Mechanism of action of allergen immunotherapy

Ethem Şahin, M.D.,[1] Sameer Ali Bafaqeeh, M.D.,[2] Selis Gülseven Güven, M.D.,[3] Erdem Atalay Çetinkaya, M.D.,[4] Nuray Bayar Muluk, M.D.,[5] Zerrin Ozergin Coşkun, M.D.,[6] Andrey Lopatin, M.D.,[7] Murat Kar, M.D.,[8] Mehmet Ozgur Pinarbasli, M.D.,[9] and Cemal Cingi, M.D.[9]

ABSTRACT

Background: *Allergen immunotherapy (AIT) leads to the production of antiallergen immunoglobulin (IgG) or "blocking antibody" in the serum and an increase in antiallergen IgG and IgA in nasal secretions. There is also a decrease in the usual rise in antiallergen IgE that occurs after the pollen season.*

Methods: *In this paper, mechanisms of action of allergen immunotherapy is reviewed.*

Results: *Regulatory T (Treg) cells and their cytokines, primarily interleukin (IL) 10 and transforming growth factor beta, suppress T-helper type 2 immune responses and control allergic diseases in many ways. AIT induces a shift in the proportion of IL-4–secreting T-helper type 2 cells in favor of IL-10-secreting inducible Treg cells specific for the same allergenic epitope that increases in number and function. Different types of inducible Treg control several facets of allergic inflammation. There are two main types of immunotherapy: subcutaneous immunotherapy and sublingual immunotherapy. Subcutaneous immunotherapy is efficacious and is indicated for the reduction of seasonal symptoms. Sublingual immunotherapy involves the regular self-administration and retention of allergen extract under the tongue for 1–2 minutes before the extract is swallowed. The allergens cross the mucosa in 15–30 minutes and are then captured by tolerogenic dendritic cells and processed as small peptides. Next,* via *the lymphatic system, a systemic immune response is created to produce an early decrease in mast cell and basophil degranulation.*

Conclusion: *AIT is indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of allergic rhinitis. AIT can be administered to those >5 years of age and has been shown to be safe in children as young as 3 years of age. In this article, AIT and other types of immunotherapies were discussed as well as the indications for immunotherapy.*

(Am J Rhinol Allergy 30, S1–S3, 2016; doi: 10.2500/ajra.2016.30.4367)

IMMUNOLOGIC RESPONSES

Allergen immunotherapy (AIT) decreases the sensitivity to allergens and often leads to lasting relief of allergy symptoms even after treatment is stopped.[1] AIT triggers multiple, sequentially activated mechanisms that work in concert, which leads to clinical events that elicit rapid desensitization to allergen, allergen-specific immune tolerance, and suppression of the allergic inflammation.[2,3] AIT leads to the production of antiallergen immunoglobulin G (IgG) or "blocking antibody" in the serum and an increase in antiallergen IgG and IgA in nasal secretions. There is also a decrease in the usual rise of antiallergen IgE that occurs after the pollen season.[4,5] The antiallergen IgE decreases with long-term immunotherapy, although it rarely disappears. Thus, there is no rationale for annual allergy skin testing as a parameter for monitoring AIT. Patients should experience definite reductions in symptoms after a year of injections.

AIT results in the reduced mononuclear cell production of histamine-releasing factors.[4] Patients who have been treated with immunotherapy show suppression of immediate and late-phase nasal reactions after allergen challenge, and it has been shown that patients have diminished eosinophil counts in nasal secretions after nasal challenge.[5–7] AIT has been associated with decreased allergen-specific $CD4^+$ cell proliferation and alterations of T-cell cytokines at local allergen challenge sites, with decreased recruitment of T cells to allergen-challenged sites. In the skin, the messenger RNA expression of T-helper (Th) 1 $CD4^+$ cell-type cytokines (interferon γ, IL-2) is upregulated after immunotherapy, but there is no effect on $CD4^+$ cell Th2 cytokine (IL-4, IL-5) expression upon allergen exposure after immunotherapy.[8,9]

