Maintenance of Certification clinical management series

Series editor: James T. Li, MD, PhD

Comparative efficacy and safety of subcutaneous versus sublingual immunotherapy

Cindy S. Bauer, MD,[a] and Matthew A. Rank, MD[b] *Phoenix and Scottsdale, Ariz*

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the instructions listed below:

1. Review the target audience, learning objectives and author disclosures.
2. Complete the pre-test online at www.jacionline.org (click on the Online CME heading).
3. Follow the online instructions to read the full version of the article, including the clinical vignette and review components.
4. Complete the post-test. At this time, you will have earned 1.00 *AMA PRA Category 1 CME Credit™*.
5. Approximately 4 weeks later you will receive an online assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive 2 MOC Part II Self-Assessment credits from the American Board of Allergy and Immunology.

Date of Original Release: September 2014. Credit may be obtained for these courses until August 30, 2015.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Cindy S. Bauer, MD, and Matthew A. Rank, MD (authors), and James T. Li, MD, PhD (series editor)

Activity Objectives

1. To summarize the effectiveness of monoallergen subcutaneous immunotherapy (SCIT) and monoallergen sublingual immunotherapy (SLIT) when compared with placebo in controlled studies.
2. To become familiar with the limited trials that directly compare multiallergen SCIT and SLIT.
3. To articulate the safety profile for SCIT and SLIT based on the current evidence in a way that allows providers and patients to make informed decisions.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: C. S. Bauer is employed by Phoenix Children's Hospital. M. A. Rank is employed by the Mayo Clinic Foundation and has received research support from the Agency for Healthcare Research and Quality (HS22126). J. T. Li has consulted for Abbott.

CLINICAL VIGNETTE

A 16-year-old girl with a history of intermittent asthma presents with perennial nasal congestion, sneezing, and ocular pruritus. Her symptoms are especially severe in the summer and when she visits her best friend's house, where 2 cats live indoors. She regularly uses intranasal steroids, intranasal antihistamines, saline rinses, and oral antihistamines, which lead to only partial relief of her nasal and ocular symptoms.

Her family history is notable for a mother with allergic rhinitis, who discontinued subcutaneous immunotherapy (SCIT) after 2 years when she experienced a systemic reaction immediately after a maintenance injection.

Percutaneous skin testing to common indoor and outdoor allergens pertinent for the Southwestern United States is performed, and results are positive for grass pollen (Bermuda, timothy, and Johnson), tree pollen (mountain cedar, sycamore, olive, white mulberry, and mesquite), cat dander, dog dander, and house dust mite.

The full review of this article, including a preview of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

From [a]the Division of Allergy and Immunology, Phoenix Children's Hospital, and [b]the Division of Allergy, Asthma, and Clinical Immunology, Mayo Clinic, Scottsdale.

Received for publication May 31, 2014; revised July 8, 2014; accepted for publication July 16, 2014.

Corresponding author: Cindy S. Bauer, MD, Department of Pediatric Pulmonology, Division of Allergy and Immunology, 1919 East Thomas Rd, Phoenix, AZ 85016. E-mail: cindysbauer@gmail.com.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.07.024

REVIEW

Overview

The 2 most commonly prescribed forms of specific immunotherapy are SCIT and sublingual immunotherapy (SLIT). The use of the former dates back to Noon and Freeman in 1911[E1] and results in reduced symptoms and medication use for both allergic rhinitis and allergic asthma and specific bronchial hyperreactivity.[E2,E3] The first randomized study for SLIT dates back to 1986,[E4] and the number of studies comparing SLIT with placebo in the subsequent 28 years has allowed for systematic reviews suggesting moderate-grade evidence for reduction in symptoms and medication use for both allergic rhinitis and asthma.[E5] After a 3- to 5-year course of SCIT or SLIT, the long-term clinical benefits of treatment often persist, distinguishing this treatment modality from medical treatment.

Despite growing confidence about the effectiveness of both SCIT and SLIT, many important questions about how to best apply these treatment modalities to our patients remain. In particular, adequately powered randomized trials comparing SCIT and SLIT directly are few and have several limitations.[E6] Herein, we will focus on studies that directly compare the efficacy and safety of SCIT and SLIT. We will review studies comparing the efficacy of monoallergen SCIT versus SLIT, multiallergen SCIT versus SLIT, the safety of SCIT versus SLIT, and other considerations for choosing SCIT or SLIT and then revisit the clinical vignette. We were unable to identify any studies that involved administering SCIT and SLIT simultaneously.

