Updating the role played by immunotherapy for allergic rhinitis: meta-analysis

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Background: **Although the effectiveness of allergen monotherapy immunotherapy for allergic rhinitis (AR) has been well established by many prior studies, other aspects of immunotherapy are still incompletely documented by high-quality studies. The many published papers describe various results. The aim of the present study was to conduct a meta-analysis on the effectiveness of allergen immunotherapy.**

Methods: **A total of 56 homogeneous studies were included in the analysis. The inclusion criteria used to select articles were as follows: (1) placebo-controlled clinical trials; (2) the use of immunotherapy; (3) participants and/or physicians were or were not blinded to immunotherapy or placebo assignment (single-blinding, double-blinding, or no-blinding studies); and (4) randomization or not of those in the immunotherapy and placebo groups.**

Results: **Between 2003 and 2013, 114 placebo-controlled clinical trials were reported in Medline. Studies describing recovery rates in immunotherapy and placebo groups numbered 56. The distribution of such works was homogeneous (heterogeneity chi-square = 16.11; degrees of freedom [df] = 55; p = 1.000). The extent of recovery in immunotherapy groups was 53.671-fold greater than in placebo groups (Mantel-Haenszel [M-H] pooled risk ratio [RR] = 53.671; 95% confidence interval [CI], 36.981 to 77.893; z = 20.96; $p < 0.001$).**

Conclusion: **Our meta-analysis suggests that immunotherapy is associated with a recovery rate 53.671-fold that of placebo.** © 2014 ARS-AAOA, LLC.

Key Words:
meta-analysis; immunotherapy; allergic rhinitis; placebo-controlled clinical trials; recovery rate.

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Allergen immunotherapy features repeated administration of allergen extracts seeking to reduce symptoms experienced on subsequent allergen exposure, improving the quality of life (QoL) and inducing long-term tolerance. To be effective, immunotherapy requires careful patient selection. Immunotherapy is safe if adequate precautions are taken. A decision to use immunotherapy depends on several personal and organizational factors, which determine whether 1 type of immunotherapy is more suitable than another (eg, subcutaneous immunotherapy [SCIT] vs sublingual immunotherapy [SLIT]).[1]

Allergen immunotherapy should be considered for patients who have measureable specific immunoglobulin E (IgE) antibodies against clinically relevant allergens. A decision to commence allergen immunotherapy may depend on several factors, including but not limited to patient-specific preference/acceptability, regime adherence, medication requirements, response to avoidance measures, and adverse effects of medications (D). (See in Appendix 1 and 2).[2] Randomized, prospective, single-blinded or double-blinded, placebo-controlled studies have demonstrated the effectiveness of specific immunotherapies used to treat allergic rhinitis (AR).[3,4] Prospective, randomized, double-blind, placebo-controlled studies have also demonstrated the utility of specific immunotherapies to treat allergic asthma.[5–8] Allergen immunotherapy is effective in many allergic patients, provided appropriate allergy evaluation has been conducted.

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Any response to allergen immunotherapy is antigen-specific and requires appropriate identification and selection of allergens based on patient history, exposure level, and diagnostic test results. Aeroallergen immunotherapy should be considered for patients who exhibit symptoms of AR, rhinoconjunctivitis, and/or asthma, after natural exposure to allergens, and for those who develop specific IgE antibodies against relevant allergens. Symptom severity and duration should also be considered when allergen immunotherapy is planned. Symptom severity may be defined subjectively or objectively. Time lost from work, visits to emergency departments or physicians, and the responses to pharmacotherapy are important objective indicators of allergic disease severity. Symptoms interfering with sleep, work, or school performance must also be considered. The effect of symptoms on QoL and the responsiveness to other forms of therapy, such as allergen avoidance or medication, should also be reviewed when a decision to prescribe allergen immunotherapy is contemplated. In addition, allergen immunotherapy should be considered if patients wish to avoid long-term pharmacotherapy. Unacceptable adverse effects of medications should favor a decision to initiate allergen immunotherapy, which may not be more costly than pharmacotherapy over a treatment course.[9–11]

Allergen immunotherapy for AR affords persistent benefits even after discontinuation, and reduces the risk of future asthma.[12–19] Coexisting medical conditions should also be considered when evaluating a patient who might be a candidate for allergen immunotherapy. Patients with coexisting AR and asthma should be managed using appropriate regimens of allergen avoidance and pharmacotherapy, but may also benefit from allergen immunotherapy. However, asthma must be stable before allergen immunotherapy is commenced.[20,21]

We conducted a meta-analysis to evaluate the effectiveness of allergen immunotherapy. In Medline, we performed a search using the key phrase "allergic rhinitis and immunotherapy and clinical study," and obtained results of 114 placebo-controlled clinical trials[15,22–134] conducted from 2003 to 2013. To ensure a homogeneous distribution, 56 works were included in our study (Table 1).

Methods

Study design

We conducted a meta-analysis of placebo-controlled clinical trials performed in line with the recommendations of the Quality of Reporting of Meta-Analysis (QUOROM) Statement.[135]

Search

A comprehensive literature search of the Medline database (March 1964 to January 2014) was conducted using the following terms: "allergic rhinitis AND immunotherapy AND clinical study." All possible hits were evaluated; we did not impose language restrictions.

We retrieved a total of 875 papers published from 1964 to 2013. Of these, 464 were published between 2003 and 2013, and were subjected to meta-analysis. We limited articles to placebo-controlled clinical trials. A total of 114 studies were controlled both clinically and by use of placebo, and were conducted between 2003 and 2013.[15,22–134] To ensure a homogeneous distribution of works, we removed 58 of these 114 studies. Thus, we ultimately evaluated 56 works (Table 1).

Selection

The following inclusion criteria were used to select articles for meta-analysis: (1) placebo-controlled clinical trials; (2) use of immunotherapy; (3) participants and/or physicians, and/or neither, blinded to immunotherapy or placebo assignment (single-blinding, double-blinding, or no-blinding); and (4) random or not assignment of participants to the immunotherapy or placebo groups. Full-text papers and/or scientific abstracts were included if they met the above criteria.

We recorded the authors, dates of publication, countries in which the studies were performed, populations (adults and/or children), departments that performed the studies, numbers in the immunotherapy and placebo groups, study types/blinding regimes, outcomes, recovery data, the numbers of patients who improved in both the immunotherapy and placebo groups, patient randomization features, the similarity (or otherwise) of baseline characteristics in the comparative groups, whether patients were blinded, whether healthcare providers were blinded, and whether patients treated other than interventionally received other treatment.

Data analysis

Statistical analyses were performed with the aid of Stata 11.0 (Stata Corp., College Station, TX) and $p < 0.05$ was considered to be statistically significant. Dichotomous data are presented as risk ratios (RRs) with 95% confidence intervals (CIs). Data were analyzed via fixed effects Mantel-Haenszel (M-H) meta-analysis. Statistical heterogeneity was assessed using the Q statistic, and $p < 0.10$ was considered to indicate significant heterogeneity. The effect of such heterogeneity was quantified using the I^2 statistic, which measures the extent of inconsistency among studies by calculating the percentages of total variation across studies. The effect of dexamethasone on recovery was assessed by construction of a forest plot. Publication bias was explored by constructing funnel plots.

Results

Trial flow

The Medline search identified 875 articles retrieved using "allergic rhinitis AND immunotherapy AND clinical study," published between 1964 and 2013 (Fig. 1). Of these, 411 were excluded. A total of 464 potentially

TABLE 1. Characteristics of included placebo-controlled clinical trials (n = 56)

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
22	Queirós[3]; 2013; Brazil	Children; Allergy and Clinical Immunology Dept.; total patients = 102; immunotherapy group (SLIT) = 70; placebo group = 32	Prospective; double-blind, placebo-controlled	All children undergoing SLIT showed clinical improvement, but a long-term reduction in symptom/medication scores with modulation of mucosal/systemic antibody responses were seen only in active groups (DPT and DPT+MRB).	70	70	0	32		Y	Y	Y	Y	Y
23	Yukselen[8]; 2013; Turkey	Children 11.5 ± 3 years; Pediatric Allergy and Immunology Dept.; total patients = 31; immunotherapy group = 21 (SCIT = 10, SLIT = 11); placebo = 9	Prospective; double-blind, double-dummy, placebo controlled immunother-apy	The clinical efficacy of SLIT is more prominent at the end of the second year, although this improvement is observed from the first year of treatment with SCIT in mite-sensitive children.	21	21	0	9		Y	Y	Y	Y	Y
25	Moed[18]; 2013; The Netherlands	Children 6–18 years; Department of General Practice; total patients = 59; SLIT = 29; placebo = 30	Prospective, a randomized placebo-controlled trial	By sublingual immunotherapy with low-dose house dust mite allergen, allergic symptoms had decreased after 2 years. Comparable to immunotherapy, allergic complaints decrease, the immunological changes of specific T-cell activity (both effector cells and regulator cells) which are observed after immunotherapy, do not change.	29	29	0	30		Y	Y			Y
28	Creticos[29]; 2013; USA	Adults; Allergy and Clinical Immunology Dept.; total patients = 784; AIT; placebo	Prospective, randomized, double-blind multinational trial, placebo-controlled	Ragweed AIT of 12 Amb a 1-U was effective and tolerable with a safety profile that permitted daily self-administration of ragweed allergen immunotherapy.	141	588	0	196		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
30	Didier[31]; 2013; France	Adults 18–50 years; Respiratory Diseases Department; total patients = 435; immunotherapy = 280; placebo = 155	Prospective, randomized, double-blind, placebo-controlled	The active groups also showed statistically significant differences compared to placebo in ARTSS, ARMS, and overall RQLQ score.	79	280	0	155		Y	Y	Y	Y	Y
31	Hylander[40]; 2013; Sweden	Adults 19–53 years; ENT Dept.; total patients = 15; immunotherapy: intralymphatic inguinal injections of ALK = 7; placebo = 8	Prospective, randomized double-blind, placebo-controlled	Intralymphatic immunotherapy (ILIT) with grass-pollen or birch-pollen extracts appears to reduce nasal allergic symptoms without causing any safety problems.	7	7	0	8		Y	Y	Y	Y	Y
35	Nayak[60]; 2012; USA	Adults 18–50 years; Sneeze, Wheeze & Itch Associates; total patients = 53; AIT = 40; placebo = 13	Prospective, randomized, double-blind, placebo-controlled	AIT increased Ig significantly more than placebo	40	40	0	13		Y	Y	Y	Y	Y
38	Klimek[71]; 2012; Germany	Adults 18–50 years; Center for Rhinology and Allergology; total patients = 50; immunotherapy = 40; placebo = 10	Prospective, randomized, double blind, placebo-controlled	The first double-blind, placebo-controlled SCIT-DRF with a mixture of recombinant Phleum allergens (Phl p 1, 2, 5a, 5b, 6) in patients with rhinoconjunctivitis plus/minus asthma showed no major side effects in very high doses up to 120 μg.	32	40	0	10		Y	Y	Y	Y	Y
39	Ahmadiafshar[75]; 2012; Iran	Children 5–18 years; Department of Pediatrics, Sub-specialist in Immunology and Allergy; total patients = 20; sublingual immunotherapy = 10; placebo = 10	Prospective, randomized, placebo-controlled trial	Significant reduction of symptoms in intervention group from 21st week of immunotherapy. This study indicates that SLIT in grass-pollen rhinitis is well tolerated, improves overall clinical symptoms, and reduces drug consumes. We recommend this therapy as a safe therapy in patients with allergic rhinitis.	10	10	0	10		Y	Y			Y

