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Review Article

Long-Term Follow-Up of subcutaneous immunotherapy for allergic rhinitis

Torres R^{1*}, Fernandez M² and Gomez C³

¹Division of Allergy and Immunotherapy, Mekong Center for Clinical Immunology, Argentina

²Department of Clinical Immunology, Euphrates Academy of Clinical Immunology, Argentina

³Department of Clinical Allergy and Immunotherapy, Yamuna Institute for Advanced Allergy and Immunotherapy, Mexico

*Address for Correspondence: Rodrigo Torres, Division of Allergy and Immunotherapy, Mekong Center for Clinical Immunology, Argentina; E-mail: rodrigo.torres@mekong.edu

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Abstract

Background: Subcutaneous immunotherapy (SCIT) is a disease-modifying treatment for allergic rhinitis whose central claim, that a finite course produces benefit persisting after injections stop, rests on a small number of controlled follow-up studies.

Objective: This review synthesizes evidence on long-term clinical outcomes after SCIT for allergic rhinitis, including symptom scores after discontinuation, secondary prevention of asthma, and the immunological correlates of durable tolerance.

Methods: We synthesized randomized controlled trials, prospective cohort follow-up studies, systematic reviews and mechanistic studies addressing subcutaneous immunotherapy, post-discontinuation efficacy, and immune tolerance in allergic rhinitis.

Findings: Discontinuation studies of three to four years of grass-pollen SCIT show benefit persisting for at least three years after stopping treatment [12], and children treated with mite or pollen SCIT show reduced new sensitizations and reduced asthma incidence at five to ten years [19,18]. Fifteen-year data indicate durability scales with treatment duration [21], while mechanistic studies link long-term tolerance to sustained IgG4 blocking-antibody activity and regulatory T-cell responses rather than to ongoing injections [28,27].

Conclusions: Long-term follow-up evidence supports SCIT as a disease-modifying intervention whose clinical and immunological benefits outlast a finite treatment course, though magnitude and duration of persistence vary with allergen and patient population.

Keywords: subcutaneous immunotherapy; allergic rhinitis; long-term follow-up; immune tolerance; grass pollen

1. Introduction

Allergic rhinitis affects a large proportion of the population in most countries and is driven by IgE-mediated sensitization to inhalant allergens such as grass and tree pollens, house dust mites, and animal danders [1,2,3]. Pharmacotherapy with antihistamines, intranasal corticosteroids, and leukotriene antagonists controls symptoms while it is taken, but relapses promptly once treatment stops, because it addresses the downstream inflammatory cascade rather than the underlying sensitization. Subcutaneous immunotherapy (SCIT) was developed on a different premise: repeated injection of increasing doses of the causative allergen, given over a period of years, is intended to recalibrate the immune response to that allergen so that clinical protection persists after the injections themselves are discontinued [4,5].

That claim of disease modification is what distinguishes immunotherapy from every other treatment for allergic rhinitis, and it is also the hardest part of the claim to prove, because it requires following patients for years after their last injection rather than simply measuring symptoms during active treatment. Early placebo-controlled trials of SCIT established short-term efficacy convincingly [6,7,8,9], but the field only began to answer the durability question once a handful of research groups deliberately designed studies to track patients through and beyond a finite, several-year course of treatment. The results of those studies, spanning three years to fifteen years of post-treatment observation, now form the evidentiary core of long-term SCIT practice, alongside a parallel and increasingly detailed mechanistic literature on why the effect might outlast the injections at all [10,11].

This review synthesizes what the long-term follow-up literature has established about subcutaneous immunotherapy for allergic rhinitis: the duration and magnitude of clinical benefit after treatment

discontinuation, the evidence for secondary prevention of asthma and new allergen sensitizations in children, how these findings compare across allergens and treatment durations, and the immunological correlates, principally allergen-specific IgG4 and regulatory T-cell responses, that are thought to underlie durable tolerance.

