Maintenance of Certification clinical management series

Series editor: James T. Li, MD, PhD

Optimal duration of allergen immunotherapy

Efren Rael, MD,[a] and Richard F. Lockey, MD[b] *Hershey, Pa, and Tampa, Fla*

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: November 2014. Credit may be obtained for these courses until October 31, 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: Efren Rael, MD, and Richard F. Lockey, MD (authors), and James T. Li, MD, PhD (series editor)

Activity Objectives

1. To enhance sublingual immunotherapy (SLIT) treatment safety.
2. To extrapolate the magnitude of treatment-related long-term responses one might expect with grass SLIT and subcutaneous immunotherapy (SCIT).
3. To recognize risk factors associated with treatment-refractory venom immunotherapy (VIT).
4. To identify methods to improve immunotherapy treatment compliance.

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

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: R. F. Lockey is a board member for the World Allergy Organization; has consultant arrangements with Merck and ALK-Abelló; is employed by the University of South Florida and the Veterans Affairs Hospital; has provided expert testimony for Shook, Hardy and Bacon and Chamberlain and McHaney; has received research support from the American Lung Association (grant no. G62326), Forest Research Institute, GlaxoSmithKline, Genentech, Merck, Pfizer, Pharming, Sanofi-Aventis, Shire, and Teva; has received payment for lectures from Merck and AstraZeneca; has received royalties from Informa Publishing; and has received travel support from the World Allergy Organization. E. Rael declares no relevant conflicts of interest. J. T. Li has consulted for Abbott.

Key words: *Short case, subcutaneous immunotherapy, sublingual immunotherapy, immunotherapy duration, venom immunotherapy, clinical allergy pearls*

CLINICAL VIGNETTE

A 15-year-old boy who lives in Richmond, Virginia (northeastern United States), presents to you in February with a history of debilitating sneezing, rhinorrhea, and nasal pruritus; stuffiness; and redness and tearing of his conjunctiva that has occurred for the last 4 summers. Treatment with over-the-counter and intranasal antihistamines have failed, and he has experienced nosebleeds with intranasal glucocorticoids. Additionally, during the summer, he needs an albuterol inhaler for wheezing and coughing associated with exercise. He experiences similar respiratory symptoms within 15 minutes of cat exposure but chooses to treat this with cat avoidance.

Further history reveals a sting by what he thinks was a honeybee on his neck while working in the yard 2 years prior. His mother removed the "stinger." Within several minutes, he experienced generalized flushing, erythema, and pruritus, followed by diffuse urticaria. Within another 10 minutes, he started to wheeze and became progressively short of breath. He was taken to the emergency department (ED). On arrival, he had a feeling of impending doom, and his mother overheard a paramedic say that his blood pressure was "low." ED admission records showed that his pulse at admission was 140 beats/min, his respiratory rate was 20 breaths/min, and his blood pressure was 80/40 mg/Hg. He was placed in the supine position with his lower extremities elevated and treated with repeated intramuscular injections of epinephrine in the anterior lateral thigh, intravenous fluids, and oxygen and 30 minutes later was given 50 mg of diphenhydramine and 40 mg of methylprednisolone,

From [a]the Section of Allergy, Asthma & Immunology, Division of Pulmonary, Allergy, and Critical Care, Department of Internal Medicine, Penn State College of Medicine, Milton S. Hershey Medical Center, Hershey; and [b]the Division of Allergy and Immunology, The University of South Florida College of Medicine, Tampa.

Received for publication June 30, 2014; revised August 11, 2014; accepted for publication August 21, 2014.

Corresponding author: Efren Rael, MD, Penn State, Milton S. Hershey Medical Center, Allergy/Immunology, C5804B, MCH0401, 500 University Drive, Hershey, PA 17033-2360. E-mail: efrenrael@gmail.com.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.08.046

both of which were administered intramuscularly in the buttocks. He was discharged several hours later without sequelae. The ED physician did not suggest follow-up for the systemic allergic reaction (SAR). Present, past, social, and family histories and review of systems were otherwise unremarkable, except for a family history of atopy and asthma.