(*Continued*)

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TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
40	Swamy[77]; 2012; USA	Children and adults 6–57 years; Division of Immunology and Allergy; total patients = 30; SLIT = 20; placebo = 10	Prospective, randomized, double-blind, controlled phase I study	Subjects treated with dual SLIT had decreased rhinoconjunctivitis scores ($p < 0.001$) and medication use scores ($p < 0.001$). Dual SLIT could be an effective means to treat subjects with sensitivities to a variety of allergens and that long-term tolerance might be induced by epigenetic modifications of Foxp3 in memory regulatory T cells.	10	20	0	10		Y	Y	Y	Y	Y
42	Shamji[101]; 2012; UK	Allergy and Clinical Immunology; total patients = 221; immunotherapy = 166; placebo = 55	Prospective, randomized double-blind placebo-controlled	A time- and dose-dependent increase in serum inhibitory activity for both the IgE-blocking factor and IgE-FAB was observed, which paralleled increases in grass pollen-specific IgG(4) antibodies	166	166	0	55		Y	Y	Y	Y	Y
45	Didier[117]; 2011; France	Adults 18–50 years; Respiratory Diseases Department; total patients = 633; immunotherapy = 414; placebo = 219	Prospective, randomized, multicenter, double-blind, placebo-controlled, phase III	The mean AAdSS was reduced by 36.0% and 34.5% at season 3 in the 2-month and 4-month preseasonal and co-seasonal active treatment groups, respectively, compared with that in the placebo group. Sustained efficacy of 2-month and 4-month preseasonal and co-seasonal treatment with the 300 IR tablet over 3 pollen seasons was demonstrated, with reduction in symptoms and rescue medication use.	136	414	0	219		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
49	Fujimura[140]; 2011; Japan	Adults 16–73 years; Department of Otolaryngology–Head and Neck Surgery; total patients = 86; immunotherapy = 51; placebo = 37	Prospective, a randomized, double-blind, placebo-controlled	Patients with increased Cry j 1-iTreg in the SLIT group had significantly improved QOL and QOL-symptom scores.	51	51	0	37		Y	Y	Y	Y	Y
50	James[142]; 2011; UK	Adults 30–37 years; Allergy and Clinical Immunology; total patients = 44; immunotherapy = 22; placebo = 22	Prospective, a randomized, double-blind, placebo-controlled	AI. Grass pollen immunotherapy induces a subpopulation of allergen-specific IgG antibodies with potent inhibitory activity against IgE that persists after treatment discontinuation and that could account for long-term clinical tolerance.	22	22	0	22		Y	Y	Y	Y	Y
51	Riechelmann[144]; 2010; Austria	Department of Otorhinolaryngology; total patients = 140; immunotherapy = 66; placebo = 74	Prospective, multicenter, randomized, placebo-controlled double-blind	The allergoid treatment for 1 year resulted in significantly greater CIS improvement and higher RQL scores. The response threshold in the titrated CPT. Allergen injection therapy with modified HDM extract is superior to placebo in allergic rhinitis therapy.	66	66	0	74		Y	Y	Y	Y	Y
52	Nelson[147]; 2011; USA	Adults 18–65 years; Division of Allergy and Immunology; total patients = 439; immunotherapy = 213; placebo = 225	Prospective, phase III, double-blind, randomized, placebo-controlled, multicenter	Timothy grass allergen units of standardized grass (AIT) treatment (cross-reactive with related Pooideae grasses) was demonstrated to be effective, generally safe, and well tolerated in North American adults with grass pollen-induced ARC	55	213	0	225		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
57	Yonekura[165]; 2010; Japan	Children 7–15 years; Department of Otolaryngology; total patients = 31; immunotherapy (SLIT) = 20; placebo = 11	Prospective, randomized, double-blind placebo-controlled	The symptom scores in the active group began to decrease about 24 weeks after initiation of treatment and significant differences between the active and placebo groups were observed after 30 weeks. The average scores for the last 4 weeks of the study were significantly lower than those for the first 4 weeks in the active group but not in the placebo group.	20	20	0	11		Y	Y	Y	Y	Y
58	Makino[171]; 2010; Japan	Adults 47.5 ± 14.7 years; Department of Medical Genetics; total patients = 24; immunotherapy (SLIT) = 15; placebo = 9	Prospective, randomized, placebo-controlled	Among the differentially expressed proteins, the serum levels of complement C4A, apolipoprotein A-IV (apoA-IV), and transthyretin were significantly increased in SLIT-treated patients but not in placebo-treated patients.	15	15	0	9		Y	Y			Y
63	Campbell[187]; 2010; USA	Dynavax Technologies; total patients = 32; immunotherapy (AIC) = 17; placebo = 15	Prospective, placebo-controlled trial	Compared with the Th2 cytokine expression measured after pretreatment ragweed exposures, placebo-treated subjects demonstrated a significantly elevated ragweed- and Amb a 1-specific T cell IL-4 and IL-13 coexpression	17	17	0	15			Y			Y
68	Nieminen[204]; 2010; Finland	Children; Department of Pulmonary Diseases and Clinical Allergology; total patients = 30; immunotherapy (SLIT) = 20; placebo = 10	Prospective, randomized, placebo-controlled	Increased allergen-induced IL-17 responses during SLIT are associated with elevated SMS. Increased tolerogenic, allergen-specific Treg responses are also observed in children during SLIT.	20	20	0	10		Y	Y			Y

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TABLE 1. Continued

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					Recovery	Total	Recovery	Total						
69	Srivastava[206]; 2009; India	Institute of Genomics and Integrative Biology; total patients = 99; immunotherapy (SLIT) = 61; placebo = 38	Prospective, double-blind placebo-controlled	IT with 2 to 3 mix extract from the same allergen group is effective for insect hypersensitivity.	61	61	0	38			Y	Y	Y	Y
75	Pauli[228]; 2008; France	Adults 18–50 years; University Hospital; total patients = 134; immunotherapy = 99; placebo = 35	Prospective, multicenter, randomized, double-blind, placebo-controlled	The rBet v 1-based vaccine (allergen-specific immunotherapy vaccine) was safe and effective in treating birch pollen allergy, and induced a highly specific immune response.	99	99	0	35		Y	Y	Y	Y	Y
77	Panzner[242]; Czech 2008; Republic	Children and adults 7–50 years; Department of Immunology and Allergology; total patients = 154; immunotherapy (SIT) = 41; placebo = 30	Prospective, double-blind, placebo-controlled, randomized	It was found that both routes of administration are effective according to subjective clinical parameters and drug consumption, with a highly significant reduction of symptoms and drug intake favoring sublingual administration where a reduction of more than 60% was achieved. The results suggest that the administration of allergens via the oral mucosa is safe and clinically effective, favoring the sublingual rather than supralingual route.	24	41	0	30		Y	Y	Y	Y	Y
79	Würtzen[249]; 2008; Denmark	Total patients = 42; SIT = 21; placebo = 21	Prospective, double-blind, placebo-controlled	SIT induces changes in the composition of serum antibodies that inhibit IgE binding, HR and FAP to a similar extent.	21	21	0	21			Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
80	Guimarães Junqueir de Queirós[252]; 2008, Brazil	Children and adults 6–50; Laboratory of Allergy and Clinical Immunology; total patients = 73; immunotherapy = 58; placebo = 15	Prospective, randomized double-blind, placebo-controlled	SIT using Dpt extract alone was effective in reducing SPT response and IgE levels to Der p 2 allergen, while bacterial extracts induced decreases in IgE levels to whole Dpt extract	58	58	0	15		Y	Y	Ye	Y	Y
82	Francis[259]; 2008; UK	Adults 30–37; Allergy and Clinical Immunology Section; Total patients = 18; immunotherapy = 12; placebo = 6	Prospective, randomized double-blind, placebo-controlled	Grass pollen immunotherapy was effective in reducing overall symptom scores and conjunctival reactivity. In the active group significant IL-10 production occurred early at low allergen doses and at a similar time as inhibition of late skin responses at 2 to 4 weeks	12	12	0	6		Y	Y	Y	Y	Y
83	Moreno-Ancillo[267]; 2007; Spain	Children and adults 14–55; Hospital Virgen del Puerto; total patients = 100; Immunotherapy (SLIT) = 51; placebo = 49	Prospective, randomized, double-blind, placebo-controlled	Allergic symptoms were significantly decreased in the active immunotherapy group ($p = 0.004$) but not in the placebo group. Once-daily sublingual immunotherapy without updosing was well tolerated.	51	51	0	49		Y	Y	Y	Y	Y
84	de Blay[270]; 2007; France	Children and adults 12–41 years; Département de Pneumologie; total patients = 127; immunotherapy (SLIT) = 51; placebo = 49	Prospective, multicenter, randomized, double-blind, placebo-controlled	SLIT with a standardized, high-dose, 3-grass pollen extract is safe and significantly improves the clinical score in patients with hay fever and without asthma during the pollen season.	51	51	0	49		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

