Immunomodulation of allergic sinonasal disease

Russell A. Settupane, M.D.,¹ Anju T. Peters, M.D.,² and Larry Borish, M.D.³

ABSTRACT

IgE hypersensitivity is important to the pathogenesis of allergic diseases and the development and persistence of airway inflammation. Allergic immunomodulation encompasses various therapies that attempt to suppress or modify the immune mechanisms responsible for IgE-mediated disease. These include allergy immunotherapy (AIT) in the forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), as well as the emergence of biological agents, such as anti-IgE, for allergic respiratory disease. Clinical evidence strongly supports the efficacy and safety of AIT for the treatment of allergic rhinitis, allergic conjunctivitis, and allergic asthma, but for chronic rhinosinusitis evidence is lacking. In allergic rhinitis, the decision to initiate AIT depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, the adverse effects of medication, the severity and duration of symptoms, and their effect on quality of life. AIT has the potential to produce sustained long-lasting immune modulation and possibly avoid or reduce lifelong requirements for medical therapy. Although SLIT is currently being evaluated, SCIT remains the preferred form of AIT in the United States because of robust efficacy data, availability of allergen extracts, and current Food and Drug Administration approval. However, SLIT holds the potential for greater patient safety and convenience. Other immunomodulators such as anti-IgE also hold promise, but require further investigation.

(Am J Rhinol Allergy 27, S59–S62, 2013; doi: 10.2500/ajra.2013.27.3930)

Allergic immunomodulation encompasses various third-line therapies that attempt to suppress or modify the immune mechanisms responsible for IgE-mediated disease. These include allergy immunotherapy (AIT) in the forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), as well as the emergence of biological agents for upper and lower airway disease such as anti-IgE.^{1–3} AIT is defined as the repeated administration of relevant allergens⁴ to patients with IgE-mediated conditions for the purpose of providing protection against allergic symptoms and inflammatory reactions associated with the natural exposure to these allergens.¹ In this article, SCIT, SLIT, and anti-IgE are briefly reviewed; however, for a more in-depth discussion regarding AIT, the reader is referred to recently published practice parameters relating to rhinitis⁵ and AIT¹ as well as a recent AIT consensus report.⁶

SUBCUTANEOUS IMMUNOTHERAPY

SCIT: Description and Indications

SCIT, commonly referred to as “allergy shots,” is the oldest form of AIT, dating back over 100 years, where allergen is administered subcutaneously for the purpose of inducing allergen-specific immune tolerance.⁷ In allergic rhinitis,⁸ SCIT may be considered if symptoms are not controlled by allergen avoidance and pharmacotherapy or if the patient prefers not to take medications or has medication-induced adverse effects. In addition, SCIT may be considered if the patient desires to avoid or reduce the need for long-term pharmacotherapy.¹ However, before SCIT can be considered, it is imperative that the

patient has evidence of sensitization to relevant aeroallergens on either skin⁹ or *in vitro*¹⁰ testing in the context of a compatible clinical history.¹¹ It is not appropriate to recommend AIT based solely on results of skin testing or *in vitro*-specific IgE tests, without appropriate clinical correlation.¹

With regard to chronic rhinosinusitis (CRS) and nasal polyps^{12,13} the role of an allergic contribution is uncertain.¹⁴ Guideline recommendations for the use of SCIT in CRS are assigned the lowest strength, level D, because of limited evidence.¹⁵ There are no randomized prospective studies on SCIT in CRS; one retrospective study indicated that immunotherapy may decrease the use of antibiotics and improve sinonasal symptoms in patients with recurrent rhinosinusitis.¹⁶ Unfortunately, this study was limited not only by its retrospective nature, but also by the absence of objective assessment of sinusitis severity. However, based on a recent report of SCIT efficacy in mixed rhinitis,¹⁷ an argument can perhaps be made for a trial of SCIT in select patients with coexisting CRS and allergic rhinitis.