Physical examination revealed a well-developed, well-nourished, and cooperative male subject oriented to time, place, and person with a blood pressure of 110/70 mm Hg, a pulse of 76 beats/min, and a respiratory rate of 14 breaths/min whose examination results were otherwise normal. Spirometric results (including a flow-volume loop before and after β-agonist) were normal. Prick puncture skin test (PPST) results were markedly positive to timothy and related northern grasses and cat and showed minimal reactivity to a few other seasonal and perennial allergens. PPST results were negative to all Hymenoptera venoms; however, a honeybee intradermal skin test (IDST) at 0.01 μg/mL revealed a wheal of 10 × 12 mm and a flare of 15 × 25 mm. Results of all other IDSTs to Hymenoptera venoms were negative up to 1.0 μg/mL. Results with histamine and saline controls were positive and negative, respectively. His tryptase level was normal.

The patient wants to begin grass sublingual immunotherapy (SLIT). You advise that such therapy is indicated but that he also should be prescribed and know how to use self-injectable epinephrine, institute avoidance measures for Hymenoptera stings, and receive honeybee venom immunotherapy (VIT). He wants long-term guidance. What do you tell him?

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.

REVIEW

Grass subcutaneous immunotherapy and SLIT

There are no validated clinical or serologic markers of long-term tolerance after a year or more of allergen immunotherapy. Similarities in the immunologic changes induced by subcutaneous immunotherapy (SCIT) and SLIT exist, with studies suggesting 2 times more change in quantitative IgG_4 levels, more competitive inhibition of IgE, and an attenuated basophil activation test in the first to third months with SCIT versus SLIT. However, these differences are less apparent after 15 months of grass SCIT or SLIT.[E1] There are few long-term studies comparing SLIT and SCIT; however, an indirect meta-analysis comparing 3014 patients with allergic rhinoconjunctivitis with 2768 control subjects suggests that SCIT is more effective in terms of symptom control and decreased medication use.[E2] Studies analyzed were of variable duration, ranging from 3 to 41 months for SLIT and 1.5 to 36 months for SCIT, with most participants receiving immunotherapy for less than 1 year.

The results of a study of 238 adults with moderate-to-severe grass-induced allergic rhinoconjunctivitis plus or minus asthma treated with 2800 BAU timothy grass (Grazax; ALK-Abelló, Hørsholm, Denmark) from 4 to 8 weeks before the start of the 2005 through the end of the 2007 grass season suggested persistent improvement for 2 years after treatment but with diminished efficacy in year 2.[E3] There was a 34% reduction (95% CI, 15% to 56%) after completion of grass season 1 and a 27% reduction (95% CI, 8% to 42%) after completion of grass season 2 versus placebo in weighted combined symptom and medication scores after completion of 3 consecutive years of grass SLIT. The article suggests lower pollen counts during postcompletion year 2, which might explain the reduction in symptom improvement versus placebo.

A European multinational 3-arm grass treatment versus placebo clinical trial comparing 4 and 2 months of preseasonal and coseasonal SLIT treatment with Oralair 5-grass pollen extract (Stallergenes S.A., Antony, France) each year for 3 years also demonstrated efficacy in improving both symptom and medication scores versus placebo. Average rhinoconjunctivitis combined symptom and medication scores decreased by 33.9% and 36.6% in the 4- and 2-month preseason treatment versus placebo groups.[E4] The average rhinoconjunctivitis combined symptom and medication score decreased by 21.0% and 27.9% in the 4- and 2-month preseason treatment versus placebo groups at year 1 after completion of 3 years of treatment.[E5] Preliminary results of year 2 after completion of 3 years of treatment have been reported to the US Food and Drug Administration in an advisory briefing; however, the complete details have not been formally written up as of the date of this publication.

Three to 4 years of grass SCIT versus placebo in adults decreased symptom and medication scores for 3 years after completion.[E6] A 3-year preseasonal grass SCIT pediatric study demonstrated long-term efficacy 12 years beyond completion with regard to medication and symptom scores and prevention of new sensitizations.[E7] The Preventive Allergy Treatment study of 145 pediatric subjects showed that standardized grass and birch SCIT versus placebo for 3 years prevented asthma up to 7 years after treatment.[E8]