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					Recovery	Total	Recovery	Total						
92	Savolainen[283]; 2007; Finland;	Children 5–15 years; Department of Pulmonary Diseases and Clinical Allergology; total patients = 30; immunotherapy (SLIT) = 20; placebo = 10	Prospective, double-blind, placebo-controlled	During SLIT, IL-18 and SLAM are upregulated, suggesting that the Th2 type inflammatory response is downregulated during SLIT by increased Th1 type response.	20	20	0	10		Y	Y	Y	Y	Y
93	Tahamiler[288]; 2007; Turkey	Department of Otolaryngology; total patients = 137; immunotherapy (SLIT) = 70; placebo = 67	Prospective, placebo-controlled	According to the study results, it was found that a greater improvement in the 3 years of SLIT compared with the 2 years of SLIT when the comparative results of the total 6 years were examined.	70	70	0	67			Y			Y
96	Charpin[306]; 2007; France	Adults; Service de Pneumologie; total patients = 32; immunotherapy (SIT) = 17; placebo = 15	Prospective, randomized double-blind, placebo-controlled	A statistically significant improvement (41%, $p < 0.02$) in the conjunctivitis symptom score was observed in actively treated patients compared to the placebo group at the peak of the 2001 pollen season.	6	17	0	15		Y	Y	Y	Y	Y
97	Chakraborty[310]; 2006; India	Adults 20–59 years; Department of Botany; total patients = 35; immunotherapy (SIT) = 18; placebo = 17	Prospective, randomized double-blind, placebo-controlled	The SIT group showed decreases of 33.5% and 57% from the baseline SMSs during the first and second treatment season, respectively.	10	18	0	17		Y	Y	Y	Y	Y
100	Creticos[315]; 2006; USA	Adults 23–60 years; Division of Allergy and Clinical Immunology; total patients = 25; immunotherapy (SLIT) = 14; placebo = 11	Prospective, randomized, double-blind, placebo-controlled, phase 2	Immunotherapy with a 6-week regimen of the a ragweed-toll-like receptor 9 agonist vaccine (AIC vaccine) appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis.	14	14	0	11		Y	Y	Y	Y	Y

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TABLE 1. Continued

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					Recovery	Total	Recovery	Total						
101	Savolainen[319]; 2006; Finland	Children aged 5–15 years; Department of Pulmonary Diseases and Clinical Allergology; total patients = 30; immunotherapy (SLIT) = 20; placebo = 10	Prospective, randomized, double-blind, placebo-controlled, dose-response, phase II	SLIT induced a dose-dependent systemic allergen-specific immunological response in children with AR.	20	20	0	10		Y	Y	Y	Y	Y
102	Valovirta[320]; 2006; Finland	Children 5–14 years; Allergy Centre; total patients = 88; immunotherapy (SLIT) = 59; placebo = 29	Prospective, randomized, double-blind, placebo-controlled	SLIT with tree pollen extract provided dose-dependent benefits in tree pollen-allergic children in terms of significantly reduced symptoms and medication use. The treatment was well tolerated.	59	59	0	29		Y	Y	Y	Y	Y
103	Larsen[321]; 2006; Denmark	Adults 18–50 years; Allergy Clinic; total patients = 30; immunotherapy (SLIT) = 23; placebo = 7	Prospective, randomized, double-blind, placebo-controlled	The data indicate that a short dose increase phase may reduce the incidence of AEs when high-dose SLIT is administered.	23	23	0	7		Y	Y	Y	Y	Y
105	Passalacqua[330]; 2006; Italy	Adults 18–50 years; Allergy and Respiratory Diseases; total patients = 56; immunotherapy (SLIT) = 28; placebo = 28	Prospective, randomized, double-blind, placebo-controlled	SLIT was clinically effective and safe in mite-induced mild disease	28	28	0	28		Y	Y	Y	Y	Y
106	Colás[343]; 2006; Spain	Adults 18–51 years; Servicio de Alergia; total patients = 60; immunotherapy = 41; placebo = 19	Prospective, randomized, double-blind, placebo-controlled	Immunotherapy with this modified vaccine of *Salsola kali* pollen is safe and efficacious to treat patients clinically sensitive to this pollen.	41	41	0	19		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient randomization	Similar baseline characteristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
107	Durham[344]; 2006; UK	Adults 18–65 years; National Heart and Lung Institute; total patients = 855; immunotherapy = 705; placebo = 150	Prospective, randomized, double-blind, placebo-controlled, multinational, multicenter	This study confirms dose-dependent efficacy of the grass allergen tablet.	204	705	0	150		Y	Y	Y	Y	Y
108	Frew[353]; 2006; UK	Adults 18–60 years; Allergy & Inflammation Research Subdivision; total patients = 410; immunotherapy (SIT) = 307; placebo = 103	Prospective, double-blind, randomized, placebo-controlled	One season of immunotherapy with Alutard grass pollen reduced symptoms and medication use and improved the quality of life of subjects with moderately severe hay fever.	125	307	0	103		Y	Y	Y	Y	Y
111	Jutel[370]; 2005; Poland	Adults 21–30 years; Department of Internal Medicine and Allergology; total patients = 57; immunotherapy (SIT) = 29; placebo = 28	Prospective, double-blind, randomized, placebo-controlled	A recombinant allergen vaccine can be a effective and safe treatment to ameliorate symptoms of allergic rhinitis.	29	29	0	28		Y	Y	Y	Y	Y
112	Ameal[375]; 2005; Spain	Children and adults 14–48 years; Allergy Department; total patients = 55; immunotherapy (SIT) = 29; placebo = 26	Prospective, double-blind, randomized, placebo-controlled	After 1 year of treatment, the modified extract of *D. pteronyssinus* demonstrated to be safe and efficacious to treat patients with asthma and allergic rhinoconjunctivitis sensitized to this mite.	29	29	0	28		Y	Y	Y	Y	Y
113	Alvarez-Cuesta[384]; 2005; Spain	Adults 18–58 years; Servicio de Alergia; total patients = 53; immunotherapy (SIT) = 25; placebo = 28	Prospective, double-blind, randomized, placebo-controlled	IT with depigmented, glutaraldehyde-modified allergen extracts was well-tolerated and added beneficial effects to AR treatment in pollen allergic patients eliciting an improvement in QOL enough to justify a change in the patient's treatment.	25	25	0	28		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
114	Corrigan[386]; 2005; UK	Adults 18–60 years; Guy's, King's and St Thomas's School of Medicine; total patients = 154; immunotherapy = 77; placebo = 77	Prospective, double-blind, multicentre placebo-controlled, phase 3 clinical trial	The grass pollen allergoid was shown to be safe and clinically efficacious in the management of hay fever with or without asthma (GINA I or II).	36	77	0	77		Y	Y	Y	Y	Y
15	Polosa[407]; 2004; Italy	Adults 20–54 years; Istituto di Malattie Apparato Respiratorio; total patients = 30; immunotherapy = 15; placebo = 15	Prospective, randomized, double-blind placebo-controlled	Parietaria-SIT reduces symptom and rescue medication scores, but no changes in BHR to methacholine or sputum eosinophilia were observed.	15	15	0	15		Y	Y	Y	Y	Y
119	Mirone[411]; 2004; Italy	Adults 23–60 years; Dipartimento Multizonale di Allergologia ed Immunologia Clinica; total patients = 30; immunotherapy = 14; placebo = 16	Prospective, randomized, double-blind, placebo-controlled	Injective immunotherapy is safe and clinically effective in European patients sensitized to Ambrosia	14	14	0	16		Y	Y	Y	Y	Y
120	Crimi[414]; 2004; Italy	Istituto di Malattie dell'Apparato Respiratorio; total patients = 30; immunotherapy = 15; placebo = 15	Prospective, randomized, double-blind, placebo-controlled	Arietaria-SIT is effective in controlling hay fever symptoms and rescue medications, but no changes in the BHR to methacholine or sputum eosinophilia were observed.	15	15	0	15		Y	Y	Y	Y	Y
122	Bufe[421]; 2004; Germany	Children 8–9 years; Experimental Pneumology; total patients = 161; immunotherapy = 82; placebo = 79	Prospective, randomized, double-blind, placebo-controlled, multicentre	In this study SLIT was accompanied by a significant placebo effect. Efficacy of treatment could only be seen in children with severe clinical symptoms and this became clinically marked after 3 years of therapy.	82	82	0	79		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient randomization	Similar baseline characteristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
123	Tonnel[422]; 2004; France	Children and adults 7–45 years; Service de Pneumologie et Immuno-Allergologie; total patients = 32; immunotherapy = 15; placebo = 17	Prospective, randomized, placebo-controlled	This study indicates the superiority of active treatment vs placebo, evaluated on efficacy criteria (rhinitis score) or objective criteria (skin reactivity).	15	15	0	17		Y	Y			Y
124	van Neerven[424]; 2004; Denmark	ALK-Abelló total patients = 42; immunotherapy = 21; placebo = 21	Prospective, randomized, double-blind, placebo-controlled	Specific allergy vaccination (SAV) leads to an inhibition of the S-FAP needed to obtain optimal T cell activation at the low allergen concentrations present in vivo.	21	21	0	21		Y	Y	Y	Y	Y
125	TePas[428]; 2004; USA	Adults 19–55 years; Division of Immunology and Allergy, Department of Pediatrics; total patients = 23; immunotherapy = 12; placebo = 11	Prospective, randomized, double-blind, placebo-controlled	Oral immunotherapy with microencapsulated allergen induces a form of immunologic tolerance to the allergen and is a safe, efficient, and effective method of allergen immunotherapy.	12	12	0	11		Y	Y	Y	Y	Y
126	Khinchi[432]; 2004; Denmark	Adults 20–58 years; Allergy Clinic; total patients = 58; immunotherapy (SLIT, SCIT) = 39; placebo = 19	Prospective, randomized, double-blind, placebo-controlled	Based on the limited number of patients the clinical efficacy of SLIT was not statistically different from SCIT, and both treatments are clinically effective compared with placebo in the treatment of birch pollen rhinoconjunctivitis.	39	39	0	19		Y	Y	Y	Y	Y
127	Pajno[435]; 2003; Italy	Children 8–14 years; Paediatric Clinic; total patient = 30; immunotherapy (SLIT) = 15; placebo = 15	Prospective, randomized, double-blind, placebo-controlled	The clinical efficacy of SLIT + fluticasone is equal to that of fluticasone alone, but the addition of SLIT has effects also on nonbronchial symptoms.	15	15	0	15		Y	Y	Y	Y	Y

