

# Efficacy and Safety of *Astragalus membranaceus* in the Treatment of Patients with Seasonal Allergic Rhinitis

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The study was designed to investigate efficacy and safety of *Astragalus membranaceus* (AM) in the treatment of patients with seasonal allergic rhinitis (SAR). AM is an active component in the herbal and mineral complex (HMC) registered in Croatia as a food supplement Lectranal®. The study was designed as a 6-weeks, double-blind, placebo-controlled clinical trial and conducted in 48 adult patients with a moderate to severe SAR. The treatment efficacy was evaluated by the mean change in the symptom score (TSS), quality of life (QoL), specific serum IgE and IgG, nasal eosinophils, and physicians' and patients' global evaluation. Compared to placebo, HMC significantly decreased the intensity of rhinorrhea while for other primary efficacy variables the treatment groups did not differ. In contrast, investigators and patients equally judged the treatment with HMC as more efficacious. In addition, the analysis of changes from baseline inside the groups for TSS, QoL, and 4 main symptoms of SAR were strikingly in favor of the active treatment. In patients with SAR due to weed pollen allergy HMC significantly improved primary variables, reflective TSS and QoL. The study revealed a significant number of positive signals indicating the therapeutic effectiveness of the HMC in patients with SAR which should be further tested in larger, multicentre trials with more patients. Copyright © 2009 John Wiley & Sons, Ltd.

**Keywords:** *Astragalus membranaceus*; seasonal allergic rhinitis; symptoms.

## INTRODUCTION

Allergic rhinitis (AR) is a very common cause of morbidity, and its prevalence seems to be increasing. The prevalence of AR in the general population in Europe, using the ARIA guidelines (Allergic Rhinitis and its Impact on Asthma) definition, was found to be around 25% (Bauchau and Durham, 2004; Bousquet *et al.*, 2008). AR is characterized by sneezing, rhinorrhea, obstruction of the nasal passages, lacrimation, and nasal, conjunctival and pharyngeal itching. These symptoms, along with systemic effects, fatigue, sleepiness and malaise, profoundly contribute to impaired quality of life (Bousquet *et al.*, 2008; Santos *et al.*, 2006). Although not a life-threatening and therefore often trivialized condition, it also has a substantial impact on public health and the economy. Affecting work and school performance and learning ability, AR is a major cause of lost school attendance and work absenteeism which in turn results in high cost to health care systems (Bousquet *et al.*, 2008; Simons, 1996; Szeinbach *et al.*, 2007). Considering the significant comorbidities of AR, particularly asthma, chronic rhinosinusitis and nasal polyps, the clinical importance of this condition seems to be even greater.

Many patients, despite the significant advances in conventional medicine, namely non-sedating antihistamines and topical corticosteroids, do not believe their symptoms are well controlled. Patient dissatisfaction often results in frequent medication changes, noncompliance or willingness to try new medications (Marple *et al.*, 2007), including complementary and alternative, particularly herbal medicine (Guo *et al.*, 2007). This frequently occurs despite the skepticism, controversy and lack of evidence that may or may not exist. Several recent studies investigated the efficacy of some herbal products and several traditional Chinese herbal medicines in the treatment of seasonal AR (SAR) and reported promising results (Guo *et al.*, 2007).

The aim of this study was to investigate the potential of a herbal–mineral complex (HMC) containing an extract of the root of *Astragalus membranaceus* (AM) as an active component in improving the symptoms and quality of life in patients with SAR. As other traditional Chinese herbal medicines, AM is thought to act by boosting the body's general vitality and strengthening the resistance to exogenous pathogens, and is regarded as a potent tonic for increasing energy levels and stimulating the immune system (Block and Mead, 2003). The present study was aimed to investigate the efficacy of HMC in a randomized, double-blind, placebo-controlled trial which included adverse-events monitoring. The primary hypothesis was one of superiority of HMC relative to placebo.

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## PATIENTS AND METHODS

The study was conducted in accordance with applicable Good Clinical Practice, European Union and International Conference on Harmonization guidelines, and under the principles of the 1996 World Medical Assembly Declaration of Helsinki, and was approved by the local Ethics Review Committee.