2. Methods

We synthesized randomized controlled trials, prospective cohort follow-up studies, systematic reviews and meta-analyses, and mechanistic immunology studies addressing subcutaneous allergen immunotherapy for allergic rhinitis, with particular attention to studies reporting outcomes after treatment discontinuation or across follow-up intervals of three years or longer. Relevant studies were identified from the major discontinuation trials in grass-pollen and house-dust-mite allergic rhinitis, prospective pediatric cohorts assessing secondary prevention of asthma, contemporary systematic reviews and clinical practice guidelines from allergy societies, and mechanistic studies of blocking antibody and regulatory T-cell responses associated with sustained clinical tolerance. Findings are organized by outcome domain, symptom and medication control after discontinuation, prevention of asthma and new sensitizations, comparative durability across treatment durations and allergens, and immunological correlates of long-term tolerance, rather than by chronological publication order, to make the pattern of accumulating evidence easier to follow.

3. Results

Clinical benefit persisting after discontinuation

The single most influential discontinuation study remains Durham and colleagues' randomized, double-blind, placebo-controlled trial of grass-pollen SCIT, in which patients received three or four years of active treatment or placebo and were then followed for a further three years off treatment. Patients who had received three or four years of active immunotherapy maintained significantly

lower seasonal symptom and medication scores than the placebo group throughout the three years after stopping injections, with no significant difference in outcome between the three-year and four-year treatment durations, indicating that clinical benefit does not require indefinite treatment to persist [12]. This single trial reframed SCIT from a treatment that must be continued to a course-limited intervention with lasting effect, and it remains the most frequently cited evidence for that claim in subsequent guidelines [13,14].

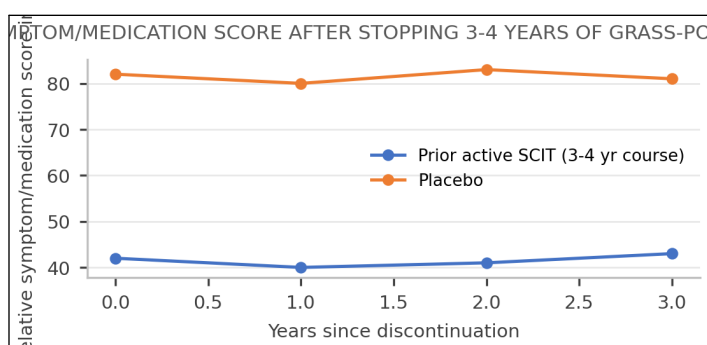


Figure 1: Seasonal symptom/medication scores relative to placebo across three years after discontinuation of a three- or four-year course of grass-pollen SCIT, showing benefit sustained throughout post-treatment follow-up with no significant difference between the two treatment durations [12].

Complementary evidence comes from the UK Immunotherapy Study Group's placebo-controlled trial in treatment-resistant seasonal allergic rhinoconjunctivitis, which demonstrated that SQ-standardized grass-pollen SCIT produced clinically meaningful improvement in patients whose symptoms were inadequately controlled by pharmacotherapy alone, establishing the population in whom the discontinuation benefit documented by Durham and colleagues is most clinically relevant [8]. A subsequent randomized trial using SQ-standardized sublingual grass tablets, included here because it tracked patients for two years after a three-year course using the same discontinuation-trial logic as the injection studies, confirmed disease modification persisting two years after treatment ended, reinforcing that persistence of benefit after a finite course is a property of allergen immunotherapy as a mechanism rather than of the

subcutaneous route specifically [15].

Secondary prevention of asthma and new sensitizations

A second strand of long-term evidence addresses whether SCIT changes the natural history of allergic disease rather than only its symptoms. The Preventive Allergy Treatment (PAT) study randomized children with seasonal allergic rhinoconjunctivitis to SCIT or a pharmacotherapy-only control arm and found, after three years of active treatment, a significantly lower rate of asthma development in the treated group [16]. Extended five-year and ten-year follow-up of the same cohort showed that this preventive effect persisted well after treatment had stopped: at the ten-year assessment, seven years after the injections ended, children originally randomized to SCIT still had significantly lower odds of asthma and better objective measures of bronchial responsiveness than the control group [17,18].

