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Title: Artemisia annua- sublingual immunotherapy: first step to cross the chasm

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The prevalence of allergic rhinitis (AR) has witnessed a progressive increase in China. A survey of self-reported AR using validated questionnaire-based telephone interviews in adult subjects conducted between 2004 and 2005 demonstrated that the prevalence of AR in 11 major cities across China was 11.1%¹. A subsequent survey of self-reported AR in adult residents of 18 major cities in China, conducted from 2005 to 2011, has reported that the prevalence of AR in 2011 had increased markedly to 17.6%². In particular, of the 11 cities in the original survey, which were also included in the second survey, the prevalence of AR had significantly increased in eight.

Allergen immunotherapy (AIT) is currently the only disease-modifying treatment available for patients with IgE-mediated allergic diseases. There are over 300 departments/ clinics administering AIT, which are scattered unevenly in China. Based on rough estimates, about 100,000 and 90,000 patients are receiving or have finished subcutaneous (SCIT) and sublingual (SLIT) immunotherapy, respectively. Despite the vast population of AR patients in China, AIT has not been widely accepted due to several factors; including insufficient training of ENT doctors, the inconvenience of allergen administration (patients usually come far-away from AIT centers), the potential risk of anaphylaxis, together with a relatively high cost of treatment³. Furthermore, currently only house dust mite allergen extracts are available and authorized in China for use *in vivo* allergy diagnosis and specific immunotherapy.

According to the statistical bulletin released by National Health Commission of China in 2019, there are only 30,000 registered ENT doctors in China. Even fewer have been trained to perform AIT. In view of the limited medical resources and highly demanding nature of conventional SCIT, it is necessary to design alternative immunotherapy strategies that are more convenient to implement, while being equally safe and efficient. In this regard, we have compared the efficacy and safety of a “clustered” 6-week build-up phase instead of the conventional 14-week schedule, and found that the cluster schedule had the advantage of achieving clinical effectiveness sooner and was a safe alternative to the conventional schedule⁴.

Although AIT has been mainly performed subcutaneously, administration of the allergen extracts via the sublingual route has been widely used in western countries with comparable safety and efficacy. Based on our own experience, about 70% patients complete a 3-year course of SCIT treatment. However, as China is a vast country and the level of medical services and patients’ compliance varies among different regions, this is likely to result in a variable overall national level of patients who complete a 3-year SCIT. Due to the convenience of self-administration without medical supervision, SLIT will contribute to better treatment compliance, especially in

children and those who cannot tolerate SCIT. As only one mite product is presently available for SLIT in China, the recent Chinese Guidelines on allergen immunotherapy for allergic rhinitis³ have called for development of more SLIT products that have been extensively investigated and tested.

Using skin prick test, Lou and colleagues⁵ have summarized the patterns of sensitization to inhalant allergens among AR patients in China and demonstrated that *Dermatophagoides farinae* (*Der f*) and mugwort were the most prevalent indoor and outdoor sensitizing allergens, respectively. Mugwort or *Artemisia* is an anemophilous genus included in the Compositae family. *Artemisia* pollen can be found in each province in mainland China; and of the 187 species of genus *Artemisia* found in China, *Artemisia annua* grows widely in northern China and is a major outdoor allergen responsible for AR and asthma⁶. According to a recent epidemiological investigation, of all the sensitizing pollen counted, *Artemisia annua* has the highest pollen count in autumn in northern China⁷. It is striking that although *Artemisia annua* is the major allergen responsible for seasonal allergic rhinitis (SAR) in northern China, to date *Artemisia annua* allergen has neither been available as a standardized commercial AIT product nor has this allergen been investigated in a well-designed SCIT or SLIT for clinical efficacy.