(*Continued*)

TABLE 1. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population[c]	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
128	Wüthrich[437]; 2003; Switzerland	Children; Allergy Unit, Department of Dermatology; total patients = 20; immunotherapy (SLIT) = 10; placebo = 10	Prospective, double-blind, placebo-controlled	SLIT with a grass pollen extract is well tolerated in children and is able to significantly reduce drug consumption during the second year of treatment.	10	10	0	10		Y		Y	Y	Y
132	Polosa[451]; 2003; Italy	Adults 20–54 years; Dipartimento di Medicina Interna e Specialistica; total patients = 30; immunotherapy = 15; placebo = 15	Prospective, randomized, double-blind, placebo-controlled	The clinical efficacy of Parietaria SIT was exclusively associated with attenuation in seasonal worsening of PC15 AMP, suggesting that AMP may be useful in monitoring changes in allergic inflammation of the airways.	15	15	0	15		Y	Y	Y	Y	Y
133	André[457]; 2003; France	Département Scientifique et Médical; total patients = 92; immunotherapy = 43; placebo = 49	Prospective, randomized, double-blind, placebo-controlled	During the whole period of pollination, the difference favoring immunotherapy was highly significant for the global assessment by the patient ($p = 0.004$) and by the investigator ($p = 0.005$). Adverse reactions were reported more often in the active treatment but mild or moderate, and they abated after dose adjustment.	43	43	0	49		Y	Y	Y	Y	Y

[a]The numbers of studies in this column are the study numbers in the reference list of this meta-analysis. All 56 studies were clinical and placebo-controlled, and exhibited a homogeneous distribution.
[b]The numbers of the studies refer to a total of 464 papers in Medline detected by searching with the key phrase "allergic rhinitis and immunotherapy and clinical study"; all papers were published between 2003 and 2013.
[c]Twenty-six of the reviewed papers used SLIT; 7 of the reviewed papers used SCIT; and 2 of the reviewed papers used both SLIT and SCIT. In the other papers, the used type of the immunotherapy was reported as immunotherapy or SIT.
AAdSS = Average Adjusted Symptom Score; AE = adverse event; AIC = Amb a 1-immunostimulatory phosphorothioate oligonucleotide conjugate; AIT = allergy immunotherapy tablet; AMP =Adenosine 5′-monophosphate; AR = allergic rhinitis; ARC = Allergic Rhinoconjunctivitis; ARMS = Average Rescue Medication Score; ARTSS = Average Rhinoconjunctivitis Total Symptom Score; BHR = bronchial hyperresponsiveness; CIS = Clinical Index Score; CPT = Conjunctival Provocation Test; DPT = *Dermatophagoides pteronyssinus*; DPT+MRB = DPT allergen + mixed respiratory bacterial extracts; DRF = dose range-finding; FAP =Facilitated Allergen Presentation; GINA = Global Initiative for Asthma; HDM = house dust mite; HR =Histamine Release ; Ig = immunoglobulin; IgE-FAB = immunoglobulin E–facilitated allergen binding; IL = interleukin; IR =Index of Reactivity ; IT = immunotherapy; QOL = quality of life; RQL = Rhinitis/Rhinoconjunctivitis Quality of Life ; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SIT = specific allergen immunotherapy; SLAM =Signalling lymphocytic activation molecule; SLIT = sublingual immunotherapy; SMS = symptom-medication score; SPT =skin prick test; Th1 = T helper 1; Th2 = T helper 2; Treg = regulatory T cell.

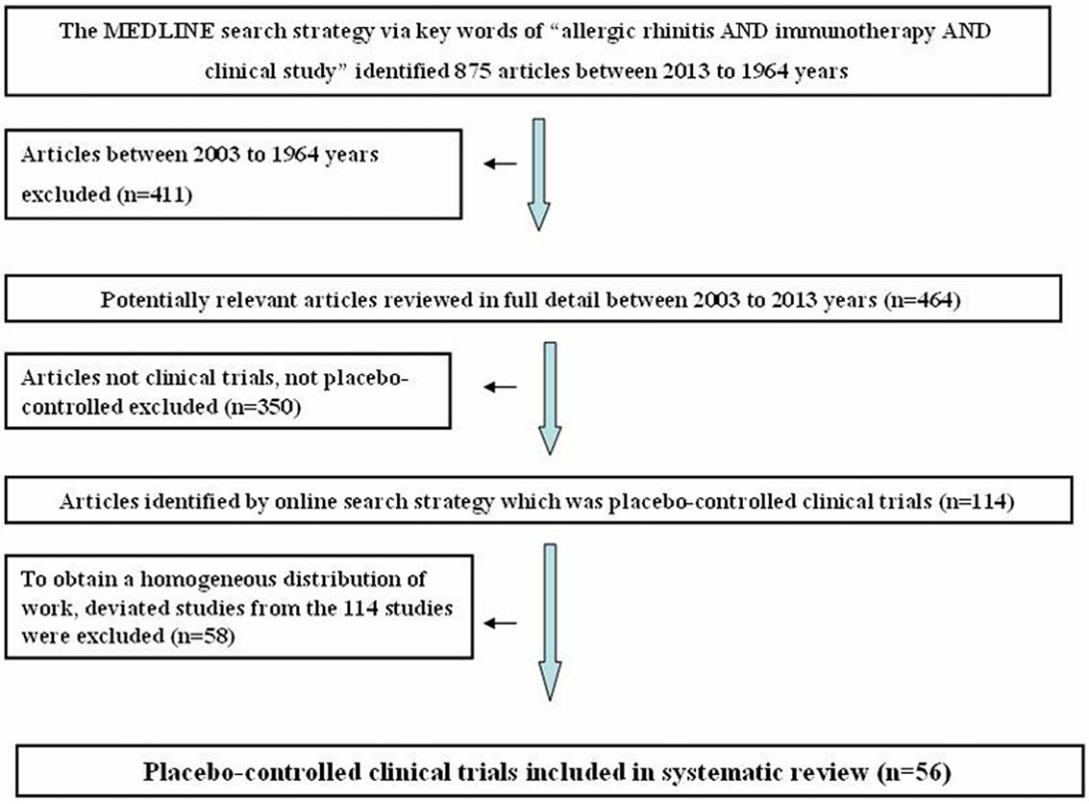

FIGURE 1. Placebo-controlled clinical trials included in meta-analysis.

relevant articles were published between 2003 and 2013. Articles that were neither clinical trials nor placebo-controlled trials were excluded (n = 350). Thus, we identified 114 placebo-controlled clinical trials.[15,22–134] To ensure a homogeneous distribution, studies deviating from our inclusion criteria were excluded (n = 58) and, ultimately, we included 56 placebo-controlled clinical trials in our systematic review (Tables 1 and 2).

Outcomes

Meta-analyses of the effects of immunotherapy and placebo in terms of recovery from AR are shown in Table 3. To obtain a homogeneous distribution, studies deviating from the norm were removed from the total of 114 and, ultimately, we included 56 studies that exhibited a homogeneous distribution (heterogeneity chi-squared = 16.11; degrees of freedom [df] = 55; $p = 1.000$). The extent of patient recovery in the immunotherapy group was 53.671-fold more than in the placebo group (M-H pooled RR = 53.671; 95% CI, 36.981 to 77.893; z = 20.96; $p < 0.001$).

Figure 2 shows a forest plot of the 56 studies included in the meta-analysis. The central square in each horizontal line represents the RR for each study. The lines demonstrate the ranges of 95% CIs. The vertical line at an RR of 1 is the line of no effect. "% Weight" indicates the influence exerted by each study on the pooled RR.

Figure 3 shows the funnel plot of the 56 studies included in the meta-analysis. The vertical solid line represents the logarithmic transformation of the overall estimated treatment effect (ie, the log [RR]). Diagonal dotted lines represent pseudo-95% CIs for the estimated treatment effects, and the circles represent the treatment effects of each of the 56 studies (RR is the risk ratio).

Discussion

The principal types of immunotherapy are SCIT and SLIT. The success of immunotherapy, as compared to placebo, is based on the immunological responses to immunotherapy. The immunological response to subcutaneous immunotherapy is characterized by decreases in the sensitivities of end-organs and changes in the humoral and cellular responses to the administered allergens (A). (See in Appendix 1 and 2).[136] Reductions in end-organ responses upon immunotherapy include less prominent early and late responses of the skin, conjunctiva, nasal mucosa, and bronchi to allergen challenge; decreased allergen-induced eosinophil, basophil, and mast cell infiltration; blunting of mucosal priming; and reduction of nonspecific bronchial sensitivity to histamine (A). (See in Appendix 1 and 2).[82,136–141]

SCIT in patients with pollen rhinitis is associated with transient increases in allergen-specific IgE levels, blunting of seasonal increases in such levels,[142] and increases in allergen-specific IgG levels (particularly IgG4)[141–143] and IgA.[141,144] A recent Cochrane systematic review of

TABLE 2. Characteristics of placebo-controlled clinical trials excluded to obtain a homogeneous distribution (n = 58)