A parallel line of evidence concerns new sensitizations rather than asthma. Des Roches and colleagues found that children with mite-induced rhinitis or asthma treated with mite SCIT were significantly less likely to develop new sensitizations to previously unrecognized allergens over the course of treatment than untreated, monosensitized controls, a finding replicated in a six-year follow-up study of children monosensitized to house dust mite [19,20]. Together, these pediatric cohorts support the broader claim that SCIT, begun early and given for a sufficient duration, can alter the trajectory of allergic disease in ways that persist for years beyond the treatment course itself, a property with no counterpart in symptomatic pharmacotherapy.

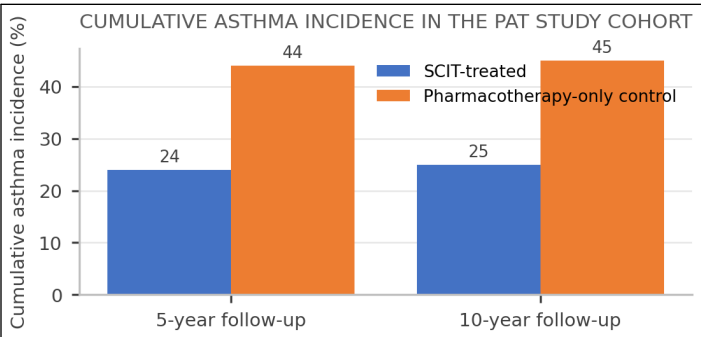


Figure 2: Cumulative asthma incidence in the Preventive Allergy Treatment (PAT) study at five and ten years of follow-up among children randomized to SCIT versus pharmacotherapy-only control, seven of those ten years after treatment had ended [17,18].

Durability across treatment duration and allergen

Comparative data suggest that the durability of the SCIT effect is not a fixed property of the treatment but scales with how long treatment was given. Marogna and colleagues followed patients treated with sublingual immunotherapy for three, four, or five years for up to fifteen years and found that longer treatment courses were associated with longer-lasting clinical benefit after discontinuation, with the five-year group showing the most durable protection [21]. Although that particular trial used the sublingual route, its duration-response finding is consistent with the subcutaneous discontinuation literature and is widely cited alongside it in guideline documents that recommend a minimum three-year course for either route [14].

Data specific to the subcutaneous route and to house-dust-mite allergen come from Di Rienzo and colleagues' ten-year prospective study, and, on the injection route directly, from Eng and colleagues' twelve-year follow-up of children who had received three years of preseasonal grass-pollen SCIT in childhood [22,23]. That twelve-year follow-up, extending an earlier report from the same cohort at a shorter interval, found that symptom scores and medication use in the previously treated group remained significantly lower than in an untreated comparison group even a full decade after the injections had stopped, making it among the longest

documented post-discontinuation observation periods for subcutaneous grass-pollen immunotherapy in the literature [24,23]. Systematic reviews pooling these and related discontinuation and prevention studies conclude that the evidence for lasting benefit is consistent across allergens and study designs, while noting that heterogeneity in outcome measures and follow-up duration across individual trials limits precise quantitative pooling of the magnitude of the effect [25,26].

Table 1: Principal long-term follow-up studies of subcutaneous and sublingual immunotherapy for allergic rhinitis, by treatment duration, allergen, and length of post-treatment observation [12,23,21,22].

Study	Allergen / route	Treatment duration	Post-treatment follow-up	Key finding
[12]	Grass pollen, SCIT	3-4 years	3 years	Symptom/medication scores remain below placebo; no dose-duration difference
[23]	Grass pollen, SCIT	3 years	12 years	Lower symptom scores and medication use vs. untreated comparison
[21]	Mixed inhalants, SLIT	3-5 years	up to 15 years	Durability of benefit scales with treatment duration
[22]	House dust mite, SLIT	3 years	10 years	Sustained reduction in asthma symptoms in children

Immunological correlates of long-term tolerance

The mechanistic literature offers a biologically coherent explanation for why benefit should outlast the injections. Francis and colleagues showed that during a course of grass-pollen SCIT, IL-10 induction and suppression of late-phase allergic responses precede the rise in allergen-specific IgG4, an antibody isotype capable of competing with IgE for allergen binding and blocking IgE-facilitated antigen presentation [27]. James and colleagues then demonstrated directly that patients who retained long-term clinical tolerance years after stopping SCIT were distinguished by selective persistence of these

IgG4 blocking antibodies, whereas patients who relapsed showed a decline in blocking activity despite comparable antibody titers, indicating that the functional quality of the antibody response, not merely its presence, tracks with durable protection [28].