**Study design.** The study had a randomized, double-blind, placebo-controlled design and was conducted between May and October 2007, at the University Hospital Dubrava in Zagreb, Croatia. The study design consisted of three patient visits. An informed consent was obtained prior to study entry. At visit 1, each patient's eligibility for the study was assessed by reviewing all inclusion and exclusion criteria. The eligible patients provided venous blood samples for IgE and IgG, nasal cytology and completed mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) (Juniper *et al.*, 2000). Briefly, the Mini-RQLQ has 14 items divided in five domains (activity limitations, practical problems, nose symptoms, eye symptoms and other symptoms). The questionnaire is in self-administered format and was completed by patients without the assistance of an interviewer. Patients were asked to consider how they have been during the previous week and to respond to each question on a 7-point scale (0, no impairment to 6, severely impaired). Scores for individual items were then combined to obtain the total quality of life score (QoLS). The severity of individual SAR symptoms (rhinorrhea, nasal congestion, sneezing, itching or burning eyes), reflecting the patient's symptoms during the preceding 24 h, was graded according to a 4-point scale (0, none present; 1, signs or symptoms clearly present but minimal awareness and easily tolerated, mild; 2, definite awareness of signs or symptoms, bothersome but tolerable, moderate; 3, signs or symptoms difficult to tolerate and may interfere with daily activities or sleeping, severe). Scores for individual symptoms were then combined to obtain the total reflective symptom score (TSS) (Spector *et al.*, 2003). After completing all requested procedures, all patients were randomly allocated to receive study drug or placebo. The allocation schedule was generated by the independent statistician. To conceal the drug allocation, the blistered capsules were packed in numbered boxes along with instruction sheets. Each subject received a tick chart as an aid to compliance. Patient's data presenting more than 90% compliance were considered as evaluable. The same procedures (with the exception of blood sampling at visit 2) were performed at the second and third visit at 3 and 6 weeks, respectively. At the last two visits the adverse-effects were monitored. At the final visit, patients and investigators separately evaluated the overall severity of AR signs or symptoms and graded the response to treatment according to a 5-point scale (1, worsening; 2, no change; 3, mild improvement; 4, moderate improvement, and 5, significant improvement). Compliance was evaluated at visits 2 and 3 by verbal questioning and counts of returned medication. The blinded cytologist who performed all nasal smears estimated the number of eosinophils on a 4-point scale (0, no eosinophils, 1, scanty eosinophils scattered throughout smear, 2,  $\frac{1}{4}$ – $\frac{1}{2}$  cells on smear eosinophils, 3, almost all cells on smear eosinophils).

The primary efficacy measures were (1) the mean TSS and QoLS, expressed as the change from baseline, at visit 2 and visit 3, respectively; (2) the mean change from baseline in four main symptoms, and (3) in IgE and IgG. The secondary efficacy measures included investigator and patient global evaluation of treatment efficacy according to a 5-point scale as well as the mean change in nasal eosinophils.

**Patients.** A total of 48 adult outpatient participants of both sexes with a known history of moderate to severe SAR during the grass ( $n = 26$ ) or weed pollen season ( $n = 22$ ) were considered as eligible for the study (Fig. 1). The seasonal allergy was diagnosed with documented symptoms of SAR in at least 2 out of the 3 previous years and a positive skin prick test to appropriate pollen allergens within 2 years of screening. Allergy to grass pollen was confirmed by means of a positive skin prick test response to a mixture of grass pollen allergens as well as to three locally common grass pollen extracts (*Phleum pratense*, *Poa pratense* and *Lolium perenne*), while weed pollen allergy was confirmed by means of a positive response to a mixture of weed pollen allergens, and to one out of two locally common weed pollen extracts (*Ambrosia elatior*, *Artemisia vulgaris*). All the participants were required to be in good general health and free of any clinically significant disease that could interfere with the evaluation of study medication. A positive response to tree pollens (preceding the pollination of the grasses) was considered an exclusion criterion. Other exclusion criteria comprised previous or present antiallergy treatments, perennial AR, acute or chronic upper respiratory (sinonasal) infection, structural nasal abnormalities and nasal polyps. Women who were breastfeeding, pregnant, or at risk of becoming so (no adequate form of birth control) were not included in the study. All patients were randomized to receive study drug or placebo for 6 weeks. This was the only pharmacological treatment allowed during the study.