In the current issue of *Allergy*, Lou and co-workers⁸ report their findings from a randomized, double-blinded, placebo-controlled clinical trial (DBPC-RCT) evaluating the clinical efficacy and immunological changes resulting from SLIT with *Artemisia annua* in SAR patients recruited from a single center in Beijing. Although a level of serum specific IgE against *Artemisia annua* greater than 3.5kU/L was employed as the main inclusion criterion in this trial, additional tests such as skin prick test and/or nasal provocation may have ruled out any possible influence of cross reactions of ImmunoCAP.

Artemisia annua SLIT manifested significant improvements in nasal/ocular symptoms and the combined symptoms medication score (CSMS), before and during the pollen season. Although the treatment was stopped 8 weeks after the end of first pollen season, the effects were sustained until the second season. The stringency of this trial, however, may have been affected as peak pollen phase was defined by total pollen count, instead of specifically *Artemisia annua* pollen count. Placebo effect in especially SLIT is common⁹. Although a placebo effect was actually demonstrable, based on >20% improvement in TNSS in a third of patients in the placebo group, it is difficult to elaborate placebo effects from the figures shown in the publication. As the average TNSS, DMS, and CSMS scores of the placebo group were quite stable, it is possible that the

placebo response may be masked by aggravation of the symptoms with the advent of 1st and 2nd PPP. The authors further demonstrated that setting the ratio of sIgE/total (t)IgE at 22% could be a potential predictor of responsiveness to SLIT. This cut-off value is also in accordance with the findings of Di Lorenzo and colleagues,¹⁰ based on both SCIT and SLIT treatment. However, whether the ratio of sIgE/tIgE was assessed at the beginning of treatment or after 16-weeks of pre-seasonal SLIT was not specified in this article by Lou and colleagues. The authors reported that after 32-weeks of the trial, 58.3% and 23.4% subjects developed new sensitizations (i.e. UniCAP $\geq$ ++ ($\geq$ 0.7kUA/L)) in the placebo and SLIT groups, respectively. It is likely that the high rate of new sensitizations noted in the placebo group was a consequence of the small sample size. However, the study has some limitations. As indicated by the authors, the course of treatment and follow-up period was relatively short compared with other AIT studies, and therefore it is difficult to draw conclusions on the long-term effects of *Artemisia annua* SLIT. This study is also limited by the relatively small sample size (47 and 24 for SLIT and placebo respectively), and inclusion of only adult patients. Furthermore, although sensitization to multiple allergens is common in real life⁵, the efficacy of *Artemisia annua* SLIT for polysensitized AR patients was not addressed in this study. As other *Artemisa* species (e.g. *Artemisa vulgaris*), and some appropriate AIT products, can be found in several other countries, it will be interesting to test for cross reactivity of these products with *Artemisia annua* SLIT.

Despite the limitations, considering the huge chasm between the large population of patients allergic to *Artemisia annua* and the paucity of allergen-specific treatment in China, this investigation provides useful information on an effective, well tolerated and convenient treatment option for those patients. Thus, on this basis, real-life studies taking into account a broader geographical range, different age groups, and over longer periods are justified for more robust evidences and for the architects of future guidelines. It is noteworthy that as SLIT is administrated as a daily dose, this could sometime be forgotten. Patient self-management monitored through telephone interview or internet-based apps to ascertain optimum adherence may overcome this problem. Besides, whilst it is difficult to achieve blinding with SLIT due to more common local side effects compared with placebo, it is possible that most patients would not be able to accurately guess which treatment they were receiving; particularly because this was a prospective study and thus patients would not be able to anticipate what AEs they may or may not experience, and also the local AEs experienced by patients in the SLIT group were mild and self-resolved.

The presence of the hundreds of millions of Chinese subjects suffering from AR and an increasing

prevalence of AR in China is associated with a significant ever increasing socioeconomic burden on both the individual and society. Because of the diverse regional characteristics of allergic disease and the special conditions of the health services of China as a developing country, Chinese rhinologists and immunologists are devoted to exploring the pathogenesis and improving the diagnosis and treatment of allergic disease. The work of Lou and colleagues published in this issue of *Allergy* sets an example in this respect, and is representative of the rapid development currently underway in AR research in China.

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