SCIT: Mechanism

The immunologic response to SCIT is characterized by decreased sensitivity of end organs and changes in the humoral and cellular responses to the administered allergens. A number of possible mechanisms for the beneficial effects of immunotherapy have been suggested. Key to this process is the induction of a T-cell-tolerant state.⁶ Allergen-specific peripheral T-cell tolerance mediated by IL-10 and transforming growth factor β causes deviation toward a regulatory T (Treg) cell response, which leads to a normal, healthy immune response to mucosal antigens. In addition to mediating T-cell tolerance, IL-10 regulates specific antibody isotype formation and skews the specific response from an IgE- to an IgG4-dominated phenotype. Treg cells acting through their production of IL-10 suppress both total and allergen-specific IgE and simultaneously increase IgG4 production. Observed immunologic changes (Table 1)^{18–20} in response to SCIT include the modulation of T- and B-cell responses by the generation of allergen-specific Treg cells; increases in allergen-specific IgG4, and IgA; decrease in IgE; and decreased tissue infiltration of mast cells and eosinophils. Additionally, successful SCIT is associated with a change toward a nonallergic Th1 cytokine profile (Th1 skewing), which occurs within the constraints of a high IL-10 milieu, allowing the associated interferon γ responses to ameliorate allergic inflamma-

From the ¹Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island, ²Division of Allergy-Immunology, Northwestern University, Chicago, Illinois, and ³Department of Medicine, Asthma and Allergic Disease Center, Carter Immunology Center, University of Virginia Health System, Charlottesville, Virginia

RA Settupane received a research grant from Genentech (clinical trial). AT Peters is a speaker for Baxter. L. Borish is funded by NIH RO1 AI057483 and UO1 AI100799. Address correspondence and reprint requests to Russell A. Settupane, M.D., Allergy & Asthma Center, 95 Pitman Street, Providence, RI 02906. E-mail address: russell_settupane@brown.edu. Copyright © 2013, OceanSide Publications, Inc., U.S.A.

Table 1 Immunologic changes associated with SCIT

Antibody changes
Increase in allergen-specific IgG (specifically IgG4)
Early increase and late decrease in serum allergen-specific IgE
Decrease in seasonal rise of allergen-specific IgE
Cellular changes
Decreased mediator release from mast cells, basophils, and eosinophils
Reduction of tissue mast cells and eosinophils
Induction of regulatory T cells and suppression of Th2 > Th1 cells
Increased secretion of IL-10 and TGF- β
Decrease in histamine-releasing factors

Source: Adapted from Refs. 15–17.

SCIT = subcutaneous immunotherapy; TGF = transforming growth factor.

tion without producing the associated proinflammatory influences of the interferon.²¹

SCIT: Efficacy and Safety in Allergic Rhinitis

Clinical research has been robust with multiple double-blind, placebo-controlled, randomized clinical trials and meta-analyses indicating SCIT to be effective in a dose-dependent manner for the nasal and ocular symptoms of allergic rhinitis.^{1,22} Additionally, SCIT acts as a long-lasting disease modifier of allergic rhinitis altering the natural history of the disease, having been shown to result in sustained benefit after discontinuation. Double-blind, placebo-controlled trials have shown that 3–4 years of grass pollen AIT remains effective for at least 3 years and up to 12 years after the discontinuation of the injections.^{6,23} In children SCIT has been shown to prevent the development of new sensitizations and possibly to prevent new onset asthma.¹

SCIT-associated anaphylactic fatalities are rare (1 in 2.5 million injections) with ~3.4 fatal reactions annually in the United States.²⁴ Large local reactions at the site of the injection are much more common, occurring in ~9% of injection visits.²⁵ An important area of clinical research is the relationship between large local reactions and systemic reactions. Unfortunately, evidence regarding the risk of systemic anaphylaxis in patients with local reactions is limited to retrospective studies, which are somewhat contradictory^{25,26}; however, it appears that large local reactions do not predict the occurrence of a systemic anaphylactic reaction in the subsequent dose and that dose adjustments based on local reactions do not appear to prevent systemic reactions.

