Symposium 2: Allergen-specific immunotherapy in AR

New Applications of Immunotherapy

Gachon University Gil Medical Center

Sang Min Lee

Allergen Immunotherapy and its Limitations

Leonard Noon and John Freeman first introduced allergen immunotherapy (AIT) as a causative treatment for allergic rhinitis in 1911. Subsequently, the therapeutic effects of AIT for various allergens have been validated for more than a century in the form of subcutaneous immunotherapy and, within the last several decades, sublingual immunotherapy. However, in real practice, less than 5% of allergy patients undergo AIT because of its limited efficacy, which necessitates a long duration of treatment, and the risk of hypersensitivity reactions.

Strategies to minimize allergenicity and maximize immunogenicity

Hypersensitivity reactions occur when allergens administered during AIT bind to their specific IgE antibodies on the surface of mast cells that trigger the degranulation of mast cells through Fc-epsilon receptors. This hypersensitivity-provoking characteristic of an allergen is called “allergenicity”. Meanwhile, some allergen peptides are presented by antigen-presenting cells through a major histocompatibility complex, recognized by T cells through T cell receptors and, consequently, modulate T cell immune responses deviating from Th2 immunity, which in allergy patients predominates over Th1, Treg, or other types of T cell immunity. This immune-modulating property of an allergen is called “immunogenicity”. To date, various strategies to minimize allergenicity and maximize immunogenicity, with the aim of overcoming the limitations of AIT, have been evaluated (Table 1).[1-34] However, most of those efforts have failed to overcome the limitations of AIT, decreasing neither the dose nor duration of therapy, or reducing the risk of hypersensitivity reactions.

Table 1. Strategies to minimize the allergenicity and maximize the immunogenicity of AIT[1-3]

Denaturation of natural allergens (allergoids)
Treatment of allergens with formaldehyde or glutaraldehyde[4,5]
Adsorption or encapsulation of allergens for slow release
Adsorption of allergens to aluminum hydroxide or tyrosine[4,5]
Encapsulation of allergens with liposome or non-biodegradable nanostructures[6,7]
Recombinant or synthetic allergens
Unmodified major allergens[8]
Fragments of major allergens[9]
Hypoallergenic hybrid molecules[10,11]
Fusions of major and chimeric allergens[12]
Polymers of major allergens[9]
T- or Bepitopes[13-15]
Fusion of allergens with immune-response modifiers
CpG oligodeoxynucleotides (TLR9 agonists)[16]
Human Fcɣ[17]
Translocation peptide[18]
Virus-like particles (VLPs)[19]
PreS from hepatitis B virus[15,35]
Carbohydrate particles20 Endoplasmic reticulum-derived type-1 protein body from rice endosperm cells[21]
Co-administration of allergens with immune-response modifiers
Monophosphoryl lipid A (MPLA)[22]
Anti-IgE monoclonal antibody (Omalizumab)[23,24]
Alternative routes other than conventional subcutaneous or sublingual pathways
Epicutaneous (or transcutaneous)[36,37]
Intralymphatic[25-34]

Intralymphatic immunotherapy

A decade ago, Kűndig and colleagues introduced intralymphatic immunotherapy (ILIT) in patients with pollen-induced allergic rhinitis, the therapeutic effect of which occurred more rapidly than SCIT and lasted for 3 years (Table 2).[25,34] In a randomized double-blind placebo-controlled trial, the same authors suggested that ILIT was effective against cat allergy.[26] Subsequently, Hylander and Patterson demonstrated the therapeutic efficacy of ILIT in patients with pollen-induced allergic rhinitis in randomized double-blind placebo controlled trials.[27-29] Nasal inflammation was reduced and the number of activated CD4+ T cells and the affinity of allergen-specific IgG4 were increased after ILIT. Regarding the mechanism underlying ILIT, Schmid and colleagues in a pilot study found that the numbers of allergen-specific plasmablasts expressing Ig isotypes other than IgE were increased after ILIT, although the allergic symptoms of the seven subjects with grass pollen-induced allergic rhinitis only tended to be alleviated.[31] Although the allergic symptoms of the subjects of the above-mentioned studies were alleviated or tended to be alleviated and only mild hypersensitivity reactions were reported, Witten and colleagues questioned the therapeutic efficacy

Table 2. Clinical trials of intralymphatic immunotherapy[34]