VIT

A 15% relapse rate 10 years after VIT discontinuation has been reported.[E9] Studies suggest 5 years of VIT is more effective than 3 years; however, subjects with severe SARs might still be at risk on re-sting, even after 5 years of VIT, and require indefinite VIT.[E9] Predictors of VIT failure include concurrent use of angiotensin-converting enzyme inhibitors, honeybee venom–induced SARs with VIT, and mastocytosis.[E10]

Compliance of SCIT versus SLIT

In the largest report on the topic, a Dutch database compared SCIT versus SLIT compliance. Among 6486 subjects, 2796 underwent SCIT, with a 1-year compliance of 80% and a 3-year compliance of 23%, in comparison with 3690 subjects treated with SLIT, with a 38% 1-year compliance and a 7% 3-year compliance.[E11]

Compliance can be improved with shared decision making through following a protocol that includes patient reminders, reassessment of treatment responses, and medication adherence.

The case revisited. The US Food and Drug Administration approved 2 forms of grass SLIT in 2014: GRASTEK 2800 BAU (Merck, Whitehouse Station, NJ) and Oralair. The patient initiated grass SLIT (GRASTEK 2800 BAUs because of insurance coverage) before and during the grass season after a discussion of the risks/benefits, treatment alternatives, and need for epinephrine for self-administration at home. The patient was advised that grass pollen tablet SLIT is approved for home use but that rare SARs occur. The first dose was administered in your clinic with you present, and the patient was observed for 30 minutes. An epinephrine autoinjector and instructions were provided for his continual SLIT home use. He also was started on honeybee VIT and achieved a maintenance dose of 100 μg per month for 1 year, followed by maintenance injections every 6 weeks.

He received grass SLIT beginning 12 weeks before the grass season for 3 years, with marked improvement in the first year and subsequent years in his seasonal allergic rhinoconjunctivitis. A year after he achieved VIT maintenance, he is stung by a honeybee (a stinger was removed and the insect was identified) without sequelae. He was retested to the same allergens after 3 years of treatment. His PPST reactivity to timothy grass and other northern grasses has diminished, but results were still positive. Results to cat allergen were unchanged. Likewise, his honeybee IDST result was positive at the 0.1 μg/mL of venom tested (5 × 5 mm wheal and 10 × 11 mm flare), a 10-fold less concentration than his previous test results. All other venom test results were negative at 1 μg/mL. The patient wants to stop both SLIT and VIT and asks for your advice.

A honeybee field sting without an SAR and decreased skin test reactivity suggests that a subsequent SAR to a honeybee sting is much less likely. However, the patient had a grade 4 SAR,[E12] and his honeybee skin test result was still positive. He was advised to continue VIT and be re-evaluated in 3 years.[E13] Grass SLIT was discontinued after 3 years, and he was advised to have his grass season symptoms monitored over the next several years. If you had initiated optimal-dose cat SCIT after reaching maintenance doses administered monthly for 3 to 5 years, it could have been discontinued with expected clinical benefit in most subjects for several years thereafter.[E14]

REFERENCES

E1. Aasbjerg K, Backer V, Lund G, Holm J, Nielsen NC, Holse M, et al. Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. Clin Exp Allergy 2014;44:417-28.

E2. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. J Allergy Clin Immunol 2012;130: 1097-107.

E3. Durham SR, Emminger W, Kapp A, de Monchy JGR, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129:717-25.

E4. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 2011;128:559-66.

E5. Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. Clin Exp Allergy 2013;43:568-77.

E6. Durham S, Walker S, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.

E7. Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61:198-201.

E8. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.

E9. Golden DBK, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol 2011;127:852-4.

E10. Rueff F, Vos B, Oude Elberink J, Bender A, Chatelain R, Dugas-Breit S, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. Clin Exp Allergy 2014;44:736-46.

E11. Kiel MA, Roder E, van Wijk RG, Al MJ, Hop WCJ, Rutten-van-Molken MPMH. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013;132: 353-60.

E12. Cox L, Larenas-Lennemann D, Lockey R, Passalacqua G. Speaking the same language: The World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125:569-74.

E13. Reisman RE. Venom immunotherapy: when is it reasonable to stop. J Allergy Clin Immunol 1991;87:618-20.

E14. Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow K, et al. Immunotherapy with cat- and dog-dander extracts. Effects of 3 years of treatment. J Allergy Clin Immunol 1991;87:955-64.