Given the risk of anaphylaxis, SCIT should be administered only in a setting where the prompt recognition and treatment of anaphylaxis (with epinephrine) is available,^{27–30} the preferred location being in the medical facility of the physician who prepared the patient's AIT extract. Patients should remain in the supervised medical facility and be monitored for at least 30 minutes postinjection.¹ Some experts advocate for prescribing automatic injectable epinephrine to all SCIT patients to address the rare occurrences of anaphylaxis beyond the 30-minute wait time.³⁰

Risk factors for severe SCIT reactions include symptomatic asthma, concomitant use of β -adrenergic blockers, and administration of injections during the height of the pollen season.¹ Patients with asthma must be assessed for degree of control before the administration of each SCIT injection.

SCIT: Administration Schedules

SCIT is usually initiated with injections administered one to three times weekly starting at a low dose unlikely to cause anaphylaxis. After 3–6 months the maintenance phase begins, and the injection

schedule interval is slowly increased to a range of every 2–4 weeks. Based on studies that show long-lasting disease modification and sustained benefit after SCIT is discontinued, AIT guidelines recommend 3–5 years duration of treatment. It is the persistence of benefit and apparent alteration of the natural history of allergic rhinitis that underlies SCIT's cost savings in comparison with standard pharmacotherapies.^{31,32} Studies comparing cost-effectiveness between patients treated for 3 years with SCIT versus those treated with pharmacotherapy alone have indicated a potential cost savings as high as 80% with SCIT.³² Despite these benefits, adhering to a 3- to 6-month long weekly build-up schedule can be challenging for patients. This has led to investigations with ultrashort (4 dose) courses³³ and accelerated schedules (referred to as “cluster” or “rush” schedules)¹; however, the advantage of convenience associated with accelerated schedules is partially negated by higher rates of systemic allergic reactions that range from 14.7 to 38% in premedicated subjects (corticosteroids/antihistamines).^{1,34}

SUBLINGUAL IMMUNOTHERAPY

SLIT: Description and Mechanism

SLIT refers to sublingual application of allergen for the purpose of inducing allergen-specific tolerance. This form of AIT has the potential to be more convenient and safer than SCIT. Although considered experimental in the United States, SLIT is widely used in Europe, and variations of SLIT are currently being used by some U.S. practitioners.¹ The precise mechanisms by which SLIT works remain unclear, but similar to SCIT, it likely includes promoting modified Th1 and Treg activity.³⁵

SLIT: Efficacy and Safety

Clinical trials now underway in the United States have demonstrated efficacy in adults and children but are limited to the study of single allergen preparations such as grass or ragweed pollen.^{36,37} A 2010 meta-analysis of SLIT revealed significant symptom improvement with SLIT for both seasonal and perennial allergic rhinitis.³⁸ Similar to SCIT, SLIT appears to result in sustained long-lasting therapeutic benefits. In the patients receiving SLIT for at least 3 years, the clinical benefit persisted for at least 7 years and there were 75% less new sensitizations in SLIT-treated patients compared with controls.³⁹ A 2013 systemic review of 63 studies with 5131 participants concluded that the available data provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis, but high-quality studies are still needed to answer questions regarding optimal dosing strategies.⁴⁰ A 2012 meta-analysis of studies comparing SCIT versus SLIT in patients with seasonal allergic rhinoconjunctivitis to grass pollen provides solid evidence that although SCIT is more effective than SLIT in controlling symptoms and in reducing the use of antiallergic medications, this higher efficacy occurs at the expense of a substantially greater anaphylaxis rate with SCIT.⁴¹ Although SLIT appears to have a more favorable safety profile, local reactions (oral pruritus and edema) are common, occurring in 40% of patients; and anaphylaxis, although rare, has been reported.¹ Several barriers exist for the implementation of SLIT, the foremost being availability. No reagents are currently available in the United States; and only a few single allergen preparations are in development, making this an unrealistic option for polysensitized (i.e. most) allergic rhinitis patients.