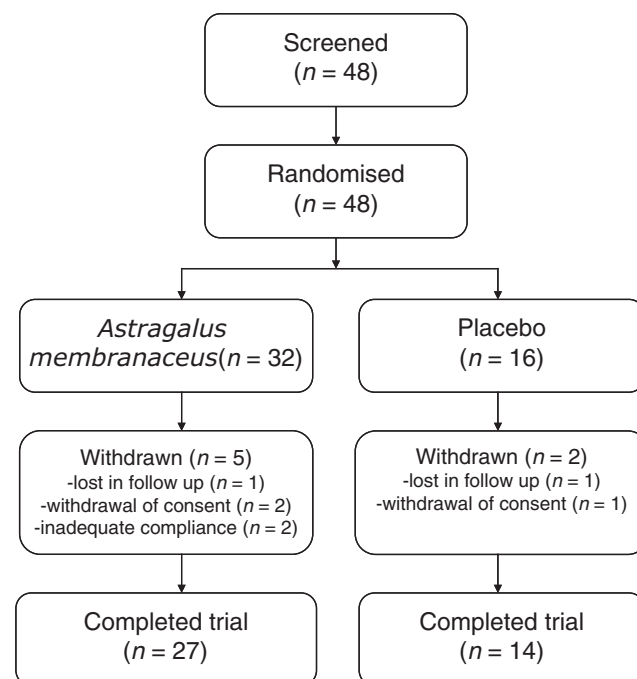


Figure 1. Flow diagram of the study.

**Study drug.** The study drug was a herbal and mineral complex containing 80 mg of *Astragalus membranaceus* (AM) root extract as an active ingredient per capsule, and standardized to contain 40% of polysaccharides determined by HPLC (high performance liquid chromatography). The plant used for the extract preparation was *Astragalus membranaceus* (Fisch.) Bunge, Fabaceae, harvested in China, Hunan Province. A water/ethanol extraction was used (solvent: water/ethanol 30%/70%), the final extract ratio was 18:1 (dried root to final extract). In 2006, this patent pending herbal and mineral complex was approved and registered by the Croatian Ministry of Health and Social Welfare as a dietary supplement for the relief of allergy symptoms. Besides AM, it contains calcium-aluminum-silicate as a mineral carrier. Earlier preclinical studies documented a synergistic activity of herbal and mineral components in inducing more pronounced immunoregulatory effects (unpublished data). The study drug or placebo (lactose powder) was randomly administered in a 2:1 ratio, for 6 weeks, starting at the very initial symptoms of SAR at the beginning of pollination. The study drug and placebo capsules were identical in size, color and smell and were to be taken with a little liquid (two capsules, two times daily).

**Safety evaluation.** Investigators evaluated adverse events (AEs) at visit 2 and visit 3. Patients were asked to describe any adverse symptoms or events that they experienced. All these events, irrespective of their relationship to study drugs, were considered as AEs. Subjects discontinued participation in the study if they were non-compliant or experienced severe exacerbation of SAR.

**Data analysis.** All analyses were prospectively planned, and the data were processed and analysed using STATISTICA, version 6.0 (StatSoft, Inc.; Tulsa, OK, USA) by an independent statistician. Power and sample size analysis was based on the assumptions that the mean difference for primary efficacy variables (mean TSS and QoLS) between the active treatment and placebo would be -3 and -4 points for the mean change in TSS from baseline after 3 or 6 weeks, respectively; and -15 and -15 points for the mean change in QoLS after 3 or 6 weeks, respectively. The calculated sample size based on at least 80% power and  $\alpha = 0.05$  with a 2:1 ratio (active treatment vs placebo) gave a required population of 45 subjects (30 on active treatment and 15 on placebo). The intention-to-treat population (ITT), consisting of all subjects who were randomized and who received at least one dose of study drug, was analysed. Student's *t*-test for normally distributed and the

Kolmogorov-Smirnov test for other quantitative variables were used to compare baseline characteristics, baseline values of efficacy variables and assessments by subjects and investigators between treatment groups. Categorical characteristics were compared using the chi-square test. A repeated measures ANOVA was used to evaluate primary and secondary endpoints. Regression analysis was used to evaluate associations between variables. Adverse events were expressed as incidence (%). Using the same methodology, additional post-hoc explorative analysis was performed in subjects treated during the weed season. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

### Patient withdrawals

Forty-eight patients were initially enrolled into study with 41 completing the study as per protocol. Three patients withdrew during the study due to severe symptoms of SAR, two were lost in follow-up, while two patients were withdrawn due to poor compliance. Five of the seven withdrawn subjects (15%) were on active treatment, while the remaining two (13%) were in the placebo group ( $p = 0.869$ ) (Fig. 1). The data of all withdrawn participants were used for ITT analysis.

