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One hundred years of allergen immunotherapy: Time to ring the changes

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Article Outline

One hundred years have passed since Noon[1] made his original observation that prophylactic inoculation with grass pollen extract in patients with hay fever resulted in effective desensitization, as shown by a decrease in immediate conjunctival sensitivity to grass pollen. Interestingly, in this centenary year of immunotherapy, despite many advances, we continue to use whole allergen extracts administered through the subcutaneous route as usual practice.

The observation by Prausnitz and Küstner[2] that a serum factor ("reagin") could transfer immediate allergen sensitivity as shown by means of skin testing was followed by the observation by Cooke et al[3] that serum obtained after pollen immunotherapy could confer "immunity as well as hypersensitivity" (Table I). These seminal observations long preceded the discovery of IgE antibody as "reagin" by Ishizaka et al[4] and Johansson and Bennich[5] and the concept of allergen-specific IgG "blocking antibodies"[6] with functional activity[7] that remains popular today. The suppressive influence of ragweed injection immunotherapy on allergic inflammation in target organs was shown by Creticos et al.[8] Passalacqua et al[9] similarly demonstrated decreased local eosinophilia and associated adhesion molecule expression during mite sublingual immunotherapy. Warner et al[10] and Rak et al[11] observed decreases in allergen-induced late asthmatic responses and associated bronchial inflammation, respectively, in children and adults.

Table I. One hundred years of allergen immunotherapy

Author(s)	Milestone	Year
Noon[1]	First grass pollen subcutaneous immunotherapy trial	1911
Prausnitz and Küstner[2]	Passive serum transfer of immediate skin prick test reactivity "reagin"	1921
Freeman[21]	First grass pollen rush immunotherapy trial	1930
Cooke et al[3]	Concept of serum blocking antibodies	1935

Frankland and Augustin[22]	First double-blind, placebo-controlled, subcutaneous grass pollen immunotherapy trial	1954
Lowell and Franklin[24]	Grass pollen effective in multiallergen mix subcutaneous immunotherapy	1965
Ishizaka et al[4] and Johansson and Bennich[5]	Discovery of IgE antibody	1966
Johnstone and Dutton[27]	Long-term benefits of subcutaneous immunotherapy in children	1968
Hunt et al[31]	Efficacy of Hymenoptera venom vs whole-body extract subcutaneous immunotherapy	1978
Warner et al[10]	Suppression of late asthmatic responses after mite immunotherapy	1978
Rocklin et al[12]	Role of antigen-specific suppressor T cells in immunotherapy	1980
Gleich et al[6]	Early increase in IgE level after ragweed subcutaneous immunotherapy, blunting of seasonal IgE	1982
Scadding and Brostoff[55]	First double-blind trial of sublingual immunotherapy	1986
Creticos et al[8]	Inhibition of allergic inflammation in the target organ after ragweed immunotherapy	1989
Rak et al[11]	Inhibition of late asthmatic responses after birch immunotherapy in adults	1991
Norman et al[73]	First T-cell peptide subcutaneous immunotherapy trial in patients with cat allergy	1996
Akdis et al[13]	Role of IL-10 and regulatory T cells in venom immunotherapy	1998
Passalacqua et al[9]	House dust mite allergoid sublingual immunotherapy	1998
Durham et al[68]	Long-term clinical efficacy of grass pollen subcutaneous immunotherapy	1999
Niederberger et al[80]	First trial of recombinant allergen subcutaneous immunotherapy in patients with birch allergy	2004
Creticos et al[76]	Ragweed Toll-like receptor 9 agonist subcutaneous immunotherapy	2006
Jacobsen[28]	Prevention of asthma after pollen subcutaneous immunotherapy in children (the PAT study)	2007
Durham et al[70]	Long-term clinical efficacy of grass pollen sublingual immunotherapy	2010

The link between altered T-cell responses and immunotherapy was first highlighted by Rocklin et al,[12] who identified peripheral antigen-specific T suppressor cells after successful desensitization. Evidence for the critical role of regulatory T cells and IL-10 was highlighted by Akdis et al,[13, 14] as well as Yamanaka et al,[15] whereas the concept of a more delayed-in-time downregulation of allergen-specific CD4 T_H2 responses in favor of T_H1 responses in the periphery and in target organs has developed in parallel.[16, 17, 18, 19] It remains unclear to what extent it is either altered memory T-cell responses, altered B-cell responses, or both that are responsible for the long-lived antigen-specific tolerance that characterizes successful allergen immunotherapy. This is in contrast to the short-lived symptomatic relief obtained with antiallergic drugs, such as antihistamines, or topical or oral corticosteroid treatment.