MONOCLONAL ANTI-IgE

Monoclonal Anti-IgE: Description

The sole Food and Drug Administration (FDA)-approved anti-IgE therapy in the United States is omalizumab, which is a recombinant humanized monoclonal anti-IgE antibody. Omalizumab is FDA ap-

proved only for adults and adolescents (aged ≥ 12 years) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and whose symptoms are inadequately controlled with inhaled corticosteroids.⁴²

Monoclonal Anti-IgE: Mechanism

By selectively targeting and binding to circulating IgE, omalizumab therapy results in a reduction of IgE binding to receptors on mast cells, basophils, and dendritic cells^{43,44} and a down-regulation of their expression of cell surface IgE receptors. This ultimately leads to a decrease in the release of mediators in response to allergen exposure. The end result is a reduction of both the acute (early phase) allergic response and the subsequent (late-phase response) inflammatory and physiological consequences.⁴⁵

Monoclonal Anti-IgE: Efficacy and Safety

Clinical data for the use of omalizumab in asthma have been robust, preliminary trials performed in patients with upper respiratory diseases have also demonstrated efficacy in patients with seasonal and perennial allergic rhinitis.^{46–49} Omalizumab has been shown to be an effective adjunct to SCIT.⁵⁰ Adding omalizumab to SCIT improves its safety and tolerability during build-up, the likelihood of the patient reaching the maintenance phase, and the therapy's overall effectiveness.⁶ Finally, anti-IgE for CRS with nasal polyps holds promise, but the two trials reported thus far have not demonstrated the same degree of benefit.^{3,51}

Safety concerns with omalizumab include anaphylaxis, which has resulted in the FDA issuing a black box warning. This anaphylaxis can be associated with a protracted course and delayed onset of symptoms even 12–24 hours after an injection.^{52,53} Retrospective evaluation of omalizumab-associated anaphylaxis cases has not identified potential risk factors to identify patients at risk.⁵³ In addition, initial clinical trials suggested a higher rate of malignancy associated with omalizumab; however, a recent pooled analysis of a larger number of patients does not show a causal link between omalizumab and malignancy.⁵⁴ Further investigation is necessary to define efficacy, safety, and cost-effectiveness in upper respiratory disease states.

SUMMARY

IgE hypersensitivity is important to the pathogenesis of allergic diseases and the development and persistence of airway inflammation. Clinical evidence strongly supports the efficacy and safety of SCIT for the treatment of allergic respiratory diseases including allergic rhinitis, allergic conjunctivitis, and allergic asthma, but for CRS evidence is lacking. Although not quite as robust, efficacy and safety data for SLIT in allergic rhinitis and asthma is growing. AIT should be considered in allergic rhinitis patients who experience poor symptom control or adverse effects resulting from medications. SCIT remains the preferred form of AIT in the United States because of robust efficacy data, availability of allergen extracts, and current FDA approval. However, SLIT holds the potential for greater patient safety and convenience. Other immunomodulators such as anti-IgE also hold promise, but require further investigation.

CLINICAL PEARLS

- With regard to respiratory allergy, specific AIT is indicated for the treatment of seasonal and perennial allergic rhinitis, but not for CRS.
- Most systemic reactions to SCIT usually occur within 30 minutes of treatment. Therefore, patients should wait in a medical facility for a full 30 minutes after a SCIT injection.
- Asthma control must be assessed before each SCIT injection in patients who also have asthma. AIT injections are contraindicated in poorly controlled asthma.

- SLIT, although not currently approved for use in the United States, has been shown to be more effective than placebo; and available data suggest that SLIT is safer than SCIT.