### Patient demographics

Forty-eight patients with SAR were studied (26 men, 22 women) and received at least one dose of active treatment ( $n = 33$ ) or placebo ( $n = 15$ ). Baseline demographic and disease characteristics were similar (Table 1), regardless of whether they were compared using ITT or per protocol (PP) populations ( $p > 0.10$ , for all characteristics). Furthermore, according to their baseline characteristics, withdrawn participants did not differ significantly compared with patients who completed the study as per protocol ( $p > 0.20$ , for all characteristics). Twenty-six participants (54%) were studied in May and June, during the season of grass pollination, while others (46%) were studied during the season of weed pollination (August–October).

### Efficacy evaluation

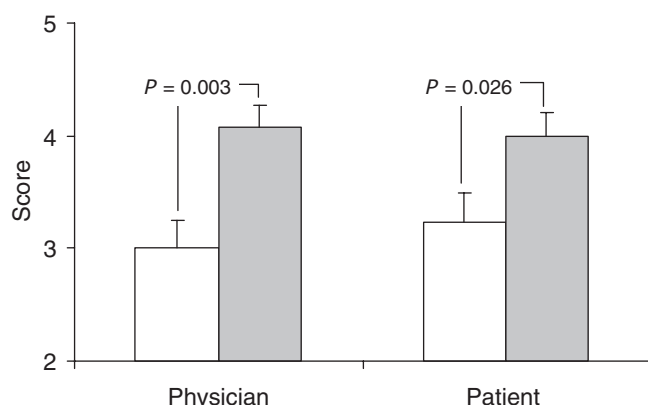
The primary efficacy variables were (1) the mean total symptom score and mini-RQLQ score (QoLS),

**Table 1. Patient baseline demographics and disease characteristics**

Characteristic	<i>Astragalus membranaceus</i> ( $n = 33$ )	Placebo ( $n = 15$ )	$p$
Age, mean (SD), years	33.3 (12.7)	31.5 (9.6)	0.634
Woman, $n$ (%)	16 (48)	6 (40)	0.584
Mean SAR duration, years	22.2	23.1	0.502
Total symptom score, mean (SD)	9.3 (4.1)	8.8 (2.7)	0.683
Mini-RQLQ score, mean (SD)	39.2 (4.6)	39.1 (3.4)	0.989
Specific IgE, median (IQR), kU/L	7.4 (1.1–25.0)	14.3 (4.2–67.1)	0.391
Specific IgG, median (IQR), kU/L	3.95 (2.00–6.11)	4.17 (2.61–5.76)	0.816
Nasal eosinophils, mean (SD)	2.3 (1.7)	2.0 (1.7)	0.573

SD, standard deviation; IQR, interquartile range.





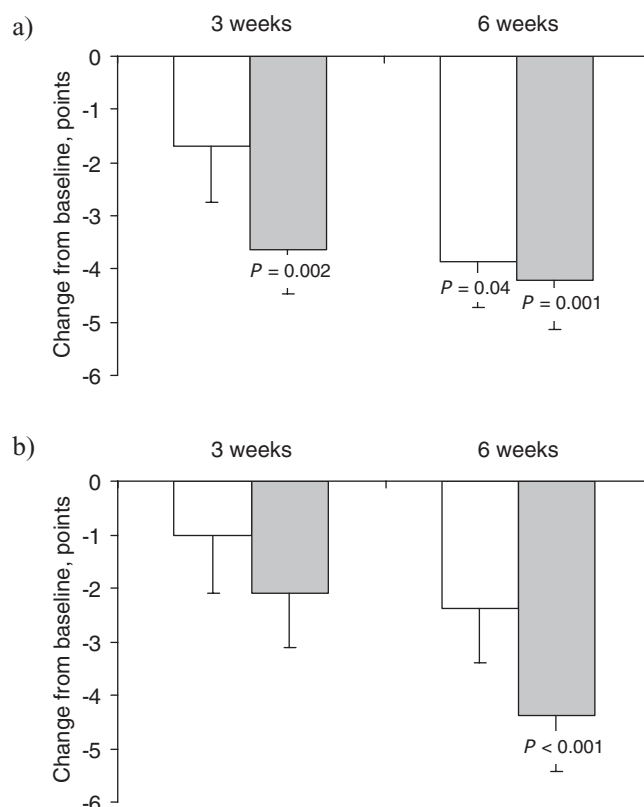
**Figure 2.** Physicians' and patients' global evaluation of treatment efficacy. Investigators and patients equally judged the treatment with HMC (closed bars) as more efficacious than placebo (open bars) ( $p = 0.003$  and  $0.026$ , respectively).