Back to Article Outline

Clinical developments

Frankland[20] summarizes clinical developments in immunotherapy over the past 100 years. After the death of Leonard Noon from tuberculosis the same year as his seminal publication, his colleague John Freeman extended observations on pollen immunotherapy to include documentation of seasonal symptoms and the introduction of modified immunotherapy protocols, including the first rush protocol in 1928.[21] The first double-blind controlled trial of pollen immunotherapy was published by Frankland and Augustin[22] in 1954 and established a firm scientific foundation for the further development of allergen immunotherapy. Frankland was a founding member of the British Allergy Society, and in his 99th year, he remains very active within the allergy community in the United Kingdom.

The practice in the United States of multiple-allergen immunotherapy is in contrast to the usual practice in Europe.[23] The elegant study of Lowell and Franklin[24] in 1964 was the first to clearly demonstrate that a single allergen (ragweed) in a multiallergen mixture was effective in reducing seasonal allergic symptoms. Norman and Lichtenstein[25] were the first to demonstrate the allergen specificity of ragweed immunotherapy. The results of one double-blind placebo-controlled trial of multiallergen immunotherapy in children was disappointing.[26] Further controlled trials with a more inclusive mix of relevant allergens in defined allergic populations are required. Johnstone and Dutton[27] first highlighted the possibility that immunotherapy in children conferred long-term benefits. This concept is supported by a more recent randomized controlled trial of 3 years of pollen injection immunotherapy in children with hay fever in whom a 2- to 3-fold reduction in the risk of

progression from rhinitis to asthma was observed that persisted for up to 7 years after discontinuation of treatment.[28] The corticosteroid dose in asthmatic children has also been reported to be reduced on immunotherapy.[29] The duration of immunotherapy (3 vs 5 years) needed for optimal clinical improvement, however, is not established.[30] Hunt et al[31] demonstrated the efficacy of purified venom over insect whole-body extract and placebo in patients with anaphylaxis to the stings of Hymenoptera.

Back to Article Outline

Guidelines

The World Health Organization position paper published in 1998 made recommendations regarding major allergen content for the efficacy of immunotherapy.[32] A major advance since 1980 has been attempts to standardize the allergen content of extracts for both diagnosis and immunotherapy in terms of both biological potency and content of major allergen. Several dose-response studies calculated on the basis of major allergen content have confirmed the dose dependency of immunotherapy in both phase II provocation studies[33, 34] and phase III trials.[35, 36, 37] The CREATE project, under the guidance of van Ree[38] and Chapman et al,[39] has resulted in the availability of several standardized allergens and laboratory assays for measurement of allergen content that should facilitate more effective standardization of extracts. Dose recommendations for US practitioners are given in the practice parameters published in this issue.[40] Continued effective cooperation among academia, industry, and regulatory agencies is necessary for further progress.

After the World Health Organization report, the Cochrane Collaboration has provided rigorous scientific evaluation and expanded the evidence base in favor of immunotherapy,[41, 42, 43] although the limitations of meta-analysis in terms of the heterogeneity of included studies and the possibility of positive publication bias are acknowledged.[44] Recent advances include the Grades of Recommendation, Assessment, Development and Evaluation approach, which focuses more critically on actual clinical value and cost effectiveness.[45] The availability of standardized allergen extracts has permitted dose-response studies that have informed more definitive phase III trials. The World Allergy Organization has provided guidelines to optimize clinical trial design,[46] and the GA2LEN collaboration has provided advice on proper reporting according to the Consolidated Standards of Reporting Trials criteria.[47, 48] These issues are discussed in the article by Calderon et al.[49] The recent "big trials" have clearly defined the value of both subcutaneous and sublingual immunotherapy in adults and children[50, 51] with seasonal pollinosis, including identification of optimal doses[33, 34] and the optimal preseasonal duration of sublingual immunotherapy.[52]