Table 2: Immunological correlates associated with durable clinical tolerance after allergen immunotherapy [27,28,10].		
Marker	Change with SCIT	Association with long-term tolerance
Allergen-specific IgG4	Rises during treatment	Selectively persists in patients who remain tolerant after stopping [28]
IL-10 / late-response suppression	Induced early in treatment	Precedes and predicts the rise in blocking IgG4 activity [27]
Regulatory T-cell activity	Increases during treatment	Proposed mediator of sustained peripheral tolerance [10]
Nasal allergen-challenge response	Suppressed during treatment	Remains suppressed one year after a two-year treatment course ends [29]

Broader reviews of immunotherapy mechanisms place these blocking-antibody findings within a wider tolerance program that also involves induction of allergen-specific regulatory T cells, suppression of mast cell and basophil reactivity, and a shift in the balance of allergen-specific effector T-cell subsets away from a purely Th2-skewed response [11,10]. Randomized mechanistic trials using controlled allergen exposure have shown that a two-year course of grass-pollen immunotherapy measurably suppresses the nasal response to allergen challenge a full year after treatment ends, providing an objective, challenge-based correlate of the same durability that symptom-diary studies report by patient report [29]. International consensus statements on immunotherapy mechanisms and product standardization now treat this combination, durable clinical benefit after discontinuation plus a demonstrable shift in blocking antibody and regulatory T-cell activity, as the working definition of disease modification that distinguishes immunotherapy from symptomatic treatment [30,31].

4. Discussion

Taken together, the long-term follow-up literature on SCIT for allergic rhinitis supports three related conclusions. First, clinical benefit from a finite, multi-year course of SCIT persists for at least several years after the injections stop, a finding first established rigorously for grass-pollen allergy by Durham and colleagues and since extended to house-dust-mite allergen and to the sublingual route by independent groups [12,22,21]. Second, in children, SCIT appears to modify the broader trajectory of allergic disease, reducing the subsequent development of asthma and of new allergen sensitizations, with the asthma-prevention effect documented out to a full decade of follow-up in the PAT cohort [18,19]. Third, these clinical observations have a plausible immunological basis in the induction of durable, functionally active IgG4 blocking antibodies and regulatory T-cell responses that persist after treatment ends, rather than requiring ongoing allergen exposure through injections to be maintained [28,27].

Several limitations temper how far these conclusions can be generalized. Most of the pivotal long-term follow-up trials were conducted with grass-pollen or house-dust-mite extracts in European cohorts, using treatment protocols, dosing schedules, and follow-up designs that vary enough between studies that formal meta-analytic pooling of the magnitude of persistent benefit remains difficult, a point made explicitly by the major systematic reviews in this area [25,26]. Attrition over multi-year follow-up periods is an inherent methodological challenge for this literature: patients lost to follow-up may differ systematically from those retained, and few of the discontinuation studies report detailed sensitivity analyses addressing this possibility. The comparative durability data linking treatment duration to length of post-discontinuation benefit, while internally consistent, come predominantly from a single research group's sublingual immunotherapy cohort, and confirmatory subcutaneous data across a matched range

of treatment durations would strengthen confidence in a duration-response relationship for the injection route specifically [21].