Regulatory T (Treg) cells and cytokines of them (IL-10 and transforming growth factor β) suppress Th2-type immune responses and control allergic diseases. In B cells, they induce IgG4 and IgA, and suppress IgE. In Th2 cells, they suppress proliferation of the tissues. In mast cells, basophils, and eosinophils, there are suppressive effects. By direct and indirect suppression, epithelial cell activation and proinflammatory properties occur. In addition, B regulatory 1 cells, which produce IL-10, suppress effector T cells and B regulatory 1 cells have a role to produce IgG4 synthesis.[10] IL-10 can decrease B-cell antigen-specific IgE production and increase IgG4 levels. Proinflammatory cytokine release from mast cells, eosinophils, and T cells decreases. Consequently, lymphoproliferative responses to allergens are reduced after immunotherapy.[11] Allergen-specific immune deviation from a Th2 to a Th1 occurs.[12–14]

AIT induces a shift in the proportion of IL-4-secreting Th2 cells in favor of IL-10–secreting inducible Treg cells specific for the same allergenic epitope that increases in number and function. Different types of inducible Treg control several facets of allergic inflammation. They are composed of positive Forkhead box protein 3 adaptive Treg cells and negative FOXP3, IL-10-producing type 1 regulatory T cells. Breg cells regulate IgG4 versus IgE and induce allergen-specific antibodies toward the nonanaphylactic and noninflammatory types.[15,16]

IMMUNOTHERAPY TYPES

Sublingual immunotherapy (SLIT) has a better safety profile, with less systemic reactions and, to date, no reported fatal reactions.[17] Subcutaneous immunotherapy (SCIT), the primary method of AIT in the United States, has a slightly better efficacy profile and readily allows for treatment of patients with polyallergy.[17]

From the [1]Ear, Nose and Throat (ENT) Clinics, Bayındır Içerenköy Hospital, Istanbul, Turkey, [2]ENT Department, King Saud University, Riyadh-Saudi, Arabia, [3]Tekirdag Corlu State Hospital, Tekirdag, Turkey, [4]ENT Department, Antalya Ataturk State Hospital, Antalya, Turkey, [5]ENT Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey, [6]Department of Otorhinolaryngology, Rize Research and Training Hospital, Recep Tayyip Erdoğan University, Rize, Turkey, [7]ENT Department, State Policlinic No. 1, Business Administration of the President of Russian Federation, Moscow, Russia, [8]ENT Clinic, Specialist Kumluca State Hospital, Antalya, Turkey, and [9]ENT Department, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Preparation of this manuscript, including design and planning, was supported by Continuous Education and Scientific Research Association. The authors extend their appreciation to the International Scientific Partnership Program (ISPP) at King Saud University for funding this research work through ISPP# 0041

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Nuray Bayar Muluk, M.D., Birlik Mahallesi, Zirvekent 2, Etap Sitesi, C-3 blok, No. 62/43, 06610 Çankaya, Ankara, Turkey

E-mail address: nuray.bayar@yahoo.com

SCIT

SCIT is associated with transient increases in allergen-specific IgE levels and IgG (particularly IgG4[18]) and IgA.[19] Serum antibody concentration is related to the dose of allergen that is administered.[19] Serum obtained after SCIT inhibits allergen-IgE binding to B cells,[20] mediated by IgG4. "Blocking" antibodies inhibits IgE-facilitated antigen presentation. SCIT decreases the numbers of effector cells at mucosal sites, both during seasonal allergen exposure[21] and after allergen challenge,[22] and reduces effector cell reactivity *in vitro*.[23] In allergic diseases, there is a relative imbalance between Treg and Th2 cells.[24] The former cell type can be divided into "naturally occurring" thymus-derived $CD4^+$ $CD25^+$ cells, which are positive for the transcription factor Forkhead box protein 3, and "adaptive" regulatory cells, either "Tr1 IL-10-secreting cells" or Th3-transforming growth factor–secreting cells.[25] Increased proportions of allergen nonspecific Treg cells have been described with SCIT, which supported the role of Treg cells and their secreted cytokines in the mechanism of successful therapy.[26,27]