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
24	Patel[12]; 2013; Canada	Allied Research International; total patients = 228; specific immunotherapy or placebo	Prospective, randomized, double-blind, placebo-controlled, phase IIb study	This study demonstrated that an ultrashort course of Ragweed MATA MPL is efficacious in reducing allergy symptoms in patients with seasonal allergic rhinitis and that it is well tolerated.						Y	Y	Y	Y	Y
26	Murphy[20]; 2013; USA	Adults 18–65 years; Boys Town National Research Hospital; total patients = 289; immunotherapy tablet (AIT) = 139; placebo = 150	Prospective, randomized placebo-controlled trial	2800 BAU grass AIT did not demonstrate significant symptom improvement vs placebo.	8	139	9	150		Y	Y			Y
27	Nolte[21]; 2013; USA	Adults; Merck Sharp & Dohme Corp.; total patients = 565; AIT; placebo	Prospective, randomized, placebo-controlled	Ragweed AIT was effective and well tolerated in ragweed-allergic North American adults.						Y	Y			Y
29	Meyer[30]; 2013; Germany	Adults; Medical Department Allergopharma GmbH & Co. KG; total patients = 37; immunotherapy = 30; placebo = 7	Prospective, randomized, double-blind, placebo-controlled	The total symptom score significantly decreased in all active groups compared with placebo.	24	30	1	7		Y	Y	Y	Y	Y
32	Bozek[43]; 2013; Poland	Adults (Elderly) 60–75 years; Dermatology and Allergology; total patients = 111; immunotherapy (SLIT) group = 51; placebo = 57	Prospective, randomized, double-blind, placebo-controlled	The total nasal symptom score decreased by 44% in the active group and 6% in the placebo group after 3 years of SLIT. Sublingual allergen-specific immunotherapy in elderly patients generated a significant clinical improvement in the active group compared with the placebo group, particularly during the heating season.	22	51	3	57		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
33	Bonvalet[53]; 2012; France	Stallergenes; total patient no:89; SLIT and placebo	Prospective, randomized, double-blind, placebo-controlled	SLIT induced a 29.3% improvement of the average rhinoconjunctivitis total symptom score in the active group, when compared to the placebo group.						Y	Y	Y	Y	Y
34	Cox[55]; 2012; USA	Adults; Nova Southeastern University; total patients = 473; immunotherapy = 233; placebo = 240	Prospective, randomized, double-blind, placebo-controlled study	The mean daily CS over the pollen period was significantly lower in the active treatment group versus the placebo group.	100	233	31	240		Y	Y	Y	Y	Y
36	Baron-Bodo[62]; 2012; France	Adults 18–50 years; Stallergenes SA; total patients = 509; immunotherapy (SLIT); placebo	Prospective, randomized, double-blind, placebo-controlled	After 1 year of SLIT, mite-specific IgE and IgG4 titers increased by 1.5-fold and 4-fold, respectively, in the active, but not in the placebo group.						Y	Y	Y	Y	Y
37	Wahn[66]; 2012; Germany	Children 4–12 years; Department for Pediatric Pneumology and Immunology; total patients = 93; study: high-dose grass pollen SLIT = 60; placebo = 23	Prospective, randomized, double-blind, placebo-controlled trial	SLIT preparation significantly reduced symptoms and medication use in children with grass pollen-allergic rhinoconjunctivitis.	30	60	7	23		Y	Y	Y	Y	Y
41	Durham[94]; 2012; UK	Adults 18–65 years; Section of Allergy and Clinical Immunology; total patients = 568; immunotherapy = 282; placebo = 286	Prospective, randomized, double-blind, placebo-controlled multinational, phase III trial	The mean rhinoconjunctivitis daily symptom score was reduced by 25% to 36% ($p \leq 0.004$) in the grass AIT group compared with the placebo group over the 5 grass pollen seasons covered by the trial.	177	282	0	286		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
43	Valovirta[106]; 2011; Finland	Children 5–12 years; Allergy Clinic; total patients = 812; immunotherapy: grass AIT; placebo 1:1 randomization	Prospective, multinational, double-blind, placebo-controlled randomized trial	Grazax Asthma Prevention (GAP) trial to assess the preventive effect of allergen-specific immunotherapy on asthma development.	406	406	0	406		Y	Y	Y	Y	Y
44	Kuna[108]; 2011; Poland	Asthma and Allergy; total patients = 46; SLIT; placebo	Prospective, randomized, double-blind, placebo-controlled trial	Symptoms and medication intake further decreased in the third year of SLIT during the grass pollen season in comparison to the previous years and the number of "well days" increased accordingly.						Y	Y	Y	Y	Y
46	Reich[119]; 2011; Germany	Adults mean 18–65years; Department of Dermatology; total patients = 276; immunotherapy: grass AIT = 210; placebo = 52	Prospective, multicenter, randomized, double-blind, placebo-controlled trial	The change from baseline in mean concentration of IgE-blocking factor was significantly greater with grass AIT compared with placebo	162	276	10	52		Y	Y	Y	Y	Y
47	Klimek[126]; 2011; Germany	Adults 18–65 years; Zentrum fuer Rhinologie & Allergologie; total patients = 299; immunotherapy = 202; placebo = 97	Prospective, double-blind, randomized, multicenter, phase IIb study	Rhinoconjunctivitis symptoms were significantly lower in patients treated with high dose of CYT003-QbG10 as compared with placebo. Treatment with high-dose CYT003-QbG10 improved disease symptoms and reduced medication use in allergic individuals thus providing first evidence for a new potential immunotherapeutic.	141	202	48	97		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
48	Panzner[133]; 2011; Czech Republic	Department of Immunology and Allergology; total patients = 51; immunotherapy (SIT, SLIT); placebo	Prospective, double-blind, placebo-controlled, randomized	The significant therapeutic effect of both SLIT and supralingual immunotherapy lasting 3 to 4 years was clearly achieved. Despite no significant difference between efficacy of both administration ways of SIT, the onset of sublingual SIT effect seems to be slightly faster than that of supralingual SIT.						Y	Y	Y	Y	Y
53	Blaiss[148]; 2011; USA	Children 5–17 years; Department of Pediatrics; total patients = 345; immunotherapy = 175; placebo = 169	Prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter	Use of once-daily Timothy grass AIT treatment effectively treats timothy grass (cross-reactive with Festucoideae grasses) pollen-induced ARC in North American children 5 years and older.	140	175	0	169		Y	Y	Y	Y	Y
54	Mösges[150]; 2010; Germany	Children 6–14 years; Informatics and Epidemiology Dept.; total patients = 54; immunotherapy = 27; placebo = 27	Prospective, randomized, double-blind, placebo-controlled, multicenter	The difference in mean PFR changes during ultra-rush titration between SLIT and placebo was not significant ($p = 0.056$). A 95% probability that SLIT does not decrease PFR during ultra-rush titration was demonstrated.	0	27	0	27		Y	Y	Y	Y	Y
55	Cortellini[152]; 2010; Italy	Children and adults 14–42 years; Internal Medicine and Rheumatology Department; total patients = 26; immunotherapy (SLIT) and placebo	Prospective, randomized, prospective, double-blind, placebo-controlled	After treatment, patients receiving SLIT had a significant improvement in symptoms and a reduction in medication intake vs placebo and vs the run-in season, whereas no change was seen in the placebo group. SPT reactivity significantly decreased only in the SLIT group.						Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
56	Pfaar[158]; 2011; Germany	Department of Otorhinolaryngology; total patients = 80; immunotherapy (SLIT) = 60; placebo = 20	Prospective, randomized, double-blind, placebo-controlled, phase I/IIa study	Patients in the 2 groups given SLIT containing the highest amount of MPL experienced the highest proportion of negative NCTs after 10 weeks (47% and 44%, vs 20% with placebo).	28	60	4	20		Y	Y	Y	Y	Y
59	Halken[173]; 2010; Denmark	Children (5–11 years) and adolescents (12–17 years); Hans Christian Andersen Children's Hospital; total patients = 267; immunotherapy (SLIT); placebo	Prospective, multinational, randomized, double-blind, placebo-controlled study	More patients in the SLIT group were satisfied with their treatment compared to placebo (83.2% vs 68.1%, $p = 0.0030$), and compliance was high (SLIT 93.9% of patients were compliant, placebo 94.8% of patients were compliant).						Y	Y	Y	Y	Y
60	Höiby[176]; 2010; Sweden	Children and adults 7–69 years; Department of Respiratory Medicine and Allergology; total patients = 61; immunotherapy (SCIT); placebo	Prospective, randomized, double-blind, placebo-controlled trial	SCIT with depigmented polymerized birch pollen extract significantly reduced symptom and medication scores when compared with the placebo, was well tolerated, and resulted in immunological changes comparable with those of native pollen extracts.						Y	Y	Y	Y	Y
62	Durham[180]; 2011; UK	Adults 34.2 years (mean); National Heart and Lung Institute; total patients = 634; immunotherapy (grass AIT) = 316; placebo = 318	Prospective, multicenter, double-blind, randomized, placebo-controlled trial	All definitions showed a reduced risk of having days with severe symptoms in the grass AIT group when compared to the placebo group.	316	316	0	318		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
64	Gallego[189]; 2010; Spain	Research and Development Department; immunotherapy; placebo	Prospective, double-blind, placebo-controlled	There was a statistically significant increase in specific IgG4, a decrease in the ratio of IgE/IgG4 to *D. pteronyssinus* and a significant increase in specific IgG4 to Der p 1 and Der p 2 in the patients allotted to active treatment.	Y						Y	Y	Y	Y
65	Ceuppens[193]; 2009; Belgium	Division of Allergy and Clinical Immunology; total patients = 62; immunotherapy; placebo	Prospective, multicenter, randomized, placebo-controlled, double-blind	Treatment with the birch pollen extract resulted in a lower CIS for the eye and nose during the peak birch pollen season of 2003, compared with placebo (reductions of 42% and 31%, respectively) (p = 0.017 and 0.039).						Y	Y	Y	Y	Y
66	Kamin[200]; 2010; Germany	Children; Children's Hospital; total patients = 221; immunotherapy; placebo	Prospective, randomized, double-blind, placebo-controlled, multicenter	Tolerability of SIT and omalizumab treatment was good (82% of patients). Most AE (93.4% in omalizumab and 87.2% in placebo group) were judged by the patients as mild to moderate.						Y	Y	Y	Y	Y
67	O'Hehir[201]; 2009; Australia	Adults 18–65 years; Department of Allergy, Immunology and Respiratory Medicine; total patients = 27; immunotherapy (HDM SLIT) = 13; placebo = 14	Prospective, randomized double-blind placebo-controlled	Allergen-induced CD4(+) T-cell division and IL-5 production were significantly decreased after 6 months and 12 months of active treatment but not placebo.	13	3	0	14		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