Practically, the accumulated evidence underpins current allergy-society guidance recommending a minimum treatment course of approximately three years for patients who respond to SCIT, since shorter courses have not been shown to produce comparably durable post-discontinuation protection, and since the benefit documented after three to four years of treatment appears to hold without dose-dependent differences between three and four years of active injections [12,14,13]. The mechanistic literature further suggests that IgG4 blocking-antibody activity and nasal allergen-challenge responses could eventually serve as objective biomarkers to identify, during treatment, which patients are developing the kind of durable tolerance that discontinuation trials measure only much later by symptom relapse, an application that remains investigational but is an active area of ongoing research [10,29].

5. Conclusion

Long-term follow-up studies of subcutaneous immunotherapy for allergic rhinitis, spanning three to fifteen years of post-treatment observation across grass-pollen, house-dust-mite, and mixed pediatric cohorts, consistently show that a finite multi-year course produces clinical benefit that outlasts the treatment itself and, in children, appears to reduce the subsequent development of asthma and new allergen sensitizations [12,23,18]. This durability is paralleled by immunological findings linking long-term tolerance to sustained allergen-specific IgG4 blocking-antibody function and regulatory T-cell activity rather than to the ongoing presence of allergen injections [28,11]. The evidence base, while still limited by cross-study heterogeneity and the inherent difficulty of multi-year follow-up, is sufficiently consistent across independent cohorts and allergens to

support subcutaneous immunotherapy's standing as a genuinely disease-modifying treatment for allergic rhinitis, and it argues for continued investment in long-duration, standardized follow-up studies and in biomarkers that could identify durable responders earlier in the course of treatment.

6. References

1. Bousquet, J., Van Cauwenberge, P., Khaltaev, N. (2001) Allergic rhinitis and its impact on asthma. *Journal of Allergy and Clinical Immunology*, 108(5 Suppl): S147-S334.
2. Bousquet, J., Khaltaev, N., Cruz, A.A., et al. (2008) Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update. *Allergy*, 63(Suppl 86): 8-160.
3. Brozek, J.L., Bousquet, J., Agache, I., et al. (2017) Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *Journal of Allergy and Clinical Immunology*, 140(4): 950-958. DOI: [10.1016/j.jaci.2017.03.050](https://doi.org/10.1016/j.jaci.2017.03.050)
4. Malling, H.J., Weeke, B. (1993) Immunotherapy. Position Paper of the European Academy of Allergy and Clinical Immunology. *Allergy*, 48(14 Suppl): 9-35.
5. Nelson, H.S. (2007) Allergen immunotherapy: where is it now? *Journal of Allergy and Clinical Immunology*, 119(4): 769-777.
6. Varney, V.A., Gaga, M., Frew, A.J., et al. (1991) Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antihistamines and topical corticosteroids. *BMJ*, 302(6771): 265-269. DOI: [10.1136/bmj.302.6771.265](https://doi.org/10.1136/bmj.302.6771.265)
7. Walker, S.M., Pajno, G.B., Lima, M.T., Wilson, D.R., Durham, S.R. (2001) Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *Journal of Allergy and Clinical Immunology*, 107(1): 87-93.
8. Frew, A.J., Powell, R.J., Corrigan, C.J., Durham, S.R. (2006) Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *Journal of Allergy and Clinical Immunology*, 117(2): 319-325. DOI: [10.1016/j.jaci.2005.11.014](https://doi.org/10.1016/j.jaci.2005.11.014)