A Cochrane systematic review showed that SCIT for seasonal allergic rhinitis (AR)[28] was efficacious and causes reductions in seasonal symptoms. SCIT and SLIT improve asthma symptoms in adults and children with atopic asthma who are clinically sensitized to seasonal and perennial allergens.[29–31] Meta-analyses of placebo-controlled trials in patients with asthma indicated small improvements in symptoms and lung function by an active therapy.[32–34] By year 3 of house-dust mite SCIT administration in adults with atopic asthma, the adults were slightly sensitized to mites and bronchodilator usage reduced. Whereas inhaled corticosteroid dosages and bronchial responsiveness to methacholine did not change.[35]

SLIT

SLIT products should be placed under the tongue, which allows the allergen to be in contact with the oral mucosa for at least 2 minutes through the dendritic cells. The allergens cross the mucosa in 15–30 minutes. They are then captured by tolerogenic dendritic cells and processed as small peptides. Next, *via* the lymphatic system, a systemic immune response is created to produce an early decrease in mast cell and basophil degranulation. Allergen-specific Treg cell, Th1 cell, and Th2 cell suppression occurs later. Specific IgE levels increase in an early step and, later, they decrease. In the early period, the IgG4 level also increases, which is dose-dependent. A significant decrease in the allergen-specific IgE:IgG4 ratio occurs after several months.[36] Recent meta-analyses showed that SLIT was efficient in children.[37,38] Serrano *et al*.[39] reported that AIT with 300IR 5-grass pollen sublingual tablets was consistently associated with AR symptom relief in adults and children. SLIT is an effective treatment modality for seasonal AR and improves quality of life and can potentially prevent asthma.[40]

INDICATIONS

AIT is indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of AR. AIT can be administered to children >5 years of age and has been shown to be safe in children as young as 3 years of age.[2,41–43] The recommended duration of AIT for AR is 5 years for both the subcutaneous and sublingual routes.[1] Significant improvement in nasal and ocular symptom scores reduced the need for symptomatic medication and improved quality of life both during and after discontinuation of AIT have been consistently demonstrated in double-blind, placebo-controlled studies.[44–46] The major advantage of AIT in the treatment of AR is the prevention of asthma and reduction in new sensitizations.[2,44–46]

When patients are selected for immunotherapy, the underlying allergic trigger should be identified by history and skin and/or blood test results for allergen-specific IgE. IgE sensitization to additional inhalant allergens is not a contraindication. Single AIT is less likely to be effective if exposure to other allergens contributes to the ongoing symptoms. Immunotherapy improves symptoms of AR and decreases use of medications to treat AR.[47,48] Specific immunotherapy should be prescribed by specialists. SCIT should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured.[49] SLIT can be used at home, and the patients can take it by themselves.[48,50,51]

To be eligible for SLIT, important items are mentioned.[49] There is a clinical history of allergy and allergen-specific IgE positive test results. For SLIT, age does not seem to be a limitation. Ideal candidates for SLIT are patients who are monosensitized. Even for patients who are polysensitized, single-allergen SLIT has been effective. Investigations are ongoing for the use of SLIT in latex allergy, atopic dermatitis, food allergies, and *Hymenoptera* venom allergy. In non-IgE–mediated hypersensitivity (for instance, nickel sensitivity), SLIT is not indicated. In the appropriate case, SLIT should be an initial treatment for respiratory allergies. In patients with uncontrolled optimal pharmacotherapy that induces undesirable adverse effects and in those who would benefit from immunotherapy and decline SCIT, SLIT should be considered.[41] SCIT is indicated in AR and asthma.[52] SCIT is also indicated in patients with a history of a systemic reaction to a *Hymenoptera* sting (especially if such a reaction is associated with respiratory symptoms, cardiovascular symptoms, or both), and there is demonstrable evidence of clinically relevant specific IgE antibodies.[1]

CONTRAINDICATIONS

Partly controlled or uncontrolled asthma with forced expiratory volume in 1 second of <70% of normal despite adequate treatment is a contraindication for AIT. The other contraindications for immunotherapy are severe autoimmune diseases and immunodeficiency states.[53]

CONCLUSION

The main mechanism of AIT is production of IgG in the serum and of IgG and IgA in nasal secretions. AIT also causes a decrease in specific IgE. Two main types of AIT are SCIT and SLIT. AIT can be administered to those patients who are >5 years of age and has been shown to be safe in children as young as 3 years of age.[2,41–43] Due to the risk of anaphylaxis, SCIT should only be administered in a medical setting where anaphylaxis can be treated.