Author	Study Design	Allergen	Allergic Symptoms	Nasal Reactivity	Skin Reactivity	Serum Allergen-Specific IgE	Serum Allergen-Specific IgG	Adverse Reactions
Kündig *et al.*[25]	ILIT (nvs. SCIT (n(open, randomized)	Grass	Improved	Decreased	Decreased	Decreased		Mild local or systemic
Kündig *et al.*[26]	Active (nvs. placebo (n(double	Cat	Prone to be improved	Decreased	Decreased	Not changed	Increased, then decreased	Mild local or systemic
Hylander *et al.*[27]	Active (nvs. placebo (n(double-blind)	Birch, grass	Improved	Decreased		Increased		Mild local or systemic
Hylander *et al.*[28]	Active (nvs. placebo (n(double	Birch, grass	Improved	Decreased		Not changed	Increased, then decreased (but without significant change)	Mild local or systemic
Patterson *et al.*[29]	Active (nvs. placebo (n(double	Grass	Improved					Mild local or systemic
Shmid *et al.*[31]	Active (n(open pilot study)	Grass	Prone to be improved	Decreased	Decreased			Mild local or systemic
Witten *et al.*[30]	ILIT ×6 (nvs. ILIT ×3 (nvs. placebo (n(double	Grass	Not improved		Decreased	Increased	Increased	Frequent local swellings at the injection sites
Lee *et al.*[32,33]	Active (n(open pilot study)	Df, Dp, Cat, Dog	Improved	Decreased	Increased	Increased, then decreased	Increased, then decreased	Moderate-to-severe local and systemic

of ILIT in a randomized double-blind placebo-controlled trial involving patients with pollen-induced allergic rhinitis.[30] In that trial, the level of IL-4, IL 10, and IFN-γ production by allergen-stimulated peripheral blood T cells, and the numbers of regulatory T cells in the treatment group, did not differ from those in the placebo group, and local swelling at the injection site frequently occurred after ILIT. In terms of adverse effects, Lee and colleagues reported that ILIT can provoke moderate-to-severe hypersensitivity reactions, including anaphylaxis, but that ILIT alleviated allergic symptoms in daily life, particularly during exposure to causal allergens.[32,33]

Summary and conclusion

In practice, less than 5% of allergy patients undergo AIT because of its limited efficacy, which necessitates a long duration of treatment, and the risk of hypersensitivity reactions. To overcome the limitations of AIT, various strategies to minimize the allergenicity and maximize the immunogenicity of allergens have been evaluated. In the last 10 years, one such strategy, ILIT, has been assessed in eight clinical trials; of these, six found ILIT to be highly efficacious and without serious adverse reactions, and two did not. The therapeutic efficacy, adverse effects, and mechanism(s) of ILIT and other AIT strategies should continue to be investigated.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2015R1D1A1A02061943).

References

1. Jutel M, Akdis CA. Novel immunotherapy vaccine development. Curr Opin Allergy Clin Immunol 2014;14: 557-63.
2. Akdis M. New treatments for allergen immunotherapy. World Allergy Organ J 2014;7:23.
3. Nelson HS. Chapter 87. Injection Immunotherapy for Inhalant Allergens. Philadelphia: Elsevier; 2014.
4. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A, Study G. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy 2005;60:801-7.
5. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. Allergy Asthma Proc 2011;32:466.
6. Basomba A, Tabar AI, de Rojas DH, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. J Allergy Clin Immunol 2002;109:943-8.
7. Pohlit H, Bellinghausen I, Frey H, Saloga J. Recent advances in the use of nanoparticles for allergen-specific immunotherapy. Allergy 2017;72:1461-74.
8. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005;116:608-13.
9. Valenta R, Campana R, Focke-Tejkl M, Niederberger V. Vaccine development for allergen-specific immuno-therapy based on recombinant allergens and synthetic allergen peptides: Lessons from the past and novel mechanisms of action for the future. J Allergy Clin Immunol 2016;137:351-7.
10. Pichler U, Hauser M, Hofer H, Himly M, Hoflehner E, Steiner M, et al. Allergen hybrids - next generation vaccines for Fagales pollen immunotherapy. Clin Exp Allergy 2014;44:438-49.
11. Asturias JA, Ibarrola I, Arilla MC, Vidal C, Ferrer A, Gamboa PM, et al. Engineering of major house dust mite allergens Der p 1 and Der p 2 for allergen-specific immunotherapy. Clin Exp Allergy 2009;39:1088-98.
12. Kussebi F, Karamloo F, Rhyner C, Schmid-Grendelmeier P, Salagianni M, Mannhart C, et al. A major allergen gene-fusion protein for potential usage in allergen-specific immunotherapy. J Allergy Clin Immunol 2005;115:

323-9.
13. Norman PS. Clinical experience with treatment of allergies with T cell epitope containing peptides. Adv Exp Med Biol 1996;409:457-61.
14. Muller U, Akdis CA, Fricker M, Akdis M, Blesken T, Bettens F, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. J Allergy Clin Immunol 1998;101:747-54.
15. Niederberger V, Neubauer A, Gevaert P, Zidarn M, Worm M, Aberer W, et al. Safety and efficacy of immunotherapy with the recombinant B-cell epitope-based grass pollen vaccine BM32. J Allergy Clin Immunol 2018.
16. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med 2006; 355:1445-55.
17. Terada T, Zhang K, Belperio J, Londhe V, Saxon A. A chimeric human-cat Fcgamma-Fel d1 fusion protein inhibits systemic, pulmonary, and cutaneous allergic reactivity to intratracheal challenge in mice sensitized to Fel d1, the major cat allergen. Clin Immunol 2006;120:45-56.
18. Crameri R, Kundig TM, Akdis CA. Modular antigen-translocation as a novel vaccine strategy for allergen-specific immunotherapy. Curr Opin Allergy Clin Immunol 2009;9:568-73.
19. Kundig TM, Senti G, Schnetzler G, Wolf C, Prinz Vavricka BM, Fulurija A, et al. Der p 1 peptide on virus-like particles is safe and highly immunogenic in healthy adults. J Allergy Clin Immunol 2006;117:1470-6.
20. Thunberg S, Neimert-Andersson T, Cheng Q, Wermeling F, Bergstrom U, Swedin L, et al. Prolonged antigen-exposure with carbohydrate particle based vaccination prevents allergic immune responses in sensitized mice. Allergy 2009;64:919-26.
21. Wakasa Y, Takagi H, Watanabe N, Kitamura N, Fujiwara Y, Ogo Y, et al. Concentrated protein body product derived from rice endosperm as an oral tolerogen for allergen-specific immunotherapy--a new mucosal vaccine formulation against Japanese cedar pollen allergy. PLoS One 2015;10:e0120209.
22. Rosewich M, Schulze J, Eickmeier O, Telles T, Rose MA, Schubert R, et al. Tolerance induction after specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A in children. Clin Exp Immunol 2010;160:403-10.
23. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117:134-40.
24. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol 2010; 125:383-9.
25. Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 2008;105:17908-12.
26. Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol 2012;129:1290-6.
27. Hylander T, Latif L, Petersson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. J Allergy Clin Immunol 2013; 131:412-20.
28. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georen S, Winqvist O, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Respir Res 2016;17: 10.
29. Patterson AM, Bonny AE, Shiels WE, 2nd, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. Ann Allergy Asthma Immunol 2016;116:

168-70.
30. Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK. Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy? J Allergy Clin Immunol 2013;132:1248-52 e5.
31. Schmid JM, Nezam H, Madsen HH, Schmitz A, Hoffmann HJ. Intralymphatic immunotherapy induces allergen specific plasmablasts and increases tolerance to skin prick testing in a pilot study. Clin Transl Allergy 2016;6: 19.
32. Lee SP, Choi SJ, Joe E, Lee SM, Lee MW, Shim JW, et al. A Pilot Study of Intralymphatic Immunotherapy for House Dust Mite, Cat, and Dog Allergies. Allergy Asthma Immunol Res 2017;9:272-7.
33. Lee SP, Jung JH, Lee SM, Joe E, Kang IG, Kim ST, et al. Intralymphatic Immunotherapy Alleviates Allergic Symptoms During Allergen Exposure in Daily Life. Allergy Asthma Immunol Res 2018;10:180-1.
34. Kim ST, Park SH, Lee SM, Lee SP. Allergen-specific intralymphatic immunotherapy in human and animal studies. Asia Pac Allergy 2017;7:131-7.
35. Niespodziana K, Focke-Tejkl M, Linhart B, Civaj V, Blatt K, Valent P, et al. A hypoallergenic cat vaccine based on Fel d 1-derived peptides fused to hepatitis B PreS. J Allergy Clin Immunol 2011;127:1562-70 e6.
36. Senti G, Freiburghaus AU, Kundig TM. Epicutaneous/transcutaneous allergen-specific immunotherapy: rationale and clinical trials. Curr Opin Allergy Clin Immunol 2010;10:582-6.
37. Agostinis F, Forti S, Di Berardino F. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. Allergy 2010;65:410-1.