Efficacy of monoallergen SCIT versus SLIT

House dust mites. In a prospective, randomized, controlled study[E7] 51 house dust mite–sensitized children with asthma were treated with (1) SCIT (weekly maintenance dose of 44 μg of Der p 1 and 62 μg of Der f 1); (2) SLIT (53 μg of Der p 1 and 53 μg of Der f 1); (3) build-up SCIT and then maintenance SLIT (43 μg of Der p 1 and 43 μg of Der f 1); or (4) no immunotherapy. In all 3 immunotherapy regimens the inhaled corticosteroid dosage and number of asthma attacks were reduced. However, the SCIT and SCIT plus SLIT groups had earlier and more sustained decreases. In a 1-year study randomizing children to house dust mite SCIT or SLIT, Yukselen et al[E8] found significantly decreased symptom and medication scores for SCIT compared with placebo for rhinitis and asthma. Although a decrease in such scores was also seen for SLIT, it was not statistically significant. However, the same authors report that in a 1-year open-label extension, the clinical efficacy of SLIT became more evident, as did a reduction in bronchial hyperreactivity.[E9] Eifan et al[E10] randomized (open label) 48 children monosensitized to house dust mite to SLIT (296 μg of Der p 1 and Der f 1 over 1 year), SCIT (111 μg of Der p 1 and 150 μg of Der f 1 over 1 year adsorbed onto aluminum hydroxide), or placebo and found no statistical difference between the SLIT and SCIT groups (with both the SLIT and SCIT groups showing reduced total rhinitis and asthma symptom scores but only the SLIT group showing a reduction in total medication scores compared with the placebo group). Mungan et al[E11] randomized 36 patients with house dust mite allergy to receive SCIT, SLIT, or SLIT placebo (not blinded), finding a reduction in rhinitis symptoms for SCIT and SLIT compared with placebo and a reduction in asthma symptoms for SCIT but not SLIT. Tahamiler et al[E12] randomized 193 adolescents and adults to house dust mite SCIT versus SLIT and found similar reductions in symptoms but that SCIT resulted in greater protection against nasal allergen challenge. Taken together, small studies, many of which lack adequate blinding, suggest that SCIT and SLIT for house dust mite lead to similar rhinitis and asthma outcomes.

Tree pollen. Khinchi et al[E13] report a 3-year blind randomized controlled trial of 71 adults treated with birch SCIT (3.28 μg of Bet v 1 monthly adsorbed onto calcium phosphate), SLIT (49 μg of Bet v 1 every 2 days), or placebo, noting that both active treatment groups had significant and similar improvements in symptom and medication scores. In a double-blind, placebo-controlled study of 40 adults monosensitized to cypress, Ventura et al[E14] found reduced clinical symptom scores in both patients undergoing SCIT and those undergoing SLIT. Finally, in a nonblinded randomized study of adults with birch allergy comparing SCIT and SLIT, the 34 participants who completed the study had similar symptom and medication scores.[E15] The available tree pollen studies comparing SLIT and SCIT suggest similar outcomes, although the studies are limited significantly by sample size.

Grass pollen. Quirino et al[E16] studied 10 matched pairs of subjects and concluded that SCIT and SLIT are equally effective based on reduction of symptoms and medication. The limited data about comparative SCIT and SLIT efficacy for grass pollen represent a major gap in knowledge.

Efficacy of multiallergen SCIT versus SLIT

Multiallergen SCIT. Pfarr et al[E17] randomized 285 patients to placebo or mixed grass and birch extract SCIT (6.75 μg of *Betula verrucosa* and 15.75 μg of *Phleum pratense* adsorbed onto aluminum hydroxide). A significant reduction was seen in symptom and medication scores in the active treatment group compared with the placebo group. Furthermore, rhinitis quality-of-life scores were significantly better for the actively treated subjects.

Multiallergen SLIT. Amar et al[E18] performed a double-blind, placebo-controlled trial in which 54 subjects were randomized to receive placebo, timothy grass extract (19 μg of Phl p 5 daily), or timothy grass extract plus 9 additional pollens. No significant differences were seen in medication or symptom scores in either treatment group compared with those seen in the placebo group. Only the timothy grass monotherapy differed significantly from placebo by increasing tolerance to titrated nasal challenge, increasing serum-specific IgG_4 levels, and decreasing IFN-γ release by timothy grass–stimulated lymphocytes.

Multiallergen SLIT versus multiallergen SCIT. We were unable to identify studies that compared multiallergen SCIT and SLIT. Therefore decisions about treatment must be made with indirect evidence. In outcomes analysis in a SLIT trial, polysensitization did not appear to affect treatment efficacy, suggesting that SLIT monotherapy remains effective in polysensitized subjects.[E19] However, using multiallergen SLIT or SCIT might be more effective but has not been directly compared. Clearly, more evaluation of the effects of multiple-allergen immunotherapy in polysensitized patients is needed.[E6]

Safety of SCIT versus SLIT

The sample sizes of studies comparing SCIT and SLIT are small, making it more difficult to make direct comparison of safety parameters. In one direct comparison study 2 of 38 patients randomized to SCIT had systemic reactions, whereas there were

none for those who received SLIT.[E7] Similarly, in another study 2 of 30 patients had a systemic reaction while undergoing SCIT, whereas none did for SLIT.[E10] In the grass immunotherapy study minor local side effects were seen with SCIT, but no systemic side effects were observed in any of the 20 subjects.[E16]

