Efficacy and tolerability of antiasthma herbal medicine intervention in adult patients with moderate-severe allergic asthma

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Background: Chinese herbal medicine has a long history of human use. A novel herbal formula, antiasthma herbal medicine intervention (ASHMI), has been shown to be an effective therapy in a murine model of allergic asthma.
Objective: This study was undertaken to compare the efficacy, safety, and immunomodulatory effects of ASHMI treatment in patients with moderate-severe, persistent asthma with prednisone therapy.
Methods: In a double-blind trial, 91 subjects underwent randomization. Forty-five subjects received oral ASHMI capsules and prednisone placebo tablets (ASHMI group) and 46 subjects received oral prednisone tablets and ASHMI placebo capsules (prednisone group) for 4 weeks. Spirometry measurements; symptom scores; side effects; and serum cortisol, cytokine, and IgE levels were evaluated before and after treatment.
Results: Posttreatment lung function was significantly improved in both groups as shown by increased FEV_1 and peak expiratory flow findings ($P < .001$). The improvement was slightly but significantly greater in the prednisone group ($P < .05$). Clinical symptom scores, use of β_2-bronchodilators, and serum IgE levels were reduced significantly, and to a similar degree in both groups ($P < .001$). T_H2 cytokine levels were significantly reduced in both treated groups ($P < .001$) and were lower in the prednisone-treated group ($P < .05$). Serum IFN-γ and cortisol levels were significantly decreased in the prednisone group ($P < .001$) but significantly increased in the ASHMI group ($P < .001$). No severe side effects were observed in either group.
Conclusion: Antiasthma herbal medicine intervention appears to be a safe and effective alternative medicine for treating asthma. In contrast with prednisone, ASHMI had no adverse effect on adrenal function and had a beneficial effect on T_H1 and T_H2 balance. (J Allergy Clin Immunol 2005;116:517-24.)

Key words: *Asthma, clinical trial, Chinese herbal medicine, prednisone, cortisol, T_H1/T_H2 balance*

Asthma is characterized by chronic airway inflammation, which adversely affects normal lung function. Corticosteroids, the most potent nonspecific anti-inflammatory agents, produce substantial improvement in objective lung functions of patients with asthma and are the cornerstone of asthma treatment.[1] However, systemic corticosteroids also induce serious systemic adverse effects when given for prolonged periods.[2] Corticosteroids also produce overall immune suppression, resulting in increased susceptibility to infections.[3] The side effects are significantly reduced with inhaled corticosteroids, but in higher doses, side effects including adrenal suppression and reduction in growth velocity have been reported.[4,5] There is a need for development of additional effective treatments with fewer side effects. Recently, there has been a surge in interest in traditional Chinese medicine (TCM) in Western countries, possibly because of the low cost and favorable safety profile. Although a role for TCM in Western medicine has not been established, TCM is in the mainstream of modern medical practice in China for treatment of various diseases, including asthma, either as monotherapy or as complementary therapy to standard Western medications. However, well-controlled clinical trials using TCM for asthma treatment are still rare.

In an attempt to develop novel herbal interventions for asthma, we previously tested Chinese herbal formula MSSM-002 (an extract of 14 herbs based on a TCM prescription used to treat childhood asthma in the Pediatric Department of the China-Japan Friendship Hospital in Beijing) on a well-characterized murine model of asthma. We found that MSSM-002 virtually eliminated airway hyperreactivity, markedly reduced the total number of cells and the percentage of eosinophils in bronchoalveolar

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Abbreviations used
ASHMI: Antiasthma herbal medicine intervention
PEF: Peak expiratory flow
TCM: Traditional Chinese medicine

lavage fluid, and inhibited mucus production in lungs of allergen-challenged mice.[6] Interestingly, in contrast with corticosteroids, which suppress both T_H1 and T_H2 responses, MSSM-002 specifically suppressed T_H2 responses (IL-4, IL-5, IgE production), but not T_H1 responses (IFN-γ, IgG2a production).[6] We further found that the immunomodulatory effects of MSSM-002 on T_H2 cells are caused, at least in part, by downregulation of GATA-3, a T_H2 transcription factor, and unlike corticosteroids, MSSM-002 does not induce apoptosis.[7] These findings suggest that MSSM-002 may be of benefit in the treatment of asthma. On the basis of the actions of individual herbs contained in MSSM-002 in our murine asthma model and on TCM formulation concepts,[8] we developed a simplified antiasthma herbal medicine intervention (ASHMI).[9] ASHMI is an extract of 3 herbs: Ling-Zhi (*Ganoderma lucidum*), Ku-Shen (Radix *Sophora flavescentis*), and Gan-Cao (Radix *Glycyrrhiza uralensis*). We found that ASHMI, like MSSM-002, exhibits the same broad spectrum of therapeutic effects on the major pathogenic mechanisms of asthma—airway hyperreactivity, pulmonary inflammation, and airway remodeling—as well as downregulating T_H2 responses and direct modulation of airway smooth muscle contraction.[10,11] In addition, ASHMI significantly suppressed T_H2 cytokine production by human PBMCs from patients with asthma. No cytotoxicity was detected at the highest effective dose tested.[12] On the basis of these findings, we undertook a study of the clinical effects, safety, and immunomodulatory effects of ASHMI treatment in patients with asthma compared with standard therapy with prednisone.