In this issue Cox et al[40] provide a comprehensive third update to their practice parameters for immunotherapy. Highlights include an algorithm for the key decision points for the use of immunotherapy and a new classification and grading of systemic reactions that should facilitate a more accurate and standardized method for reporting side effects. Controversial issues, such as circumstances in which concomitant use of β-blockers might be reasonable and whether to recommend a prophylactic adrenaline autoinjector to patients undergoing immunotherapy, are carefully considered. Hankin and Lockey[53] discuss patient adherence to immunotherapy. Sadly, the main conclusion is the lack of data in contrast to studies evaluating compliance with pharmacologic treatment. Hankin and Lockey highlight several simple approaches that could be pursued, and this must surely represent an opportunity for professional organizations to support studies to evaluate adherence to improve patient selection for immunotherapy and outcomes. Lockey and Hankin[54] review the limited data available from the United States and elsewhere concerning the economic costs of immunotherapy. Although acknowledging the methodologic shortcomings of these studies and the need for more robust data, they conclude that subcutaneous immunotherapy is associated with significant health care savings, with one study showing up to an 80% reduction in health costs at 3 years after completion of treatment.

Back to Article Outline

Sublingual immunotherapy

After the first double-blind trial in mite-sensitive adults,[55] sublingual immunotherapy has emerged as an effective alternative to the subcutaneous route and is widely practiced in Europe, although at present to a lesser extent in the United States.[56, 57] Unlike subcutaneous immunotherapy, sublingual immunotherapy might act primarily through its effects on oral Langerhans cells.[58] Several published definitive trials of grass pollen tablets have confirmed their efficacy, safety, and tolerability in both adults and children.[35, 36, 50, 51] The sublingual route appears safe and has broadened the availability of immunotherapy to include self-administration, although continued vigilance after registration of products in Europe is ongoing and a proper standardized reporting system for side effects of sublingual immunotherapy is required. The repertoire of large sublingual studies needs to be extended to include seasonal allergens other than grass and also perennial allergens, including mites, molds, cockroach, and animal dander. If safety and tolerability continue to be acceptable, this should allow a broadening of the evaluations from rhinitis to include asthma, eczema,[59, 60] and food allergies. In the case of food allergies, there have also been several studies suggesting a beneficial effect of oral immunotherapy,[61, 62, 63] but further studies are required to establish the safety and efficacy of this approach, particularly in patients with peanut allergy.[64, 65] It is noteworthy that unlike the Lowell and Franklin[24] study of subcutaneous immunotherapy reported above, grass pollen sublingual immunotherapy was ineffective when administered as part of a multiallergen mix,[66] which questions the likely value of multiallergen sublingual immunotherapy in contrast to the single-allergen approach favored in Europe. There is a need to evaluate more patient-centered outcomes and cost-effectiveness of the sublingual approach, as addressed by Canonica and Passalaqua[67] in their article.

Back to Article Outline

Long-term benefits

The demonstration of clinical and immunologic tolerance to seasonal pollens[68] (persistence of benefit for several years after

discontinuation of immunotherapy) and the possibility that pollen immunotherapy might reduce progression to asthma[28] and prevent new sensitizations[69] are reviewed by Canonica and Passalaqua.[67] These observations raise the question of whether immunotherapy should be introduced earlier in the course of allergic disease, as suggested in the recent World Allergy Organization position paper, rather than be restricted to those patients who do not respond to the usual antiallergic drugs or those who experience unacceptable side effects of pharmacotherapy. One recent large double-blind trial of grass pollen tablets has confirmed long-term remission after 3 years of immunotherapy.[70] A recent open, partially randomized study of mite immunotherapy suggested that 4 rather than 3 years of sublingual immunotherapy might be optimal for long-term tolerance.[71] Further large, double-blind, randomized trials are needed to rigorously test the preventive effects of immunotherapy on the development of new sensitizations and disease progression before firm recommendations can be made.

Back to Article Outline

Novel approaches and future directions

Casale and Stokes[72] herein review novel approaches to immunotherapy, commencing with the use of subcutaneous allergen in combination with anti-IgE treatment. Other approaches summarized include peptide immunotherapy that uses short, linear T-cell epitopes that retain immunogenicity while losing the potential to cross-link IgE and induce anaphylaxis.[73, 74] Allergoids are an alternative attempt to reduce allergenicity,[75] whereas adjuvants such as CpG-containing bacterial DNA fragments[76] and bacterial cell wall LPSs (MPL)[77] combined with allergen have been shown to be effective in inducing immune deviation and suppressing symptoms. The recent successful development of recombinant wild-type[78, 79] and modified[80] allergens holds promise in terms of optimal standardization and the potential for personalized immunotherapy tailored to individual IgE sensitivities.[81] The use of intra–lymph node injections of allergen[82] and, more recently, of allergen-containing patches for transdermal use[83] have stimulated great interest.