expressed as the change from baseline, at visit 2 and visit 3, respectively (2) the mean change from baseline in four main symptoms, and (3) IgE and IgG. The secondary efficacy measures included investigator and patient global evaluation of treatment efficacy according to a 5-point scale and the change in nasal eosinophils. For primary efficacy variables a statistically significant difference between treatment groups for the individual SAR symptom, rhinorrhea, after 3 weeks was observed ( $p = 0.048$ ). Other variables had no statistically significant differences between treatment groups although a trend toward significant difference ( $p < 0.20$ ) for some variables was obvious (TSS at visit 2,  $p = 0.12$ ). Similarly, no statistically significant differences were detected between treatment groups for serum IgE, IgG and nasal eosinophils. A positive signal toward a change in IgG was detected ( $p = 0.18$ ). In fact, only the treatment with AM decreased the serum specific IgG, while in patients on placebo the IgG slightly increased. In contrast, investigator and patient global evaluation of treatment efficacy according to a 5-point scale, as the secondary efficacy variable, showed a significant difference between treatment groups. Investigators and patients equally judged the treatment with AM as more efficacious (Fig. 2;  $p = 0.003$  and  $0.025$ , respectively). Moreover, a significant correlation of these outcomes with all other outcome variables was observed ( $p < 0.05$ , for all variables).

The analysis of changes from baseline in the groups for TSS, QoLS and four main symptoms of SAR was strikingly in favor of the observed trends. Compared with baseline values, the HMC significantly improved TSS and QoLS (Fig. 3a and 3b), as well as the intensity of rhinorrhea, sneezing and itching, almost uniformly at visit 2 and visit 3 (Fig. 4a, b, c). The placebo was significantly less effective (Figs 3 and 4).

### Post hoc analysis

Because of the significantly different course of weed pollination, characterized by a rapid increase in the number of air-born pollen grains, and an instant burst of AR symptoms in most patients, it was decided to perform a *post hoc* analysis of the results obtained in the group of patients with SAR due to weed pollen allergy ( $n = 21$ ). In contrast to the results for all participants, in this subgroup analysis, significant differences



**Figure 3.** Total symptom score and quality of life changes from baseline. HMC (closed bars) significantly improved (a) total symptom score in patients with SAR after 3 and 6 weeks of treatment ( $p = 0.002$  and  $0.001$ , respectively); (b) quality of life in patients with SAR after 6 weeks of treatment ( $p < 0.001$ ). Placebo (open bars) was effective only for TSS at visit 3 ( $p = 0.04$ ).

**Table 2.** Adverse events

Adverse event	<i>n</i>	% of participants
Rhinosinusitis	4	8.3
Pharyngitis	7	14.6
Enterocolitis	1	2.1
Nausea	1	2.1
Lacunar angina	1	2.1
Vulvitis	1	2.1
Total	15	31.3

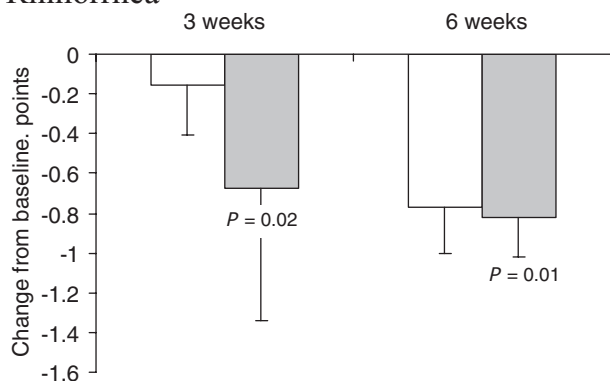
between the treatment groups were observed for the majority of outcomes. HMC significantly improved primary variables. The mean reflective TSS was improved after 3 and 6 weeks of treatment ( $p = 0.037$  and  $0.022$ , respectively) as well as QoLS ( $p = 0.017$  and  $0.001$ , respectively) when compared with placebo (Fig. 5). Most individual symptoms as part of the QoL questionnaire were statistically significantly improved in the HMC group compared with the placebo.

Similarly, investigator and patient global evaluation of treatment efficacy showed a more striking difference between the treatment groups. Investigators and patients equally judged the treatment with HMC as more efficacious ( $p = 0.001$  and  $0.001$ , respectively).