70	Ventura[208]; 2009; Italy	Immunology and Infectious Diseases; total patients = 40; immunotherapy (SLIT and SCIT); placebo	Prospective, double-blind, placebo-controlled	After SCIT and SLIT the levels of ECP and ECA were reduced in nasal lavage. A clinical improvement correlated with a decline in inflammation parameters after 1 year of immunotherapy.							Y	Y	Y	Y
71	Tsai[216]; 2009; Taiwan	Department of Education and Research; total patients = 35; immunotherapy (LNIT); placebo	Prospective, double-blind, placebo-controlled	When the symptomatic and immunological changes were compared between active treatment and placebo groups, the improvements were greater in the active treatment groups for all 3 symptom scores							Y	Y	Y	Y
72	Malling[218]; 2009; Denmark	Adults 18–45; Allergy Clinic; total patients = 628; immunotherapy = 447; placebo = 181	Prospective, multinational, randomized, double-blind, placebo-controlled	The risk-benefit ratio validates the use of 300 IR tablets in clinical practice in all of these patient subgroups, regardless of severity profile, sensitization status, and presence of asthma.	447	447	0	181		Y	Y	Y	Y	Y
73	Tseng[225]; 2008; Taiwan	Children 6–18 years; Department of Pediatrics; total patients = 59; immunotherapy SLIT = 28; placebo = 31	Prospective, multicenter, randomized, double-blind, placebo-controlled	Specific IgE increased significantly in both placebo and SLIT groups after treatment but did not differ between the 2 groups.	28	28	31	31		Y	Y	Y	Y	Y
74	Wahn[226]; 2009; Germany	Children 5–17 years; Berlin Children's Hospital; total patients = 266; immunotherapy SLIT = 131; placebo = 135	Prospective, multinational, randomized, double-blind, placebo-controlled	Five-grass-pollen SLIT tablets (300 IR) reduce both symptom scores and rescue medication use in children and adolescents with grass pollen-related rhinoconjunctivitis.	85	131	67	135		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient randomization	Similar baseline characteristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
76	Röder[239]; 2008; The Netherlands	Children 6–18; Section of Allergology; total patients = 154; immunotherapy (SLIT); placebo	Prospective, randomized, placebo-controlled	Symptom scores did not differ between adherent and nonadherent participants. In adherent as well as nonadherent participants, no difference was found between verum and placebo group with respect to symptom scores.						Y	Y			Y
78	Purohit[246]; 2008; France	Service de Pneumologie; total patients = 124; immunotherapy; placebo	Prospective, double-blind, placebo-controlled	Single courses of injection immunotherapy with Bet v 1 allergen derivatives showed trends toward improved well-being and reduced reactivity to specific allergen provocation							Y	Y	Y	Y
81	Pfaar[255]; 2008; Germany	Rhinology and Allergology Center; total patient = 185; immunotherapy SLIT; placebo	Prospective, double-blind, placebo-controlled	Active treatment was associated with a significant and clinically relevant improvement. High-dose, sublingual, specific immunotherapy with an extract of a 6-grass pollen mixture showed a significant and clinically relevant improvement in subjects with grass pollen-associated rhinitis or rhinoconjunctivitis, with or without asthma.							Y	Y	Y	Y
85	Didier[273]; 2007; France	Adults 18–45 years; Department of Pneumology; total patients = 628; immunotherapy (SLIT) = 472; placebo = 156	Prospective, multinational, randomized, double-blind, placebo-controlled	In the first pollen season, the efficacy and safety of sublingual immunotherapy with grass tablets was confirmed. The 300-IR and 500-IR doses both demonstrated significant efficacy compared with placebo.	472	472	0	156		Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
86	Srivastava[274]; 2007; India	Allergy and Immunology Sections; total patients = 40; immunotherapy; placebo	Prospective, randomized, double-blind, placebo-controlled	Allergen immunotherapy with mosquito extract was well tolerated, with improvement in symptoms and airway reactivity. Good clinical outcome was associated with increased IgG4 antibody levels.						Y	Y	Y	Y	Y
87	Powell[277]; 2007; UK	Adults 37–38 years; Clinical Immunology Unit; total patients = 410; immunotherapy = 307; placebo = 103	Prospective, double-blind, randomized, placebo-controlled	Treatment with Alutard SQ significantly improved the seasonal QoL of patients suffering from allergic rhinoconjunctivitis.	307	307	0	103		Y	Y	Y	Y	Y
88	Kopp[278]; 2007; Germany	Children and adolescents (6.3–17.6 years; University Children's Hospital; total patients = 170; immunotherapy; placebo	Prospective, phase III, randomized, placebo-controlled, multicenter	One year after omalizumab or placebo treatment, there was no significant difference in SLT release between the 4 groups. These results strongly suggest that the observed effects of decreased SLT release after omalizumab treatment were attributable to the treatment with omalizumab, rather than to SIT therapy.						Y	Y			Y
89	Ibañez[279]; 2007; Spain	Children 5–12 years; Servicio de Alergia; total patients = 60; immunotherapy (SLIT); placebo	Prospective, randomized, placebo-controlled	Grazax was in general tolerated in a pediatric population and considered suitable for further clinical investigations in children						Y	Y			Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
90	Klunker[281]; 2007; UK	Adults 21–51 years; Section of Allergy and Clinical Immunology; total patients = 36; immunotherapy = 27; placebo = 9	Prospective, randomized, double-blind, placebo-controlled	The combination of ragweed immunotherapy and anti-IgE resulted in prolonged inhibition of allergen-IgE binding compared with either treatment alone, events that might contribute to enhanced efficacy.	27	27	0	9		Y	Y	Y	Y	Y
91	Calderon[282]; 2007; UK	Adults 18–65; National Heart and Lung Institute; total patients = 934; immunotherapy (SLIT) = 480; placebo = 454	Prospective, randomized, double-blind, placebo-controlled, multicenter	Sublingual immunotherapy with Grazax) must be initiated at least 8 weeks prior to the grass pollen season to provide a significant clinical efficacy. A longer preseasonal treatment period (>8 weeks) improves the clinical efficacy (relative to placebo) during the grass pollen season.	480	480	454	454		Y	Y	Y	Y	Y
94	Williams[289]; 2007; UK	Homerton University Hospital; total patients = 154; immunotherapy (SIT); placebo	Prospective, randomized, double-blind, multicenter, placebo-controlled	Preseasonal short-term immunotherapy with the high-dose, hypoallergenic allergen preparation Allergovit has been shown to be efficacious and safe.						Y	Y	Y	Y	Y
95	Worm[304]; 2007; Germany	Klinik für Dermatologie und Allergologie; total patients; immunotherapy (SCIT); placebo	Prospective, multicenter, randomized, double-blind, placebo-controlled	Difference of 46% in mean symptom medication score between active and placebo group was seen. High dose sublingual immunotherapy can therefore be considered as an efficient therapeutic option in the management of IgE-mediated allergic airway diseases.						Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
98	Vervloet[311]; 2007; France	Service de Pneumologie; total patients = 74; immunotherapy (SLIT); placebo	Prospective, double-blind placebo-controlled	There was a marked and significant decrease of the medication score (about 50%) and nasal steroid consumption (about 75%) in the active treatment group.							Y	Y	Y	Y
99	Palma-Carlos[314]; 2006; Portugal	Adults 19–43 years; Clinical Allergy Immunology; total patients = 32; immunotherapy (SLIT); placebo	Prospective, randomized, double-blind, placebo-controlled	The results of this study show that the allergoid SLIT is safe and effective in decreasing symptom scores and drug use in rhinitic patients allergic to grass pollen.						Y	Y	Y	Y	Y
104	Dahl[326]; 2006; Denmark	Adults 18–65 years; Department of Respiratory Diseases; total patients = 634; immunotherapy (SLIT) = 316; placebo = 318	Prospective, randomized, double-blind, placebo-controlled, multicenter	SLIT with grass allergen tablets was effective in grass pollen-induced rhinoconjunctivitis.	120	316	0	318		Y	Y	Y	Y	Y
109	Dokic[358]; 2005; Republic of Macedonia	Clinic of Pulmonology and Allergology; total patients = 40; immunotherapy (SIT) = 20; placebo = 20	Prospective, double-blind, randomized, placebo-controlled	Specific immunotherapy with a mite depot allergoid induced significant clinical improvements vs placebo.	20	20	0	20		Y	Y	Y	Y	Y
110	Marcucci[369]; 2005; Italy	Children 4–16 years; Clinica Pediatrica; total patients = 24; immunotherapy (SLIT) = 13; placebo = 11	Prospective, double-blind, randomized, placebo-controlled	SLIT in children monosensitized to mites reverted the spontaneous increase in nasal IgE and in local parameters of allergic inflammation.	Y13	13	0	11		Y	Y	Y	Y	Y
115	Bodtger[392]; 2005; Denmark	Adults 19–45 years; Allergy Clinic; total patients = 35; immunotherapy; placebo	Retrospective, double-blind, placebo-controlled	Despite being comparable pretreatment, only the SIT group had a significant decrease in recollected total drug use during SIT.							Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
116	Bowen[402]; 2004; Canada	Children and adults; Department of Medicine and Pediatrics; total patients = 76; immunotherapy; placebo	Prospective, randomized, double-blind placebo-controlled	Sublingual swallow immunotherapy seems to be safe and efficacious for ragweed rhinoconjunctivitis even when started immediately before the ragweed pollen season.						Y	Y	Y	Y	Y
117	Rolinck-Werninghaus[404]; 2004; Germany	Children 3–14 years; Department of Pediatric Pneumology and Immunology; total patients = 97; immunotherapy = 49; placebo = 48	Prospective, randomized, double-blind placebo-controlled, multicenter	SLIT had a positive effect on the reduction of a multiple symptom-medication score, but had no significant effect on symptoms alone in children with rhinoconjunctivitis to grass pollen compared with a placebo.	27	49	4	48		Y	Y	Y	Y	Y
118	Smith[406]; 2004; UK	Adults 18–60 years; Wessex Research Network; total patients = 140; immunotherapy = 94; placebo = 46	Prospective, randomized, double-blind, placebo-controlled	High-dose SLIT has beneficial effects on nasal symptoms during the peak pollen season in patients with severe seasonal allergic rhinitis. At least 2 years of treatment with SLIT is required to show a benefit.	52	94	23	46		Y	Y	Y	Y	Y
121	Bez[417]; 2004; Germany	Children 6–17 years; University Children's Hospital; total patients = 201; immunotherapy = 111; placebo = 90	Prospective, randomized, double-blind, placebo-controlled	The combination of SIT and anti-IgE is associated with prevention of nasal ECP increase and decreased tryptase levels in nasal secretions.	111	111	0	90		Y	Y	Y	Y	Y
129	Ascione[442]; 2003; Italy	ENT Institute; total patients; immunotherapy (LNIT); placebo	Prospective, randomized, double-blind, placebo-controlled	Compared to placebo the clinical efficacy of LNIT was confirmed by a reduction of clinical symptoms and drug intake.						Y	Y	Y	Y	Y

