Sublingual immunotherapy (SLIT): An emerging therapy?

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With allergic rhinitis affecting 20% of adults and 40% of children, the impact of this disease can be staggering.[1] Among chronic illnesses, allergic rhinitis and asthma are the leading causes of absenteeism,[2] with two million annual lost school days attributed to allergic rhinitis.[3] While pharmacotherapy reduces symptoms of allergic rhinitis, immunotherapy (IT) is the only treatment offering potential long-term immune modification. Conventional subcutaneous immunotherapy (SCIT) requires frequent injections, and often results in patient noncompliance due to inconvenience or intolerance. In the 1980's, SCIT was deemed responsible for several deaths, causing the British Committee for the Safety of Medicine to raise concerns about its safety.[4]

Due to SCIT safety concerns, multiple non-injection IT routes have been investigated. Sublingual immunotherapy (SLIT) has been the most promising of the non-injection IT routes and has now been in use in Europe for over 20 years. SLIT efficacy in controling adult rhinoconjunctivitis symptoms has been shown in two large double-blind, placebo-controlled trials in Europe. Durham et al. showed improved quality of life scores and dose-dependent reduction in medication use for SLIT patients in a study of 855 grass pollen allergy patients.[5] In a study of 634 patients, Dahl et al. demonstrated a significant reduction in symptom score and medication use for SLIT patients as compared to placebo.[6] In a recent review by Leatherman et al., 30 of 36 studies showed SLIT to be

effective in controlling rhinitis, conjunctivitis, and/or asthma in adults and children.[7]

SLIT has been reported to be safe for both adults and children in multiple clinical trials.[7,8] Common, yet mild, reactions may include pruritis of the oral cavity, throat irritation, nausea and other gastrointestinal complaints. For many years, no anaphylactic events were reported with SLIT. Recently, however, two cases of anaphylaxis have been linked to SLIT.[9,10] These reports indicate that the administration of any type of immunotherapy should proceed with vigilance and caution.

While many SLIT studies have been conducted worldwide, U.S. SLIT literature is lacking, and SLIT is not currently approved by the U.S. Food and Drug Administration. In a preliminary patient cohort at the Medical University of South Carolina, we have demonstrated improved symptom scores in SLIT patients at post-escalation and maintenance timepoints, as compared to baseline.[11,12] We anticipate that larger multicenter randomized placebo-controlled trials will be necessary before U.S. Food and Drug Administration approval is granted for this method of immunotherapy.

As we undertake further SLIT studies in the U.S., a number of other factors should be addressed in addition to efficacy and safety. First, many worldwide SLIT studies are performed with single-antigen monotherapy, whereas SCIT protocols involve multiple-antigen polytherapy. At our institution, skin testing typically results in positive results for multiple (9 or greater) allergens.[11,12] Determination of the benefit of monotherapy versus polytherapy has not been

undertaken in previous SLIT studies. Secondly, escalation and dosing regimens for SLIT exhibit significant hererogeneity amongst published studies. In a study by Dahl et al.,[6] no SLIT antigen escalation was performed, whereas in 2007 the American Academy of Otolaryngic Allergy published its 12-week SLIT escalation protocol.[13] The current Medical University of South Carolina protocol uses a 4 week escalation phase and has demonstrated improvement in clinical symptoms after this one month period.[11,12] With regard to dosing, SLIT has been reported to be effective between 3 and 375 times the dose of SCIT.[14] Optimal SLIT escalation and dosing regimens require evaluation. Finally, immunologic changes occurring with SLIT are incompletely understood and warrant additional investigation. With additional studies designed to address these issues, as well as efficacy and safety in U.S. populations, SLIT may become a viable option for a larger number of Americans.

References

1. Corren J. Allergic rhinitis: treating the adult. J Allergy Clin Immunology 2000;105.
2. Bender B, Fischer T. Differential impacts of allergic rhinitis and allergy medications of childhood learning. Pediatr Asthma Allergy Immunol 1998;12.
3. Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. Allergy 2000;55.
4. Committee on the Safety of Medicines update: desensitizing vaccines. Brit Med J 1986;293:948.
5. Durham S, Yang W, Pedersen M, et al. Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:802-9.
6. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;118:434-40.
7. Leatherman BD, Owen S, Parker M, et al. Sublingual Immunotherapy: Past, present, paradigm for the future? A review of the literature. Otolaryngol Head Neck Surg 2007;136:S1-20.
8. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol 2005;95:254-8.
9. Dunsky E, Goldstein M, Dvorin D, et al. Anaphylaxis to sublingual immunotherapy. Allergy 2006;61:1235.
10. Gidaro G, Marcucci F, Sensi L, et al. The safety of sublingual-swallow immunotherapy: An analysis of published studies. Clin Exp Allergy 2005;35:565-71.
11. Wise S, Woody J, Koepp S, et al. Sublingual Immunotherapy (SLIT): Quality of Life Outcomes. In: American Rhinologic Society. San Diego, CA; 2007.
12. Woody J, Wise S, Koepp S, et al. Clinical Improvement after Rapid Escalation for Sublingual Immunotherapy (SLIT): A Pilot Study. In: American Academy of Otolaryngic Allergy. Washington, DC; 2007.
13. Leatherman BD. AAOA consensus sublingual immunotherapy dosing protocol. 2007:3-4.
14. Moingeon P, Batard T, Fadel R, et al. Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy 2006;61:151-65.