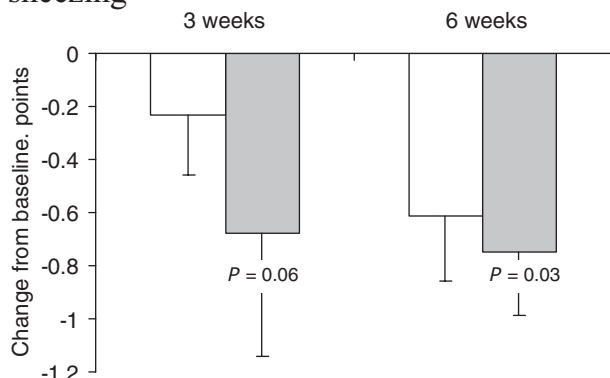
### Adverse events

During the study, a total of ten participants reported adverse events (Table 2). All adverse effects were mild

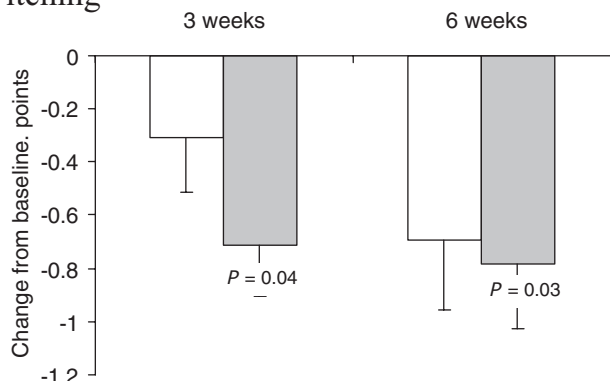
## a) Rhinorrhea



## b) sneezing



## c) itching



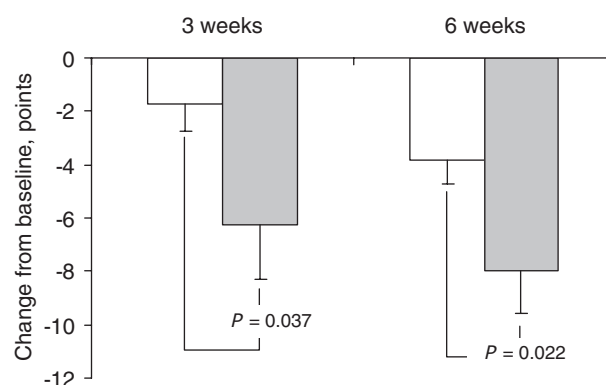
**Figure 4.** Rhinorrhea, sneezing and itching, changes from baseline. HMC (closed bars) significantly improved intensity of (a) Rhinorrhea in patients with SAR after 3 and 6 weeks of treatment, ( $p = 0.02$  and  $0.01$ , respectively); (b) sneezing in patients with SAR after 6 weeks of treatment ( $p = 0.03$ ); (c) itching after 3 and 6 weeks of treatment, ( $p = 0.04$  and  $0.03$ , respectively). Placebo (open bars) was ineffective.

or moderate in severity and in most cases may represent symptoms of the studied condition. Adverse events were not connected with the study drug.

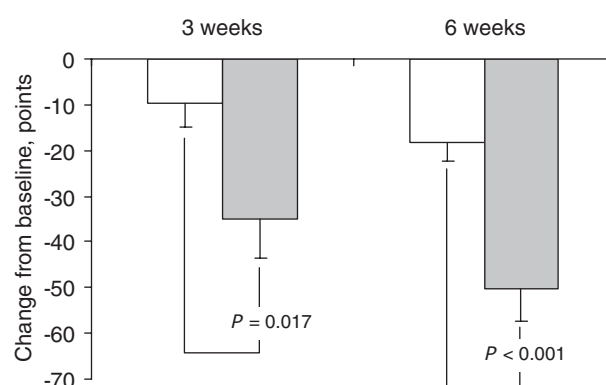
## DISCUSSION

*Astragali radix* is a popular traditional herbal medicine used to treat allergic diseases in Korea, Japan and China. In spite of a generally accepted clinical impression of its activity in boosting the body's general vitality and strengthening resistance to allergens, it has rarely been investigated in randomized controlled clinical

## a)



## b)



**Figure 5.** Total symptom score and quality of life changes from baseline in patients allergic to weed pollen. Compared with placebo (open bars), in patients allergic to weeds, HMC (closed bars) significantly improved (a) total symptom score after 3 and 6 weeks of treatment ( $p = 0.037$  and  $0.022$ , respectively); (b) quality of life ( $p = 0.017$  and  $< 0.001$ , respectively).

trials. Since a herbal and mineral complex containing *Astragalus membranaceus* (AM) as the active component was recently registered in Croatia as a food supplement which helps to relieve the symptoms of allergy, it was decided to test its efficacy in patients with SAR.