The jewel in the crown of allergen immunotherapy is its ability to induce long-term tolerance (ie, clinical efficacy after its discontinuation). The demonstration that both the subcutaneous and sublingual routes might induce tolerance should broaden the indications for immunotherapy in the future.[55] Novel approaches, including the sublingual route, that achieve tolerance effectively,[84, 85] safely, and in a more convenient and cost-effective manner require enthusiastic support and further development rather than a continued reliance on the current traditional subcutaneous immunotherapy with its acknowledged limitations. The progress made in these past 100 years of immunotherapy combined with new technologic and scientific advances on the horizon portend dramatic changes for the next 100 years (Fig 1).

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Fig 1.
January 2011 cover image.

Back to Article Outline

References

1. Noon L. **Prophylactic inoculation against hayfever.** *Lancet*. 1911;1:1572
View In Article

2. Prausnitz C, Küstner H. **Studien über die Ueberempfindlichkeit.** *Zentralbl Bakteriol*. 1921;86:160–169
View In Article

3. Cooke RA, Barnard JH, Hebald S, Stull A. **Serological immunity with co-existing sensitisation in a type of human allergy (hay fever).** *J Exp Med*. 1935;62:733–750
View In Article | CrossRef

4. Ishizaka K, Ishizaka T, Hornbrook MM. **Physiochemical properties of reaginic antibody V. Correlation of reaginic activity with yEglobulin antibody.** *J Immunol*. 1966;97:840–853
View In Article | MEDLINE

5. Johansson SGO, Bennich H. Studies on a new class of human immunoglobulins. 1. Immunological properties. Nobel symposium 3, gamma globulins, structure and control of biosynthesis. P193. (Stockholm, June 12-17, 1967.) Almqvist and Wiksell.
View In Article

6. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. **Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study.** *J Allergy Clin Immunol*. 1982;70:261–271
View In Article | MEDLINE | CrossRef

7. Shamji MH, Wilcock LK, Wachholz PA, Dearman RJ, Kimber I, Wurtzen 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*. 2006;17:71–79
View In Article

8. Creticos PS, Marsh DG, Proud D, Kagey-Sobotka A, Adkinson NF, Friedhoff L, et al. **Responses to ragweed-pollen nasal challenge before and after immunotherapy.** *J Allergy Clin Immunol*. 1989;84:197–205
View In Article | MEDLINE | CrossRef

9. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, et al. **Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis.** *Lancet*. 1998;351:629–632
View In Article | Abstract | Full Text | Full-Text PDF (69 KB) | CrossRef

10. Warner JO, Price JF, Soothill JF, Hey EN. **Controlled trial of hyposensitisation to Dermatophagoides pteronyssinus in children with asthma.** *Lancet*. 1978;2:912–915
View In Article | MEDLINE

11. Rak S, Björnson A, Håkanson L, Sörenson S, Venge P. **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*. 1991;88:878–888
View In Article | MEDLINE | CrossRef

12. Rocklin RE, Sheffer AL, Greineder DK, Melmon KL. **Generation of antigen-specific suppressor cells during allergy desensitization.** *N Engl J Med*. 1980;302:1213–1219
View In Article | MEDLINE | CrossRef

13. Akdis CA, Blesken T, Akdis M, Wüthrich B, Blaser K. **Role of interleukin 10 in specific immunotherapy.** *J Clin Invest*. 1998;1021:98–106
View In Article

14. Akdis CA, Akdis M. **Mechanisms of allergen-specific immunotherapy.** *J Allergy Clin Immunol*. 2011;127:18–27
View In Article | Abstract | Full Text | Full-Text PDF (474 KB) | CrossRef

15. Yamanaka K, Yuta A, Kakeda M, Sasaki R, Kitagawa H, Gabazza EC, et al. **Induction of IL-10-producing regulatory T cells with TCR diversity by epitope-specific immunotherapy in pollinosis.** *J Allergy Clin Immunol*. 2009;124:842–845
View In Article | Full Text | Full-Text PDF (712 KB) | CrossRef

16. Varney VA, Hamid QA, Gaga M, Ying S, Jacobson M, Frew AJ, et al. **Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses.** *J Clin Invest*. 1993;92:644–651
View In Article | MEDLINE | CrossRef

17. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, et al. **Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen.** *Clin Exp Allergy*. 1997;27:1007–1015
View In Article | MEDLINE | CrossRef

18. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al. **Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma.** *J Allergy Clin Immunol*. 1996;97:1356–1365
View In Article | Abstract | Full Text | Full-Text PDF (1814 KB) | CrossRef

19. Tulic MK, Fiset PO, Christodoulopoulos P, Vaillancourt P, Desrosiers M, Lavigne F, et al. **Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response.** *J Allergy Clin Immunol*. 2004;113:235–241
View In Article | Abstract | Full Text | Full-Text PDF (123 KB) | CrossRef

20. Frankland AW. **Immunotherapy [allergy archives].** *J Allergy Clin Immunol*. 2011;127:160
View In Article

21. Freeman J. **Rush inoculation with special reference to hay fever treatment.** *Lancet*. 1930;1:744
View In Article | MEDLINE

22. Frankland AW, Augustin R. **Prophylaxis of summer hayfever and asthma: controlled trial comparing crude grass pollen extracts with isolated main protein component.** *Lancet*. 1954;1:1055
View In Article | MEDLINE

23. Cox Calderon MA. **Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of treatment practices in the US and Europe.** *Curr Med Res Opin*. 2010;26:2723–2733

View In Article | CrossRef

24. Lowell FC, Franklin W. **A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever.** *N Engl J Med.* 1965;273:675–679
View In Article | MEDLINE | CrossRef

25. Norman PS, Lichtenstein LM. **The clinical and immunologic specificity of immunotherapy.** *J Allergy Clin Immunol.* 1978;61:370–377
View In Article | MEDLINE | CrossRef

26. Adkinson NF, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. **A controlled trial of immunotherapy for asthma in allergic children.** *N Engl J Med.* 1997;336:324–331
View In Article

27. Johnstone DE, Dutton A. **The value of hyposensitization therapy for bronchial asthma in children-a 14-year study.** *Pediatrics.* 1968;42:793–802
View In Article | MEDLINE

28. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst 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;62:943–948
View In Article | CrossRef

29. Zielen S, Kardos P, Madonini E. **Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial.** *J Allergy Clin Immunol.* 2010;126:942–949
View In Article | Abstract | Full Text | Full-Text PDF (217 KB) | CrossRef

30. Tabar AI, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ, Arroabarren E. **Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy.** *J Allergy Clin Immunol.* 2011;127:63–67
View In Article

31. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. **A controlled trial of immunotherapy in insect hypersensitivity.** *N Engl J Med.* 1978;299:157–161
View In Article | MEDLINE | CrossRef

32. Bousquet J, Lockey R, Malling HJ. **Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper.** *J Allergy Clin Immunol.* 1998;102:558–562
View In Article | Abstract | Full Text | Full-Text PDF (53 KB) | CrossRef

33. Haugaard L, Dahl R, Jacobsen L. **A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects.** *J Allergy Clin Immunol.* 1993;9:709–722
View In Article

34. Nanda A, O'connor M, Anand M, Dreskin SC, Zhang L, Hines B, et al. **Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract.** *J Allergy Clin Immunol.* 2004;114:1339–1344
View In Article | Abstract | Full Text | Full-Text PDF (265 KB) | CrossRef

35. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. **Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis.** *J Allergy Clin Immunol.* 2006;117:802–809
View In Article | Abstract | Full Text | Full-Text PDF (258 KB) | CrossRef

36. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, et al. **Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis.** *J Allergy Clin Immunol.* 2007;120:1338–1345
View In Article | Abstract | Full Text | Full-Text PDF (648 KB) | CrossRef

37. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. **Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis.** *J Allergy Clin Immunol.* 2006;117:319–328
View In Article | Abstract | Full Text | Full-Text PDF (201 KB) | CrossRef

38. van Ree R The CREATE partnership. **The CREATE project: EU support for the improvement of allergen standardization in Europe.** *Allergy.* 2004;59:571–574
View In Article | MEDLINE | CrossRef

39. Chapman MD, Ferreira F, Villalba M, Cromwell O, Bryan D, Becker WM, et al. **The European Union CREATE project: a model for international standardization of allergy diagnostics and vaccines.** *J Allergy Clin Immunol.* 2008;122:882–889
View In Article | Abstract | Full Text | Full-Text PDF (456 KB) | CrossRef