(*Continued*)

TABLE 2. Continued

Study number in the reference list of the meta-analysis (this article)[a]	Author (study number in total of 464 papers in Medline); date; country[b]	Population	Study type/ blinding	Outcomes	Immunotherapy group		Placebo group		Recruitment of consecutive patients	Patient random-ization	Similar baseline charac-teristics in all groups	Patient blinded	Health care provider blinded	Equal treatment of patients other than intervention
					Recovery	Total	Recovery	Total						
130	Varney[446]; 2003; UK	Adults 19–55; RCMB Research Division; total patients = 28; immunotherapy = 15; placebo = 13	Prospective, randomized, double-blind, placebo-controlled	One year of SIT for *D. pteronyssinus* in patients with poorly controlled rhinitis (+/− mild asthma) produced clinically useful improvement as shown by symptom-medication diary cards and reductions in immediate skin reactions compared with placebo treatment.	15	15	0	13		Y	Y	Y	Y	Y
131	Radcliffe[448]; 2003; UK	Adults 18–64; Infection Inflammation and Repair Research Division; total patient = 183; immunotherapy = 90; placebo = 93	Prospective, randomized, double-blind, placebo-controlled	The active treatment group and the placebo group did not differ in the proportion of problem-free days, quality of life scores, symptom severity scores, change in quantitative skin prick provocation threshold, or change in conjunctival provocation threshold.	0	90	0	93		Y	Y	Y	Y	Y
134	Bodtger[460]; 2003; Denmark	Allergy Clinic; total patients = 35; immunotherapy; placebo	Retrospective, randomized, double-blind placebo-controlled	Only in the SIT-treated group was a significant decrease in postseason ratings of severity of rhinoconjunctivitis apparent						Y	Y	Y	Y	Y

[a]The numbers of studies in this column are the study numbers in the reference list of this meta-analysis. All 56 studies were clinical and placebo-controlled, and exhibited a homogeneous distribution.
[b]The numbers of the studies refer to a total of 464 papers in Medline detected by searching with the key phrase "allergic rhinitis and immunotherapy and clinical study"; all papers were published between 2003 and 2013.
AE = adverse event; AIR = allergy immunotherapy tablet; BAU = bioequivalent allergy unit; CIS = Clinical Index Score; CS = Combined Score; ECA = eosinophil chemotactic activity; ECP = eosinophil cationic protein; HDM = house dust mite; Ig = immunoglobulin; IL = interleukin; IR = Index of Reactivity; LNIT = local nasal immunotherapy; MPL = monophosphoryl lipid A ; NCT = nasal challenge test; SCIT = subcutaneous immunotherapy; PFR = peak flow rate; QoL = quality of life; SIT = specific immunotherapy; SLIT = sublingual immunotherapy; SLT = Sulfidoleukotriene release; SPT = skin-prick test.

TABLE 3. Meta analysis studies on effects of ımmunotherapy and placebo in the recoverement of allergic rhinitis

Study number in the reference list of the meta-analysis[a]	Study number in total of 464 papers in Medline[b]	Study cited	Intervention group: immunotherapy		Control group: placebo			95% CI		
			Those showing recovery	Total	Those showing recovery	Total	RR	Lower	Upper	%Weight
22	3	Queirós et al., 2013	70	70	0	32	65.54	4.19	1025.96	2.08
23	8	Yukselen et al., 2013	21	21	0	9	19.55	1.31	291.52	2.09
25	18	Moed et al., 2013	29	29	0	30	60.97	3.90	953.45	1.50
28	29	Creticos et al., 2013	141	588	0	196	94.65	5.92	1513.58	2.28
30	31	Didier et al., 2013	79	280	0	155	88.27	5.51	1413.78	1.96
31	40	Hylander et al., 2013	7	7	0	8	16.88	1.13	251.01	1.43
35	60	Nayak et al., 2012	40	40	0	13	27.66	1.82	420.74	2.27
38	71	Klimek et al., 2012	32	40	0	10	17.44	1.16	262.78	2.40
39	75	Ahmadiafshar et al., 2012	10	10	0	10	21.00	1.40	315.98	1.52
40	77	Swamy et al., 2012	10	20	0	10	11.00	0.71	170.64	2.00
42	101	Shamji et al., 2012	166	166	0	55	111.66	7.07	1763.26	2.28
45	117	Didier et al., 2011	136	414	0	219	144.72	9.05	2314.35	1.99
49	140	Fujimura et al., 2011	51	51	0	37	75.27	4.79	1181.71	1.76
50	142	James et al., 2011	22	22	0	22	45.00	2.90	698.44	1.52
51	144	Riechelmann et al., 2010	66	66	0	74	148.88	9.40	2358.49	1.44
52	147	Nelson et al., 2011	55	213	0	225	117.22	7.29	1885.73	1.48
57	165	Yonekura et al., 2010	20	20	0	11	23.43	1.55	353.62	1.94
58	171	Makino et al., 2010	15	15	0	9	19.38	1.30	289.18	1.87
63	187	Campbell et al., 2010	17	17	0	15	31.11	2.03	476.68	1.61
68	204	Nieminen et al., 2010	20	20	0	10	21.48	1.43	322.42	2.00
69	206	Srivastava et al., 2009	61	61	0	38	77.37	4.93	1215.23	1.87
75	228	Pauli et al., 2008	99	99	0	35	71.64	4.57	1123.47	2.24
77	242	Panzner et al., 2008	24	41	0	30	36.17	2.29	572.12	1.75
79	249	Würtzen et al., 2008	21	21	0	21	43.00	2.77	666.52	1.52
80	252	Guimarães Junqueir de Queirós et al., 2008	58	58	0	15	31.73	2.07	485.65	2.39
82	259	Francis et al., 2008	12	12	0	6	13.46	0.93	195.01	1.98
83	267	Moreno-Ancillo et al., 2007	51	51	0	49	99.04	6.28	1561.73	1.55
84	270	de Blay et al., 2007	51	51	0	49	99.04	6.28	1561.73	1.55
92	283	Savolainen et al., 2007	20	20	0	10	21.48	1.43	322.42	2.00
93	288	Tahamiler et al., 2007	70	70	0	67	135.04	8.53	2137.21	1.55
96	306	Charpin et al., 2007	6	17	0	15	11.56	0.71	189.36	1.61
97	310	Chakraborty et al., 2006	10	18	0	17	19.89	1.26	315.22	1.56
100	315	Creticos et al., 2006	14	14	0	11	23.20	1.54	350.45	1.69
101	319	Savolainen et al., 2006	20	20	0	10	21.48	1.43	322.42	2.00
102	320	Valovirta et al., 2006	59	59	0	29	59.50	3.81	929.54	2.03

(*Continued*)

TABLE 3. Continued

Study number in the reference list of the meta-analysis[a]	Study number in total of 464 papers in Medline[b]	Study cited	Intervention group: immunotherapy		Control group: placebo			95% CI		
			Those showing recovery	Total	Those showing recovery	Total	RR	Lower	Upper	%Weight
103	321	Larsen et al., 2006	23	23	0	7	15.67	1.07	229.51	2.28
105	330	Passalacqua et al., 2006	28	28	0	28	57.00	3.65	890.05	1.52
106	343	Colás et al., 2006	41	41	0	19	39.52	2.56	610.36	2.06
107	344	Durham et al., 2006	204	705	0	150	87.48	5.48	1395.50	2.51
108	353	Frew et al., 2006	125	307	0	103	84.75	5.32	1350.40	2.28
111	370	Jutel et al., 2005	29	29	0	28	57.03	3.65	890.55	1.55
112	375	Ameal et al., 2005	29	29	0	28	57.03	3.65	890.55	1.55
113	384	Alvarez-Cuesta et al., 2005	25	25	0	28	56.88	3.64	888.35	1.44
114	386	Corrigan et al., 2005	36	77	0	77	73.00	4.56	1168.51	1.52
15	407	Polosa et al., 2004	15	15	0	15	31.00	2.02	475.12	1.52
119	411	Mirone et al., 2004	14	14	0	16	32.87	2.14	505.13	1.43
120	414	Crimi et al., 2004	15	15	0	15	31.00	2.02	475.12	1.52
122	421	Bufe et al., 2004	82	82	0	79	159.04	10.03	2520.76	1.55
123	422	Tonnel et al., 2004	15	15	0	17	34.88	2.26	537.12	1.43
124	424	van Neerven et al., 2004	21	21	0	21	43.00	2.77	666.52	1.52
125	428	TePas et al., 2004	12	12	0	11	23.08	1.53	348.79	1.58
126	432	Khinchi et al., 2004	39	39	0	19	39.50	2.56	610.00	2.03
127	435	Pajno et al., 2003	15	15	0	15	31.00	2.02	475.12	1.52
128	437	Wüthrich et al., 2003	10	10	0	10	21.00	1.40	315.98	1.52
132	451	Polosa et al., 2003	15	15	0	15	31.00	2.02	475.12	1.52
133	457	André et al., 2003	43	43	0	49	98.86	6.27	1559.06	1.42

[a]The numbers of studies in this column reflect study numbers in the reference list of this meta-analysis. All 56 studies were clinical and placebo-controlled; and exhibited a homogeneous distribution.
[b]The numbers of the studies refer to a total of 464 papers in Medline detected by searching with the key phrase "allergic rhinitis and immunotherapy and clinical study"; all papers were published between 2013 and 2003.
CI = confidence interval; RR = risk ratio.