The safety of SLIT and SCIT might be better estimated by using studies that do not directly compare outcomes because larger sample sizes are available. Although severe reactions are rare with SLIT, local side effects, including angioedema and pruritus of the lips and floor of the mouth, are experienced in most subjects, especially in the first few weeks of treatment.[E5,E6] This notion is important because SLIT is administered by subjects in their homes; despite this excellent safety record, recently approved SLIT formulations are recommended to be first taken under medical supervision, and patients are recommended to carry an epinephrine autoinjector.[E6]

Other considerations in choosing SCIT versus SLIT

Optimal dosing. The optimal dosing for SCIT has been established for some of the common aeroallergens through clinical trials, with most allergens ranging between 5 and 20 μg of major allergen per injection.[E6] There are 19 standardized SCIT extracts, including venom (n = 6), grass pollen (n = 8), short ragweed, cat dander (n = 2), and house dust mite (n = 2). Effective doses for SLIT can be derived from multiple trials comparing monoallergen SLIT and placebo, and there are only 3 US Food and Drug Administration (FDA)–approved SLIT tablet formulations for use in the United States. For both multiallergen SCIT and multiallergen SLIT, dose-ranging studies are lacking.

Patient and family preference. As mentioned above, SLIT can be administered at home, whereas SCIT is recommended to occur in a supervised medical setting. Furthermore, the comfort of oral versus subcutaneous administration is likely to be preferred, especially in children.

Adherence. Adherence to SCIT and SLIT is similarly poor, ranging from 6% to 84% for SCIT and 14% to 93% for SLIT, which is similar in rate to medication adherence, as summarized in a recent review.[E20]

Costs. Cost-effectiveness studies have favored SCIT versus pharmacologic treatment and SLIT versus pharmacologic treatment.[E6] However, direct cost comparisons of SCIT versus SLIT, especially for multiallergen therapy, are lacking.

THE CASE REVISITED

Currently in the United States, the only FDA-approved products for SLIT are for timothy grass and ragweed pollen. Although the patient had positive skin test responses to timothy grass (which would cross-react with a locally important grass pollen, perennial rye grass), she had a negative skin test response to ragweed. Because she had perennial symptoms likely related to multiple pollen and indoor allergies and, in particular, had severe symptoms around cat dander, she and her mother opted to receive SCIT. This was decided after learning that the FDA-approved SLIT formulations would only be able to address a single pollen that contributed to her symptoms for only part of the year. She and her mother were aware of the increased risk of systemic reactions and inconvenience of receiving treatment in a supervised setting that would occur with SCIT. Although aware of the efficacy of single-allergen SLIT, the hope that SCIT would address her multiple allergies and the information from the physician that very few studies are available that directly compare single-allergen SLIT and multiallergen SCIT were the main factors influencing the decision.

REFERENCES

E1. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1:1572-3.
E2. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007;(1):CD001936.
E3. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;(8):CD001186.
E4. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy 1986;16:483-91.
E5. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA 2013;309:1278-88.
E6. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Clin Immunol 2010;127:30-8.
E7. Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. J Allergy Clin Immunol 2011;128:808-15.
E8. Yukselen A, Kendirli SG, Yilmax M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol 2012;157:288-98.
E9. Yukselen A, Kendirli SG, Yilmaz M, Altinata SU, Karakoc GB. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. Asian Pac J Allergy Immunol 2013;31:233-41.
E10. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanism of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922-32.
E11. Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma—a placebo controlled study. Ann Allergy Asthma Immunol 1999;82:485-90.
E12. Tahamiler R, Saritzali G, Canakcioglu S, Ozcora E. Comparison of the long-term efficacy of subcutaneous and sublingual immunotherapies in perennial rhinitis. ORL J Otorhinolaryngol Relat Spec 2008;70:144-50.
E13. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy 2004;59:45-53.
E14. Ventura MT, Carretta A, Tummolo RA, Buquicchio R, Arsdieni A, Murgia N. Clinical data and inflammation parameters in patient with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy. Int J Immunopathol Pharmacol 2009;22:403-13.
E15. Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety, and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. Eur Ann Allergy Clin Immunol 2007;39:119-22.
E16. Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. Clin Exp Allergy 1996;26:1253-61.
E17. Pfaar O, Biedermann T, Klimek L, Sager A, Robinson DS. Depigmented–polymerized mixed grass/birch pollen extract immunotherapy is effective in polysensitized patients. Allergy 2013;68:1306-13.
E18. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol 2009;124:150-6.
E19. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. Clin Exp Allergy 2009;39:387-93.
E20. Cox LS, Hankin C, Lockey R. Allergen immunotherapy and delivery route: location does not matter. J Allergy Clin Immunol Pract 2014;2:156-60.