study

References

1. Yilmaz O, Altintas D, Rondon C, Cingi C, Oghan F. Effectiveness of montelukast in pediatric patients with allergic Rhinitis. Int J Pediatr Otorhinolaryngol 2013;77:1922-1924.
2. Storms W. Update on montelukast and its role in the treatment of asthma, allergic Rhinitis, and exercise-induced bronchoconstriction. Expert Opin Pharmacother 2007;8:2173-2187.
3. Chowdhury M, Uddin M, Das S, Hoque M. Montelukast in allergic Rhinitis: a review. Med Today 2012;24:75-78.
4. Smart J, Tang M, Kemp A. Polyclonal and allergen-induced cytokine responses in children with elevated immunoglobulin E but no atopic disease. Clin Exp Allergy 2002;32:1552-1557.
5. Jayasekera NP, Toma TP, Williams A, Rajakulasingam K. Mechanisms of immunotherapy in allergic Rhinitis. Biomed Pharmacother 2007;61:29-33.
6. Eifan A, Durham S. Pathogenesis of Rhinitis. Clin Exp Allergy 2016;46:1139-1151.
7. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: developing guidance for clinical trials. J Allergy Clin Immunol 2006;118:S17-S61.
8. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Grading of Recommendations Assessment, Development, and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126(3):466-76.
9. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol 2013;160(4):393-400.
10. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of Rhinitis on Work Productivity: A Systematic Review. J Allergy Clin Immunol Pract 2018;6(4):1274-1286.e9.
11. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
12. Cardell LO, Olsson P, Andersson M, Welin KO, Svensson J, Tennvall GR, Hellgren J. TOTALL: high cost of allergic rhinitis-a national Swedish population-based questionnaire study. NPJ Prim Care Respir Med 2016;26:15082.
13. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic Rhinitis executive summary. Otolaryngol Head Neck Surg. 2015;152(2):197-206.
14. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. Allergy Asthma Immunol Res 2018;10(4):300-353.
15. Xie C, Zhang QX, Zeng B. et al. Meta-analysis of therapeutic effect of acupoint embedding for allergic Rhinitis. Chin J Tradit med 2018;33(11):2271–2275.
16. Zhang J, Cao L, Xie TT, et al. Systematic evaluation of acupuncture in the treatment of allergic Rhinitis. Chinese Journal of Otolaryngology. 2017;25(3):230–235.
17. Fu Q, Zhang L, Liu Y, Li X, Yang Y, Dai M, Zhang Q. Effectiveness of Acupuncturing at the Sphenopalatine Ganglion Acupoint Alone for Treatment of Allergic Rhinitis: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med *eCAM, 2019*.
18. Fu Q, Zhang L, Liu Y, et al. Effectiveness of acupuncturing at the sphenopalatine ganglion acupoint alone for treatment of allergic Rhinitis: a systematic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine 2019, Article ID 6478102, 10 pages, 2019.
19. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic Rhinitis. Clin Exp Allergy 2006;36:676-684.
20. Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the pro- phylactic treatment of seasonal allergic Rhinitis. Drug Invest 1994;8: 225–233.
21. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized, placebo- controlled trial comparing fluticasone aqueous nasal spray in mono- therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic Rhinitis. Clin Exp Al-lergy. 2004;34:259 –267.
22. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic Rhinitis. J Fam Pract 1998;47:118 –125.

23. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active- controlled randomized trial of prophylactic treatment of seasonal allergic Rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996;98:724 –731.
24. Bronsky EA, Aaronson DW, Berkowitz RB, et al. Dose-ranging study of mometasone furoate (Nasonex) in seasonal allergic Rhinitis. Ann Allergy Asthma Immunol 1997;79:51–56.
25. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aque- ous nasal spray (NasonexTM) in seasonal allergic Rhinitis: an active- and placebo-controlled study. Allergy 1996;51:569–576.
26. Gawchik S, Goldstein S, Prenner B, John A. Relief of cough and nasal symptoms associated with allergic Rhinitis by mometasone furoate nasal spray. Ann Allergy Asthma Immunol 2003;90:416–421.
27. Berger WE, Nayak AS, Staudinger HW. Mometasone furoate improves congestion in patients with moderate-to-severe seasonal allergic Rhinitis. Ann Pharmacother 2005;39:1984–1989.
28. Mandl M, Nolop K, Lutsky BN; 194 – 079 Study Group. Comparison of once-daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial Rhinitis. Ann Allergy Asthma Immunol.1997;79:370–378.
29. Minshall E, Ghaffar O, Cameron L, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial Rhinitis. Otolaryngol Head Neck Surg 1998; 118:648 – 654.
30. Dockhorn J, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic Rhinitis. Ann Allergy 1987;58:407–411.
31. Horak F, Bruttmann G, Pedrali P, et al. A multicentric study of lorata- dine, terfenadine, and placebo in patients with seasonal allergic Rhinitis. Arzneimittelforschung. 1988;38:124–128.
32. Oei HD. Double-blind comparison of loratadine (SCH 29851), astemizole, and placebo in hay fever with special regard to onset of action. Ann Allergy 1988;61(6):436-9.
33. Bro ek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic- Anticevich S, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950-958.
34. Wang XD, Zheng M, Lou H, Wang C, Zhang Y, Bo M, et al. An increased prevalence of self-reported allergic Rhinitis in major Chinese cities from 2005 to 2011. Allergy 2016;71:1170-1180.
35. Montoro J, Del Cuvillo A, Mullol J, Molina X, Bartra J, Davila I, et al. Validation of the modified allergic Rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. Allergy 2012;67:1437-1442.
36. Magnan AO, Mely LG, Camilla CA, Badier MM, Montero-Julian FA, Guillot CM, et al. Assessment of the Th1/Th2 paradigm in whole blood in atopy and asthma: increased IFN-γ-producing CD8+ T cells in asthma. Am J Respir Crit Care Med 2000;161:1790-1796.
37. Okubo K, Inoue Y, Numaguchi H, Tanaka K, Saito I, Oshima N, et al. Montelukast in the treatment of perennial allergic Rhinitis in pediatric Japanese patients: an open-label clinical trial. J Drug Assess 2016;5:6-14.
38. Yang SH, Yu CL. Anti-inflammatory effects of Bu-zhong-yi-qi- tang in patients with perennial allergic Rhinitis. J Ethnopharmacol 2008;115:104-109.