



Current Specific Immunotherapy for Allergic Rhinitis: Perspectives from Otorhinolaryngologists

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The prevalence of allergic rhinitis (AR) in the general population is increasing and currently estimated to be approximately 10-25%.^{1,2} Although AR is not associated with a risk of death, the disorder can have a considerable effect on a patient's quality of life. Consideration of comorbid diseases, including asthma, nasal polyp, olfactory dysfunction and chronic rhinosinusitis, results in a tremendous increase in the medical cost for AR treatment, which has come to entail more than just treating the rhinitis itself.¹ Among the current treatment options for AR, specific allergen immunotherapy (SIT) is the only medical intervention that modifies fundamental immunologic mechanisms by inducing tolerance, and it can also modify the natural course of the disease. SIT for AR has been used for more than a century since first reported by Noon.³ SIT refers to the repeated administration of allergenic extracts to atopic individuals over a period of 3 to 5 years either subcutaneously (SCIT) or sublingually (SLIT) for the treatment of allergic diseases. At first, SCIT was used for allergic diseases caused by pollen allergens, such as hay fever or seasonal AR; however, today the indications extend to hymenoptera venom, house dust mites (HDMs), animal dander and allergic diseases related to fungi.⁴ SCIT has been demonstrated to be effective for asthma and AR; yet, it has several disadvantages, such as its inconvenience, invasiveness and potentially severe systemic reactions. Thus, SLIT has recently received much attention around the world as a primary treatment for AR and is now widely used as a replacement for subcutaneous administration, even in Korea.^{5,6} The efficacy and safety of SIT have been established by many clinical trials, studies, and meta-analyses, and its long-term effects and prevention of asthma progression have been suggested.⁷⁻¹⁰

In the Asia-Pacific region, the majority of patients with AR are diagnosed by ENT specialists or general practice physicians.¹¹ Published data suggest that ENT specialists most commonly

encounter patients with AR triggered by one or multiple inhaled allergens. Thus, ENT specialists are mainly responsible for the primary treatment of AR. In this regard, important information has been provided by a Chinese survey conducted among ENT specialists on their knowledge and clinical usage of SIT.¹² Most of the survey respondents considered AR (96.0%) and allergic asthma (96.0%) the most suitable indications for SIT. Of all respondents, 77.0% recommended the use of SIT as early as possible; in addition, SIT was considered 'relatively controllable and safe' by most respondents (80.6%). With regard to the indications for SIT, ENT specialists in South China (69.1%) preferred SIT as 'the first choice of treatment'; however, those in West China (78.2%) preferred the response 'pharmacotherapy is invalid'. In terms of the choice between SCIT and SLIT, physicians tended to choose SCIT for those patients who are of good financial status (84.1%), have high-efficacy expectations (82.5%), are adult (76.4%) or are well educated (71.5%), suggesting that ENT specialists in China believe that SCIT is more efficient, more expensive, less safe, and more careful in its follow-up schedule than SLIT. However, only 15.8% of them believed that SIT could be implemented in a primary hospital due to the need for standardized diagnostic processes, professionally trained staff and a valid emergency rescue system. This implies that although many ENT specialists now agree with the efficacy of SIT, they are concerned about the safety issues of this

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therapy, especially those of SCIT. In terms of safety issues, most ENT specialists cannot justify using SCIT, which can lead to potentially fatal systemic complications in patients with AR, which is not a fatal disease but does affect quality of life. According to a Belgium survey, of the different types of SIT, SLIT is the most frequently performed by ENT physicians of longstanding practice, working in private practice and/or in the French-speaking part of Belgium.¹³ Most data suggest that ENT specialists may transition to practicing SLIT instead of SCIT because of its safety and convenience.