REFERENCES

1. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: A practice parameter third update. J Allergy Clin Immunol 127(suppl.): S1–S55, 2011.
2. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 136:556–568, 2015.
3. 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 131:1288–1296.e3, 2013.
4. Kuna P, Alam R, Kuzminska B, and Rozniecki J. The effect of preseasonal immunotherapy on the production of histamine-releasing factor (HRF) by mononuclear cells from patients with seasonal asthma: Results of a double-blind, placebo-controlled, randomized study. J Allergy Clin Immunol 83:816–824, 1989.
5. Iliopoulos O, Proud D, Adkinson NF Jr, et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: Changes in inflammatory mediators and cells. J Allergy Clin Immunol 87:855–866, 1991.
6. Wilson DR, Irani AM, Walker SM, et al. Grass pollen immunotherapy inhibits seasonal increases in basophils and eosinophils in the nasal epithelium. Clin Exp Allergy 31:1705–1713, 2001.
7. Rak S, Björnson A, Håkanson L, et al. The effect of immunotherapy on eosinophil accumulation and production of eosinophil chemotactic activity in the lung of subjects with asthma during natural pollen exposure. J Allergy Clin Immunol 88:878–888, 1991.
8. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. J Clin Invest 92:644–651, 1993.

9. Maggi E. T cell responses induced by allergen-specific immunotherapy. Clin Exp Immunol 161:10–18, 2010.
10. van de Veen W, and Akdis M. Mechanisms of immune regulation in allergy. In Global Atlas of Allergy. Part 23. Akdis CA, and Agache I (Eds), Zurich, Switzerland. European Academy of Allergy and Clinical Immunology, 90–91, 2014. Available online at http://www.eaaci.org/GlobalAtlas/GlobalAtlasAllergy.pdf; accessed August 1, 2016.
11. Evans R, Pence H, Kaplan H, and Rocklin RE. The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest 57:1378–1385, 1976.
12. Till SJ, and Durham SR. Immunological responses to allergen immunotherapy. Clin Allergy Immunol 18:85–104, 2004.
13. Till SJ, Francis JN, Nouri-Aria K, and Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 113:1025–1034; quiz 1035, 2004.
14. Durham SR, Ying S, Varney VA, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol 97:1356–1365, 1996.
15. Akdis M, and Akdis CA. Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 133:621–631, 2014.
16. Jutel M, and Akdis CA. Novel immunotherapy vaccine development. Curr Opin Allergy Clin Immunol 14:557–563, 2014.
17. Tabatabaian F, and Casale TB. Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT) [review]. Allergy Asthma Proc 36:100–104, 2015. Erratum in: Allergy Asthma Proc 36:217, 2015.
18. Nouri-Aria KT, Wachholz PA, Francis JN, et al. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol 172:3252–3259, 2004.
19. Pilette C, Nouri-Aria KT, Jacobson MR, et al. Grass pollen immunotherapy induces an allergen-specific IgA2 response associated with mucosal TGF-beta expression. J Immunol 178:4658–4666, 2007.
20. Shamji MH, Wilcock LK, Wachholz PA, et al. The IgE-facilitated allergen binding (FAB) assay: Validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. J Immunol Methods 317:71–79, 2006.
21. Wilson DR, Irani AM, Walker SM, et al. Grass pollen immunotherapy inhibits seasonal increases in basophils and eosinophils in the nasal epithelium. Clin Exp Allergy 31:1705–1713, 2001.
22. Furin MJ, Norman PS, Creticos PS, et al. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 88:27–32, 1991.
23. Mothes N, Heinzkill M, Drachenberg KJ, et al. Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: Reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies. Clin Exp Allergy 33:1198–1208, 2003.
24. Ling EM, Smith T, Nguyen XD, et al. Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. Lancet 363:608–615, 2004.
25. Robinson DS, Larche M, and Durham SR. Tregs and allergic disease. J Clin Invest 114:1389–1397, 2004.