REFERENCES

1. Cox L, Nelson H, Lockett R, et al. Allergen immunotherapy: A practice parameter third update. *J Allergy Clin Immunol* 127(suppl): S1–S55, 2011.
2. Wise SK, and Schlosser RJ. Subcutaneous and sublingual immunotherapy for allergic rhinitis: What is the evidence? *Am J Rhinol Allergy* 26:18–22, 2012.
3. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 131:110–116.e1, 2013.
4. Shah R, and Grammer LC. An overview of allergens. *Allergy Asthma Proc* 33(suppl 1):S2–S5, 2012.
5. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122:S1–S84, 2008.
6. Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/ European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013 Mar 13 DOI: 10.1016/j.jaci.2013.01.049. [Epub ahead of print].
7. Larenas Linnemann DE. One hundred years of immunotherapy: review of the first landmark studies. *Allergy Asthma Proc* 33:122–128, 2012.
8. Settipane RA, and Schwindt C. Allergic rhinitis. *Am J Rhinol Allergy* 27:S52–S55, 2013.
9. Carr TF, and Saltoun CA. Skin testing in allergy. *Allergy Asthma Proc* 33(Suppl 1):S6–8, 2012.
10. Makhija M, and O'Gorman MR. Common *in vitro* tests for allergy and immunology. *Allergy Asthma Proc* 33(Suppl 1):S108–S111, 2012.
11. Settipane RA, Borish L, and Peters AT. Determining the role of allergy in sinonasal disease. *Am J Rhinol Allergy* 27:S56–S58, 2013.
12. Settipane RA, Peters AT, and Chandra R. Chronic rhinosinusitis. *Am J Rhinol Allergy* 27:S11–S15, 2013.
13. Settipane RA, Peters AT, and Chiu AG. Nasal polyps. *Am J Rhinol Allergy* 27:S20–S25, 2013.
14. Kennedy JL, and Borish L. Chronic sinusitis pathophysiology: The role of allergy. *Am J Rhinol Allergy* DOI: 10.2500/ajra.2013.27.3906 [Epub ahead of print date April 18, 2013].
15. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl* 23:1–298, 2012.
16. Nathan RA, Santilli J, Rockwell W, and Glassheim J. Effective of immunotherapy for recurring sinusitis associated with allergic rhinitis as assessed by Sinusitis Outcomes Questionnaire. *Ann Allergy Asthma Immunol* 92:668–672, 2004.
17. Smith AM, Rezvani M, and Bernstein JA. Is response to allergen immunotherapy a good phenotypic marker for differentiating between allergic rhinitis and mixed rhinitis? *Allergy Asthma Proc* 32:49–54, 2011.
18. Frew A. Allergen immunotherapy. *J Allergy Clin Immunol* 125:S306–S313, 2010.
19. Grammer LC, and Harris KE. Principles of immunologic management of allergic diseases due to extrinsic antigens. In Patterson's Allergic Diseases, 7th ed. Grammer LC, and Greenberger PA (Eds). Philadelphia, PA: Lippincott, Williams & Wilkins, 187–196, 2009.
20. Georgy MS, and Saltoun CA. Allergen immunotherapy: Definition, indication, and reactions. *Allergy Asthma Proc* 33(suppl 1):S9–S11, 2012.
21. Akdis M, and Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 119:780–791, 2007.
22. Calderon MA, Penagos M, Sheikh A, et al. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy* 41:1263–1272, 2011.
23. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 341:468–475, 1999.
24. Bernstein DI, Wanner M, Borish L, et al. Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 113:1129–1136, 2004.
25. Calabria CW, Stolli A, and Tankersley MS. The REPEAT study: Recognizing and evaluation periodic local reactions in allergen im-