40. Cox LS, Nelson H, Lockey R, Calabria C, Chacko T, Fingegold I, et al. **Allergen immunotherapy: a practice parameter third update.** *J Allergy Clin Immunol.* 2011;127(suppl):S1–55
View In Article | Full Text | Full-Text PDF (1071 KB) | CrossRef

41. Abramson MJ, Puy RM, Weiner JM. **Allergen immunotherapy for asthma. An update.** *Cochrane Database Syst Rev.* 2003;(4):CD001186
View In Article

42. 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
View In Article

43. Wilson DR, Torres-Lima M, Durham SR. **Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis.** *Allergy.* 2005;60:4–12
View In Article | MEDLINE | CrossRef

44. Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. **Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses.** *J Allergy Clin Immunol.* 2009;24:157–161
View In Article

45. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. **Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision.** *J Allergy Clin Immunol.* 2010;126:466–476
View In Article | Abstract | Full Text | Full-Text PDF (170 KB) | CrossRef

46. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. **Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce.** *Allergy.* 2007;62:317–324
View In Article | MEDLINE | CrossRef

47. Bousquet PJ, Brozek J, Bachert C, Bieber T, Bonini S, Burney P, et al. **The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper.** *Allergy.* 2009;64:1737–1745
View In Article | CrossRef

48. Bousquet PJ, Calderon MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. **The CONSORT statement applied to allergen-specific immunotherapy with inhalant allergens. A GA2LEN paper.** *J Allergy Clin Immunol.* 2011;127:49–56
View In Article | Abstract | Full Text | Full-Text PDF (2667 KB) | CrossRef

49. Calderon M, 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.* 2011;127:30–38
View In Article | Abstract | Full Text | Full-Text PDF (147 KB) | CrossRef

50. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. **Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis.** *J Allergy Clin Immunol.* 2009;123:160–166
View In Article | Abstract | Full Text | Full-Text PDF (489 KB) | CrossRef

51. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. **Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy.** *J Allergy Clin Immunol.* 2009;123:167–173
View In Article | Abstract | Full Text | Full-Text PDF (345 KB) | CrossRef

52. Calderon MA, Birk AO, Andersen JS, Durham SR. **Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy.** *Allergy.* 2007;62:958–961
View In Article | CrossRef

53. Hankin C, Lockey RF. **Patient characteristics associated with allergen immunotherapy initiation and adherence.** *J Allergy Clin Immunol.* 2011;127:46–48
View In Article | Full Text | Full-Text PDF (175 KB) | CrossRef

54. Lockey RF, Hankin C. **Health economics of allergen specific immunotherapy in the United States of America.** *J Allergy Clin Immunol.* 2011;127:39–43
View In Article | Full Text | Full-Text PDF (172 KB) | CrossRef

55. Scadding GK, Brostoff J. **Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite.** *Clin Allergy.* 1986;16:483–491
View In Article | MEDLINE

56. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. **Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009.** *Allergy.* 2009;64(suppl 91):1–59
View In Article | CrossRef

57. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. **Sublingual immunotherapy: a comprehensive review.** *J Allergy Clin Immunol.* 2006;117:1021–1035
View In Article | Abstract | Full Text | Full-Text PDF (242 KB) | CrossRef

58. Larche M. **Immune mechanisms of sublingual immunotherapy: are oral Langerhans cells the masters of tolerance?.** *J Allergy Clin Immunol.* 2010;126:646–647
View In Article | Full Text | Full-Text PDF (50 KB) | CrossRef

59. Dahl R, Stender A, Rak S. **Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis.** *Allergy.* 2006;61:185–190
View In Article | MEDLINE | CrossRef

60. Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. **Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis?.** *J Allergy Clin Immunol.* 2006;118:1292–1298
View In Article | Abstract | Full Text | Full-Text PDF (125 KB) | CrossRef

61. Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, et al. **Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy.** *J Allergy Clin Immunol.* 2009;124:610–612
View In Article | Full Text | Full-Text PDF (80 KB) | CrossRef

62. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. **Clinical efficacy and immune regulation with peanut oral immunotherapy.** *J Allergy Clin Immunol.* 2009;124:292–300
View In Article | Abstract | Full Text | Full-Text PDF (860 KB) | CrossRef

63. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. **Oral peanut immunotherapy in children with peanut anaphylaxis.** *J Allergy Clin Immunol.* 2010;126:83–91
View In Article | Abstract | Full Text | Full-Text PDF (605 KB) | CrossRef