METHODS

Patients

A randomized, double-blind, placebo-controlled study was performed at Weifang Asthma Hospital from September 2003 to September 2004. Weifang Asthma Hospital is a chronic asthma treatment facility receiving patients nationwide. The 4-week study was conducted in the inpatient unit. The recruiting process involved 3 screening steps: clinical history, clinical testing, and laboratory testing. Patients prescreened and recruited from the outpatient facility were admitted to the hospital for purposes of the study. Ninety-two atopic, nonsmoking patients with asthma (43 men and 49 women, age 18-65 years) meeting the criteria of moderate-severe, persistent asthma[13] were recruited into this study. Inclusion criteria included (1) a history of allergic asthma for at least 1 year; (2) a serum IgE level above 100 IU/mL; (3) daily asthma symptoms; (4) exacerbations affecting activity and sleep; (5) nocturnal symptoms more than once a week; (6) FEV_1 ≥59% to <72% predicted or peak expiratory flow (PEF) ≥59% to <72%, PEF or FEV_1 variability >30%; (7) daily use of a β_2-agonist in the past month; (8) 2 short courses (3-7 days) of oral corticosteroids in the previous 6 months; (9) no use of oral corticosteroids in the previous 4 weeks; and (10) understanding the research protocol and consent to participate. Exclusion criteria in this study included (1) use of oral corticosteroids within the past 4 weeks; (2) heart, liver, kidney, or other organ diseases; (3) allergy or intolerance to the individual herbs in ASHMI; (4) pregnant and lactating women; and (5) being unable to comply with the research protocol because of severity of asthma (needed additional therapy). The study was approved by the hospital medical ethics committee, and all patients gave written informed consent.

Study design

There was a 1-week run-in period before initiating treatment. During the run-in period, patients were allowed to use β_2-agonist and/or theophylline. Any patient showing exacerbation of symptoms requiring additional medications was excluded from the study before the study began. The subjects were randomly assigned to receive ASHMI (n = 46) or prednisone (n = 46). Subjects in the ASHMI group received oral ASHMI capsules (4 capsules, three times a day) and placebo tablets similar in appearance to prednisone. Subjects in the prednisone group received oral prednisone tablets (20 mg once a day in the morning) and ASHMI placebo capsules for 4 weeks. For the duration of the study, leukotriene modifiers, antihistamines, and inhaled and intravenous glucocorticoids were prohibited. β_2-Agonist inhalation was allowed as needed. Subjects requiring additional intervention at any time because of disease severity were withdrawn from the study.

Each ASHMI capsule contained 0.3 g dried aqueous extract. The total daily dose of 12 capsules (3.6 g) is equivalent to extracts of a mixture of the raw herbs Ling-Zhi (Ganoderma Lucidum) 20 g, Ku-Shen (Radix Sophorae Flavescentis) 9 g, and Gan-Cao (Radix Glycyrrhiza) 3 g. ASHMI capsules and ASHMI placebo capsules were prepared by Weifang Pharmaceutical Manufacturing Factory, affiliated with Weifang Asthma Hospital. Prednisone placebo tablets were made by Shandong Luoxin Ltd, Weifang. Before and after completing treatment, symptom scores, use of salbutamol (puffs/d), and lung function were evaluated. Serum total IgE, IL-5, IL-13, IFN-γ, and cortisol levels also were measured. Symptom scores, adverse events, and β_2-agonist use were recorded daily. Grading of adverse events followed the World Health Organization Recommendations for Grading of Acute and Subacute Toxicity.[14] Hematology and serum chemistry testing and electrocardiograms were performed before and after the treatment.

Clinical and laboratory evaluation

Evaluation of symptom scores and use of β_2-agonist. Average daily symptom scores were evaluated over a 1-week period before treatment to establish a baseline. The effect of treatment on symptom scores was evaluated by analyzing average daily symptom scores in weeks 1, 2, 3, and 4 of treatment on the basis of 3 categories: daytime symptoms, nocturnal symptoms, and allergic nasal and ocular symptoms. Each category was scored by physicians from 0 to 3, with a maximum possible score of 9.[15] The daytime symptom scores (cough, chest tightness, wheezing or dyspnea) were 0, no symptoms; 1, mild symptoms or intermittent occurrence; 2, moderate symptoms with frequent occurrence that may affect normal activity at least 1 time; and 3, persistent symptoms, affecting all activities. Nocturnal symptoms scores were 0, no night awakening; 1, 1 night awakening or early morning awakening caused by dyspnea; 2, 2 night awakenings caused by dyspnea (including early morning awakening); and 3, multiple night awakenings caused by dyspnea. The score of signs and symptoms of allergic rhinitis (nasal pruritus, rhinorrhea, sneezing, and periocular pruritus and tearing) were 0, no symptoms; 1, symptoms <4 d/wk, no effect on comfort level, sleep, and daily