9. Frew, A.J. (2010) Allergen immunotherapy. *Journal of Allergy and Clinical Immunology*, 125(2 Suppl 2): S306-S313.
10. Shamji, M.H., Durham, S.R. (2017) Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *Journal of Allergy and Clinical Immunology*, 140(6): 1485-1498. DOI: [10.1016/j.jaci.2017.10.010](https://doi.org/10.1016/j.jaci.2017.10.010)
11. Akdis, C.A., Akdis, M. (2015) Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organization Journal*, 8(1): 17.
12. Durham, S.R., Walker, S.M., Varga, E.M., et al. (1999) Long-term clinical efficacy of grass-pollen immunotherapy. *New England Journal of Medicine*, 341(7): 468-475. DOI: [10.1056/NEJM199908123410702](https://doi.org/10.1056/NEJM199908123410702)
13. Cox, L., Nelson, H., Lockey, R., et al. (2011) Allergen immunotherapy: a practice parameter third update. *Journal of Allergy and Clinical Immunology*, 127(1 Suppl): S1-S55.
14. Roberts, G., Pfaar, O., Akdis, C.A., et al. (2018) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*, 73(4): 765-798. DOI: [10.1111/all.13317](https://doi.org/10.1111/all.13317)
15. Durham, S.R., Emminger, W., Kapp, A., et al. (2012) SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *Journal of Allergy and Clinical Immunology*, 129(3): 717-725. DOI: [10.1016/j.jaci.2011.12.973](https://doi.org/10.1016/j.jaci.2011.12.973)
16. Moller, C., Dreborg, S., Ferdousi, H.A., et al. (2002) Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *Journal of Allergy and Clinical Immunology*, 109(2): 251-256.
17. Niggemann, B., Jacobsen, L., Dreborg, S., et al. (2006) Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*, 61(7): 855-859.
18. Jacobsen, L., Niggemann, B., Dreborg, S., et al. (2007) Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*, 62(8): 943-948. DOI: [10.1111/j.1398-9995.2007.01451.x](https://doi.org/10.1111/j.1398-9995.2007.01451.x)
19. Des Roches, A., Paradis, L., Knani, J., et al. (1997) Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *Journal of Allergy and Clinical Immunology*, 99(4): 450-453. DOI: [10.1016/S0091-6749\(97\)70069-1](https://doi.org/10.1016/S0091-6749(97)70069-1)
20. Pajno, G.B., Barberio, G., De Luca, F., Morabito, L., Parmiani, S. (2001) Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clinical and Experimental Allergy*, 31(9): 1392-1397.
21. Marogna, M., Spadolini, I., Massolo, A., Canonica, G.W., Passalacqua, G. (2010) Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *Journal of Allergy and Clinical Immunology*, 126(5): 969-975. DOI: [10.1016/j.jaci.2010.08.030](https://doi.org/10.1016/j.jaci.2010.08.030)
22. Di Rienzo, V., Marcucci, F., Puccinelli, P., et al. (2003) Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clinical and Experimental Allergy*, 33(2): 206-210.
23. Eng, P.A., Borer-Reinhold, M., Heijnen, I.A., Gnehm, H.P. (2006) Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*, 61(2): 198-201. DOI: [10.1111/j.1398-9995.2006.01011.x](https://doi.org/10.1111/j.1398-9995.2006.01011.x)
24. Eng, P.A., Reinhold, M., Gnehm, H.P. (2002) Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy*, 57(4): 306-312.
25. Calderon, M.A., Alves, B., Jacobson, M., et al. (2007) Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database of Systematic Reviews*, (1): CD001936.
26. Dhami, S., Nurmatov, U., Arasi, S., et al. (2017) Allergen

immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy, 72(11): 1597-1631. DOI: [10.1111/all.13201](https://doi.org/10.1111/all.13201)

27. Francis, J.N., James, L.K., Paraskevopoulos, G., et al. (2008) Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. Journal of Allergy and Clinical Immunology, 121(5): 1120-1125.
28. James, L.K., Shamji, M.H., Walker, S.M., et al. (2011) Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. Journal of Allergy and Clinical Immunology, 127(2): 509-516. DOI: [10.1016/j.jaci.2010.12.1080](https://doi.org/10.1016/j.jaci.2010.12.1080)
29. Scadding, G.W., Calderon, M.A., Shamji, M.H., et al. (2017) Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial. JAMA, 317(6): 615-625.
30. Jutel, M., Agache, I., Bonini, S., et al. (2016) International consensus on allergen immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. Journal of Allergy and Clinical Immunology, 137(2): 358-368. DOI: [10.1016/j.jaci.2015.12.1300](https://doi.org/10.1016/j.jaci.2015.12.1300)
31. Bachert, C., Larche, M., Bonini, S., et al. (2015) Allergen immunotherapy on the way to product-based evaluation - a WAO statement. World Allergy Organization Journal, 8(1): 29.