64. Thyagarajan A, Varshney P, Jones SM, Sicherer S, Wood R, Vickery BP, et al. **Peanut oral immunotherapy is not ready for clinical use.** *J Allergy Clin Immunol.* 2010;126:31–32
View In Article | Full Text | Full-Text PDF (51 KB) | CrossRef

65. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al. **Adverse reactions during peanut oral immunotherapy home dosing.** *J Allergy Clin Immunol.* 2009;124:1351–1352
View In Article | Full Text | Full-Text PDF (60 KB) | CrossRef

66. 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;124:150–156
View In Article | Abstract | Full Text | Full-Text PDF (392 KB) | CrossRef

67. Canonica WG, Passalacqua G. **Disease modifying effect and economic implications of sublingual immunotherapy.** *J Allergy Clin Immunol.* 2011;127:44–45
View In Article | Full Text | Full-Text PDF (50 KB) | CrossRef

68. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. **Long-term clinical efficacy of grass-pollen immunotherapy.** *N Engl J Med.* 1999;341:468–475
View In Article | MEDLINE | CrossRef

69. Des Roches A, Paradis L, Menardo J-L, Bouges S, Daures J-P, Bousquet J. **Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children.** *J Allergy Clin Immunol.* 1997;99:450–453
View In Article | Abstract | Full Text | Full-Text PDF (391 KB) | CrossRef

70. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. **Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet.** *J Allergy Clin Immunol.* 2010;125:131–138
View In Article | Abstract | Full Text | Full-Text PDF (825 KB) | CrossRef

71. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. **Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study.** *J Allergy Clin Immunol.* 2010;126:969–975
View In Article | Abstract | Full Text | Full-Text PDF (823 KB) | CrossRef

72. Casale TB, Stokes JR. **Future forms of immunotherapy.** *J Allergy Clin Immunol.* 2011;127:8–15
View In Article | Abstract | Full Text | Full-Text PDF (444 KB) | CrossRef

73. Norman PS, Ohman JL, Long AA, Creticos PS, Gefter MA, Shaked Z, et al. **Treatment of cat allergy with T-cell reactive peptides.** *Am J Respir Crit Care Med.* 1996;154:1623–1628
View In Article

74. Oldfield WL, Larche M, Kay AB. **Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial.** *Lancet.* 2002;360:47–53
View In Article | Abstract | Full Text | Full-Text PDF (592 KB) | CrossRef

75. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A Study Group. **Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid.** *Allergy.* 2005;60:801–807
View In Article | MEDLINE | CrossRef

76. 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;355:1445–1455
View In Article | CrossRef

77. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. **A well tolerated grass pollen- specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections.** *Allergy.* 2001;56:498–505
View In Article | MEDLINE | CrossRef

78. Jutel M, Jäger L, Suck R, Meyer H, Fiebig H, Cromwell O. **Allergen-specific immunotherapy with recombinant grass pollen allergens.** *J Allergy Clin Immunol.* 2005;116:608–613
View In Article | Abstract | Full Text | Full-Text PDF (219 KB) | CrossRef

79. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. **Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis.** *J Allergy Clin Immunol.* 2008;122:951–960
View In Article | Abstract | Full Text | Full-Text PDF (509 KB) | CrossRef

80. Niederberger V, Horak F, Vrtala S, Spitzauer S, Krauth MT, Valent P, et al. **Vaccination with genetically engineered allergens prevents progression of allergic disease.** *Proc Natl Acad Sci U S A.* 2004;101:14677–14682
View In Article | CrossRef

81. Valenta R, Ferreira F, Focke-Tejkl M, Linhart B, Niederberger V, Swoboda I, et al. **From allergen genes to allergy vaccines.** *Annu Rev Immunol.* 2010;28:211–241
View In Article

82. 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;105:17908–17912
View In Article | CrossRef

83. Senti G, Graf N, Haug S, Rüedi N, von Moos S, Sonderegger T, et al. **Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy.** *J Allergy Clin Immunol.* 2009;124:997–1002
View In Article | Abstract | Full Text | Full-Text PDF (264 KB) | CrossRef

84. Larche M, Akdis CA, Valenta R. **Immunological mechanisms of allergen specific immunotherapy.** *Nat Rev Immunol.* 2006;6:761–771
View In Article | MEDLINE

85. Scadding G, Durham S. **Mechanisms of sublingual immunotherapy.** *J Asthma.* 2009;46:322–334
View In Article | CrossRef

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