The primary hypothesis was one of superiority of HMC over placebo. The efficacy variables resembled those used in clinical trials in patients with SAR, and included symptom score and QoL, reduction of main symptoms of SAR, as well as physician and patient evaluation of treatment efficacy expressed as the change from baseline. The study also measured the specific IgE, IgG and nasal eosinophils before and after the treatment. For primary efficacy variables a statistically significant difference between treatment groups for individual SAR symptom rhinorrhea after 3 weeks was observed. Other primary efficacy variables had no statistically significant differences between treatment groups although a trend toward a significant difference for some variables was obvious. This may be caused primarily by the lack of statistical power due to smaller differences between treatment groups than predicted in the initial sample size calculation. Based on the observed trends, it was calculated that a sample of 71 participants in both treatment groups would be necessary to give a statistical power of 80% to confirm the superiority of HMC over placebo. In the subgroup of weed allergic patients the differences in primary efficacy measures were bigger than predicted, so a significant superiority of HMC over placebo was confirmed. Besides the

number of participants, we believe that the time of starting the treatment for SAR may influence its efficacy. Based on the fact that non-sedating antihistamines are more efficacious when administered before the season (Montoro *et al.*, 2007), it may be speculated that an earlier, pre-seasonal start of treatment with HMC would be more effective. However, it was decided to start the treatment at the beginning of the season of pollination (confirmed by later insight in pollen counts) believing that in this clinical setting the possible beneficial effect of HMC may be more objectively examined.

In the scientific literature, no comparable study of AM in patients with SAR was found. There are few reports of traditional Chinese and Japanese medicines containing AM among other herbal extracts in patients with AR (Xue *et al.*, 2003) or in experimental animal models of AR (Makino *et al.*, 2004; Sakaguchi *et al.*, 1999). On the contrary, some other herbal medicines are very popular among patients with AR, and in the past decade their use has increased tremendously (Passalacqua *et al.*, 2006). Consequently, the number of published randomized controlled trials (RCTs) with herbal medicines has increased substantially, making it imperative that allergists, confronted with patients using alternative treatments, become familiar with the scientific literature surrounding them (Resnick *et al.*, 2008). Guo and coworkers (2007) analysed 16 RCTs testing 10 different herbal products against placebo or active comparator. Six studies tested *Patasites hybridus* (butterbur) and suggested its superiority to placebo or similar efficacy compared with non-sedating antihistamines (Guo *et al.*, 2007; Schapowal, 2002, 2004).

Analysing the possible underlying mechanisms that may explain the beneficial effects of AM in allergic conditions, many reports suggested its significant immunomodulatory effects demonstrated in different experimental settings. Chinese, Korean and Japanese herbal

medicines containing AM were documented as being capable of modulating Th1/Th2 specific cytokine production in allergic animals (Kang *et al.*, 2004; Ko *et al.*, 2004; Nagai *et al.*, 2004). More specifically, Astragali radix extract has been documented selectively as altering *in vitro* Th1/Th2 cytokine secretion patterns, providing a basis for its clinical application in allergic diseases (Kang *et al.*, 2004). In addition, in a mouse model of asthma, AM was documented to have similar immunomodulatory potential by preventing airway hyperreactivity related to Th2-response inhibition (Shen *et al.*, 2008). In this study, AM prevented an allergen-induced decrease of INF- $\gamma$ , as well as an elevation of IL-5 and IL-13 (Shen *et al.*, 2008). In the present study, possibly to its short duration, a significant change in nasal eosinophils and serum IgE was not observed, but a positive signal toward a significant decrease in specific IgG was shown. In fact, only the treatment with AM in HMC decreased the serum specific IgG, while in patients on placebo the IgG increased slightly. This was in agreement with animal experimental data showing an IgG reduction upon treatment with traditional Japanese medicine containing AM (Ishimitsu *et al.*, 2001).

We are aware that it would be too pretentious to analyse the results of the present study in the context of cited experimental results. Anyhow, our results indicated many signs of a beneficial effect of AM in patients with SAR. It was more obvious in patients with ragweed-induced SAR who were exposed to higher concentrations of allergens and who did have a higher level of initial symptoms.