The highest allergen-positive rates of AR patients showed marked differences among geographical regions as well as age groups.^{12,14} A study of the Global Allergy and Asthma European Network demonstrated sensitization patterns to different inhalant allergens across Europe and the appropriate battery of tests on inhalant allergens needed for an epidemiological study.¹⁵ Japanese Cedar is the most common allergen in Japan. House dust mites (HDM) comprised the larger proportion of sensitized allergens among the younger compared with the older age groups in Korea.¹⁴ A recent Chinese study found that HDMs were the major allergen affecting patients; in addition, patients in northern China showed significantly greater sensitization to pollens than did those from the other regions.¹⁶ However, the majority of individuals who were surveyed in the Asia-Pacific region reported never having had a diagnostic test to confirm the presence of AR. Forty-one percent of adults and 43% of children surveyed reported having had a diagnostic test (either a skin or blood test) to confirm the diagnosis of AR. On average, roughly equal percentages of the survey population reported having had a skin-prick test (~10%), blood test (~14%), or both (~16%).¹¹ Thus, for the application of SIT as well as the diagnosis of AR, allergen tests to determine offending allergens should be performed and tailored to individual age groups and epidemiological studies.

AR is often induced by a variety of allergens. Among the patients seeking treatment for moderate to severe respiratory AR, polysensitization is more prevalent (range, 50-80%) than monosensitization in the United States, Europe and Korea. A monosensitized patient would be the ideal candidate for SIT. Nonetheless, it appears that polysensitized patients would also benefit from appropriately prescribed SIT, even though the use of single or multi-allergen SIT is still debatable in polysensitized patients. Although multi-allergen immunotherapy increases the risk of adverse reactions during SIT, some clinical trials have demonstrated its efficacy in AR and asthma,¹⁷ while others have not.¹⁸ In Korea, a comparative study performed on 134 patients demonstrated that mite-SLIT is equally effective between monosensitized and polysensitized patients.¹⁹ One of the most striking differences in SIT approaches between Europe and the United States is the use of allergen mixtures, which are a common practice in the United States but usually not applied in European countries. In Europe, the predominant view is that poly-

allergy does not always constitute a clinical problem, and that the most troublesome allergies only should be treated using the corresponding monoallergen SIT. In contrast, the predominant view in the United States is that one should treat as many of a patient's allergies as possible by administering all the relevant allergens (either as a mixture or as separate extracts). Data suggest that ENT specialists in China tend to use a similar SIT approach to treating patients as that used in the United States.¹² According to published data, the use of single- or multi-antigen immunotherapy in polysensitized patients, whether delivered sublingually or subcutaneously, requires more supporting data.²⁰

Lastly, the Chinese survey indicated that the 'high cost of SIT' (86.6%) and the 'lack of patient knowledge of SIT' (85.2%) were likely the main reasons for the lower clinical usage of SIT among Chinese ENT specialists. In a United Kingdom survey conducted among ENT consultants, 26% recommend SIT, yet only 6.6% currently administer the immunotherapy.²¹ In Belgium, 81% of Belgian ENT physicians have concluded that there is an indication for immunotherapy in AR patients, while 19% neglect such an indication, the main reasons being a lack of doctor expertise on, lack of patient knowledge about, and the high costs associated with SIT. In addition, its high cost is also an important reason that may prevent the usage of SIT during maintenance therapy. Chronic pharmacotherapy is recommended to patients with persistent moderate to severe AR. SIT, however, can not only improve the quality of life and the physical burden of allergies as well as change the course of the disease but can also reduce long-term costs. Published data have shown a significant cost benefit with SIT versus the use of drugs alone for AR and asthma treatments.²² However, this cost-benefit effect usually depends on the healthcare and insurance systems of each country. In Korea and most regions of China, the healthcare system does not cover the costs of SIT or the Medicare payment for SIT is low, which could increase the economic burden to patients. Additional healthcare policies should be adopted to promote and improve immunotherapy awareness and to support the implementation of SIT for allergic diseases, which can improve patients' health and happiness.

Previously published data suggest that it is most commonly ENT specialists who diagnose and manage AR patients. Most of them are aware of the efficacy and safety of SIT for AR patients. Among the different types of SIT, conventional SCIT is the preferred method in China, yet likely to change among ENT specialists to SLIT because of safety and convenience. However, the wide acceptance of SIT has been a serious issue due to its high cost, which will require financial support by means of adopting a new healthcare and reimbursement system. Finally, there is room for improving knowledge of specific immunotherapy options among general practitioners as well as patients. This would enhance synergy among specialists, primary care physicians and patients.

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