26. Francis JN, Till SJ, and Durham SR. Induction of IL-10+ CD4+CD25+T cells by grass pollen immunotherapy. J Allergy Clin Immunol 111:1255–1261, 2003.
27. James LK, and Durham SR. Update on mechanisms of allergen injection immunotherapy. Clin Exp Allergy 38:1074–1088, 2008.
28. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev (1):CD001936, 2007.
29. Bousquet J, Hejjaoui A, and Michel FB. Specific immunotherapy in asthma. J Allergy Clin Immunol 86:292–305, 1990.
30. Cantani A, Arcese G, Lucenti P, et al. A three-year prospective study of specific immunotherapy to inhalant allergens: Evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 7:90–97, 1997.
31. Peroni DG, Piacentini GL, Martinati LC, et al. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. Allergy 50:925–930, 1995.
32. Olaguibel JM, and Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol 15:9–16, 2005.
33. Calamita Z, Saconato H, Pela AB, and Atallah AN. Efficacy of sublingual immunotherapy in asthma: Systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 61:1162–1172, 2006.
34. Abramson M, Puy R, and Weiner J. Immunotherapy in asthma: An updated systematic review. Allergy 54:1022–1041, 1999.
35. Maestrelli P, Zanolla L, Pozzan M, and Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 113:643–649, 2004.
36. Calderon MA, Pfaar O, and Demoly P. Sublingual immunotherapy for allergic rhinitis. In Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis. Akdis CA, Hellings P, and Agache I (Eds), Zurich, Switzerland. European Academy of Allergy and Clinical Immunology, 210–212, 2014.
37. Calderon MA, Birk AO, Andersen JS, and Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapyincreases clinical efficacy. Allergy 62:958–961, 2007.
38. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: A meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 97:141–148, 2006.
39. Serrano E, Wahn HU, Didier A, and Bachert C. 300IR 5-Grass pollen sublingual tablet offers relief from nasal symptoms in patients with allergic rhinitis [review]. Am J Rhinol Allergy 28:471–476, 2014.
40. Lee S, Nolte H, and Benninger MS. Clinical considerations in the use of sublingual immunotherapy for allergic rhinitis [review]. Am J Rhinol Allergy 29:106–14, 2015.
41. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 64(suppl. 91):1–59, 2009.
42. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 7:6, 2014.
43. Wilson DR, Lima MT, and Durham SR. Sublingual immunotherapy for allergic rhinitis: Systematic review and meta-analysis. Allergy 60:4–12, 2005.
44. Jacobsen L, Niggemann B, Dreborg S, et al. The PAT Investigator Group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 62:943–948, 2007.
45. Des Roches A, Paradis L, Menardo JL, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 99:450–453, 1997.
46. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 31:1295–1302, 2001.
47. Bousquet J, Lockey R, and Malling HJ. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 102:558–562, 1998.
48. Kavut AB, and Kalpaklıoğlu F. Diagnostic tools for allergic rhinitis and asthma. J Med Updates 2:22–30, 2012.
49. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 63(suppl. 86):8–160, 2008.
50. Malling H, and Weeke B. Immunotherapy. Position Paper of the European Academy of Allergy and Clinical Immunology. Allergy 48(suppl. 14):9–35, 1993.
51. Global strategy for asthma management and prevention. GINA. Update from NHLBI/WHO Workshop Report 1995, Revised 2006. Available online at www.ginasthma.com; accessed August 1, 2016.
52. Cox L, Calderón M, and Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: Examining efficacy, safety and cost-effectiveness of current and novel formulations. Immunotherapy 4:601–616, 2012.
53. Brehler R, Klimek L, Kopp MV, and Christian Virchow J. Specific immunotherapy—Indications and mode of action. Dtsch Arztebl Int 110:148–158, 2013. □