It is concluded that the present study revealed a significant number of positive signals indicating the therapeutic effectiveness of the HMC in patients with SAR. HMC should be further tested in multicentre trials with a larger number of patients (80–100 patients per group) in order to confirm all the positive trends observed.

## REFERENCES

- Bauchau V, Durham SR. 2004. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* **24**: 758–764.
- Block KI, Mead MN. 2003. Immune system effects of echinacea, ginseng, and astragalus: a review. *Integr Cancer Ther* **2**: 247–267.
- Bousquet J, Khaltaev N, Cruz AA *et al.* 2008. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* **63**(Suppl 86): 8–160.
- Guo R, Pittler MH, Ernst E. 2007. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol* **99**: 483–495.
- Ishimitsu R, Nishimura H, Kawauchi H *et al.* 2001. Dichotomous effect of a traditional Japanese medicine, bu-zhong-yi-qiang on allergic asthma in mice. *Int Immunopharmacol* **1**: 857–865.
- Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. 2000. Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire. *Clin Exp Allergy* **30**: 132–140.
- Kang H, Ahn KS, Cho C, Bae HS. 2004. Immunomodulatory effect of Astragali Radix extract on murine Th1/Th2 cell lineage development. *Biol Pharm Bull* **27**: 1946–1950.
- Ko E, Rho S, Lee EJ *et al.* 2004. Traditional Korean medicine (SCRT) modulate Th1/Th2 specific cytokine production in mice CD4+ T cell. *J Ethnopharmacol* **92**: 121–128.
- Makino T, Ito Y, Sasaki SY *et al.* 2004. Preventive and curative effects of Gyokuheifu-san, a formula of traditional Chinese medicine, on allergic rhinitis induced with Japanese cedar pollens in guinea pig. *Biol Pharm Bull* **27**: 554–558.
- Marple BF, Fornadley JA, Patel AA *et al.* 2007. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg* **136**(Suppl 6): S107–S124.
- Montoro J, Sastre J, Jáuregui I *et al.* 2007. Allergic rhinitis: continuous or on demand antihistamine therapy? *J Investig Allergol Clin Immunol* **17**(Suppl 2): 21–27.
- Nagai T, Arai Y, Emori M *et al.* 2004. Anti-allergic activity of a Kampo (Japanese herbal) medicine 'Sho-seiryu-to (Xiao-Qing-Long-Tang)' on airway inflammation in a mouse model. *Int Immunopharmacol* **4**: 1353–1365.
- Passalacqua G, Bousquet PJ, Carlsen KH *et al.* 2006. ARIA update: I – Systematic review of complementary and alternative medicine for rhinitis and asthma. *J Allergy Clin Immunol* **117**: 1054–1062.
- Resnick ES, Bielory BP, Bielory L. 2008. Complementary therapy in allergic rhinitis. *Curr Allergy Asthma Rep* **8**: 118–125.
- Sakaguchi M, Mase A, Ikeda Y *et al.* 1999. Effects of Sho-seiryu-to on experimental allergic rhinitis in guinea pigs. *Methods Find Exp Clin Pharmacol* **21**: 303–308.
- Santos CB, Pratt EL, Hanks C *et al.* 2006. Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol* **97**: 579–586.
- Schapowal A. 2002. Petasites Study Group. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *Br Med J* **324**: 144–146.

- Schapowal A. 2004. Petasites Study Group. Butterbur Ze339 for the treatment of intermittent allergic rhinitis: dose-dependent efficacy in a prospective, randomized, double-blind, placebo-controlled study. *Arch Otolaryngol Head Neck Surg* **130**: 1381–1386.
- Shen HH, Wang K, Li W *et al.* 2008. *Astragalus membranaceus* prevents airway hyperreactivity in mice related to Th2 response inhibition. *J Ethnopharmacol* **116**: 363–369.
- Simons FE. 1996. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* **17**: 185–189.
- Spector SL, Nicklas RA, Chapman JA *et al.* 2003. Symptom severity assessment of allergic rhinitis: part 1. *Ann Allergy Asthma Immunol* **91**: 105–114.
- Szeinbach SL, Seoane-Vazquez EC, Beyer A, Williams PB. 2007. The impact of allergic rhinitis on work productivity. *Prim Care Respir J* **16**: 98–105.
- Xue CC, Thien FC, Zhang JJ *et al.* 2003. Treatment for seasonal allergic rhinitis by Chinese herbal medicine: a randomized placebo controlled trial. *Altern Ther Health Med* **9**: 80–87.