- munotherapy and associated systemic reactions. *Ann Allergy Asthma Immunol* 106:49, 2011.
26. Roy SR, Sigmon JR, Olivier J, et al. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 99:82–86, 2007.
  27. Greenberger PA, and Ditto AM. Anaphylaxis. *Allergy Asthma Proc* 33(suppl 1):S80–S83, 2012.
  28. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. *Am J Rhinol Allergy* 26:469–474, 2012.
  29. Phillips JF, Lockey RF, Fox RW, et al. Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. *Allergy Asthma Proc* 32:288–294, 2011.
  30. Wallace DV. Anaphylaxis in the allergist's office: Preparing your office and staff for medical emergencies. *Allergy Asthma Proc* 34:120–131, 2013.
  31. Hankin CS, Cox L, and Bronstone A. The health economics of allergen immunotherapy. *Immunol Allergy Clin North Am* 31:325–341, 2011.
  32. Hankin CS, Cox L, Bronstone A, et al. AIT: Reduced health care costs in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 131:1084–1091, 2013.
  33. DuBuske LM, Frew AJ, Horak F, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc* 32:239–247, 2011.
  34. Cox L. Accelerated immunotherapy schedules: Review of efficacy and safety. *Ann Allergy Asthma Immunol* 97:126–137, 2006.
  35. Guida G, Boita M, Scirelli T, et al. Innate and lymphocytic response of birch-allergic patients before and after sublingual immunotherapy. *Allergy Asthma Proc* 33:411–415, 2012.
  36. Nayak AS, Atiee GJ, Dige E, et al. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. *Allergy Asthma Proc* 33:404–410, 2012.
  37. Blaiss M, Maloney J, Nolte H, et al. Efficacy and safety of timothy grass AIT tablets in North American children and adolescents. *J Allergy Clin Immunol* 127:64–71, 71.e1–4, 2011.
  38. Radulovic S, Wilson D, Calderon M, and Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 66:740–752, 2011.
  39. Marogna M, Spadolini I, Massolo A, et al. Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study. *J Allergy Clin Immunol* 126:969–975, 2010.
  40. Lin SY, Ereksomima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: A systematic review. *JAMA* 309:1278–1288, 2013.
  41. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A meta-analysis-based comparison. *J Allergy Clin Immunol* 130:1097–1107.e2, 2012.
  42. Genentech, Inc. XOLAIR prescribing information. South San Francisco, CA; 2007. Last revision July, 2010.
  43. Soresi S, and Togias A. Mechanisms of action of anti-immunoglobulin E therapy. *Allergy Asthma Proc* 27:S15–S23, 2006.
  44. Prussin C, Griffith D, Boesel K, et al. Omalizumab treatment down-regulates dendritic cell FcεpsilonRI expression. *J Allergy Clin Immunol* 112:1147–1154, 2003.
  45. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 155:1828–1834, 1997.
  46. Adelloth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 106:253–259, 2000.
  47. Nayak A, Casale T, Miller SD, et al. Tolerability of retreatment with omalizumab, a recombinant humanized monoclonal anti-IgE antibody, during a second ragweed pollen season in patients with seasonal allergic rhinitis. *Allergy Asthma Proc* 24:323–329, 2003.
  48. Chervinsky P, Casale T, Townley R, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 91:160–167, 2003.
  49. Berger WE. Treatment of allergic rhinitis and other immunoglobulin E-mediated diseases with anti-immunoglobulin E antibody. *Allergy Asthma Proc* 27:S29–S32, 2006.
  50. Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 109:274–280, 2002.
  51. Pinto JM, Mehta N, DiTineo M, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 48:318–324, 2010.
  52. Cox L, Lieberman P, Wallace D, et al. American Academy of Allergy Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol* 128:210–212, 2011.
  53. Limb SL, Starke PR, Lee CE and Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 120:1378–1381, 2007.
  54. Busse W, Buhl R, Vidaurre CF, et al. Omalizumab and the risk of malignancy: Results from a pooled analysis. *J Allergy Clin Immunol* 128:983–989, 2012. □