SCIT to treat of seasonal AR[4] showed that the approach was efficacious, as revealed by reductions in seasonal symptoms and the need for rescue medication, compared with placebo. SLIT involves the regular self-administration and retention of allergen extract under the tongue for 1 to 2 minutes before the extract is swallowed. Recent systematic reviews with meta-analyses have demonstrated the efficacy of SLIT in children.[91,145] It is not yet clear from these studies whether SCIT and SLIT are of equivalent efficacy.

The aim of the present study was to conduct a meta-analysis on the effectiveness of allergen immunotherapy. A total of 56 homogeneous studies were included in the analysis. The inclusion criteria used to select articles were: (1) placebo-controlled clinical trials; (2) the use of immunotherapy; (3) participants and/or physicians were or were not blinded to immunotherapy or placebo assignment (single-blinding, double-blinding, or no-blinding studies); and (4) randomization or not of those in the immunotherapy and placebo groups.

Between 2003 and 2013, 114 placebo-controlled clinical trials were reported in Medline. Studies describing recovery rates in immunotherapy and placebo groups numbered 56. The distribution of such works was homogeneous (heterogeneity chi-squared = 16.11; df = 55; $p = 1.000$). The results of our meta-analysis suggest that the extent of recovery in the immunotherapy group was 53.671-fold greater than in the placebo group (M-H pooled RR = 53.671; 95% CI, 36.981 to 77.893; z = 20.96; $p < 0.001$).

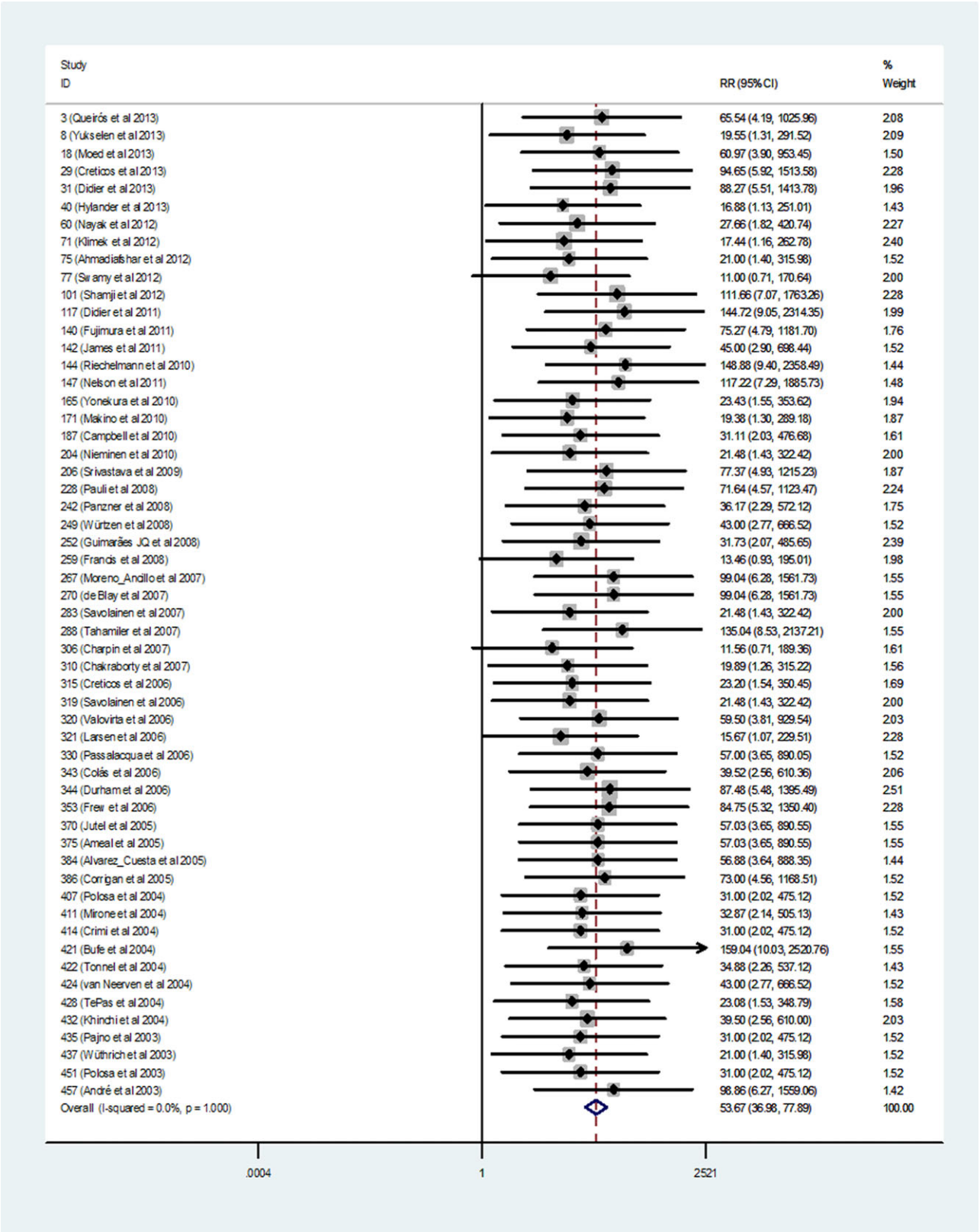

FIGURE 2. Forest plot. The central square on each horizontal line represents the RR for each study. The lines delimit the 95% CI intervals. The vertical line at an RR of 1 is the line of no effect. The [%weight] values indicate the influence exerted by each study on the pooled RR. The results of 56 studies are summarized in this figure. The reference numbers of the studies refer to a total of 464 papers in Medline detected by searching with the key phrase "allergic rhinitis and immunotherapy and clinical study"; all papers were published between 2003 and 2013. The meta-analysis numbers of the studies appear in Tables 1 and 2. All 56 studies were clinical and placebo-controlled; and exhibited a homogeneous distribution. RR = risk ratio; CI = confidence interval.

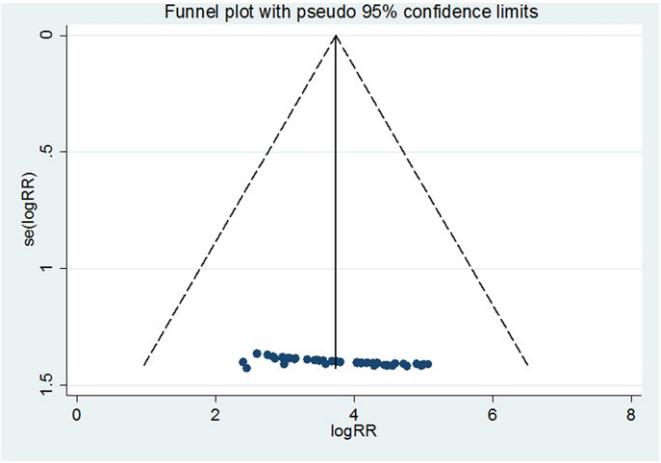

FIGURE 3. Funnel plot. The vertical solid line represents the logarithmic transformation of the overall estimated treatment effect (ie, the log [RR]). Diagonal dotted lines represent pseudo-95% confidence limits for estimated treatment effects, and the circles show the treatment effects of each of the 56 studies. The results of 56 studies are shown in this figure. The reference numbers of the studies refer to a total of 464 papers in Medline detected by searching with the key phrase "allergic rhinitis and immunotherapy and clinical study"; all papers were published between 2013 and 2003. The meta-analysis numbers of the studies appear in Tables 1 and 2. All 56 studies were clinical and placebo-controlled; and exhibited a homogeneous distribution. In the immunotherapy arms of the 56 studies, the mean number of the patients was 76.4 (minimum 7.0, maximum 705.0). RR = risk ratio.

When immunotherapy was applied, shortly after initiation of immunotherapy, an increase in the level of CD41-CD251 regulatory T lymphocytes secreting interleukin-10 (IL-10) and transforming growth factor β (TGF-β) is evident, associated with immunological tolerance, defined as a long-lived decrease in allergen-specific T-cell responsiveness.[82,137–141] Upon continued immunotherapy, the response wanes to some extent, and immune deviation from a T helper 2 (TH2) to a T helper 1 (TH1) cytokine response to the administered allergen comes into play (A).[136] Specific IgE levels initially increase and then gradually decrease. The levels of specific IgG1, IgG4, and IgA increase.[82,137–141]

Many controlled studies have shown that both SCIT and SLIT improve asthma symptoms in atopic asthmatic adults and children clinically sensitized to seasonal and perennial allergens.[146–148] Meta-analyses[149–151] of placebo-controlled trials in asthma patients suggest that small but significant improvements in symptoms and lung function develop upon active therapy, compared with placebo.

After 3 to 4 years of SCIT, no significant change in either symptom or medication score was evident during the subsequent 3 pollen seasons.[152] The data suggest that 3 years of grass pollen SCIT affords benefits that persist for a further 3 years after discontinuation, whereas any potential long-term benefit after discontinuation of SCIT using perennial allergens remains to be determined. SLIT may also have long-term effects. A double-blind, randomized, controlled trial of grass allergen tablet immunotherapy in adults with moderate/severe persistent seasonal AR showed that 3 years of treatment resulted in an approximately 30% reduction in symptoms and a 40% decrease in the use of antiallergic drugs; these reductions were maintained for 1 year after treatment cessation. A disease-modifying effect was also evident.[153]

SLIT is safer than SCIT, although severe [155]reactions may occur rarely.[154,155] SLIT is administered at home and patients should be educated on how to recognize and treat a reaction if it occurs. It is also important to explore the time course of severe reactions developing after immunotherapy.[155] SCIT is also safe when performed on selected individuals, in a specialist clinic with adequate facilities, by trained healthcare professionals. Patients treated with SCIT are at risk of both local and systemic adverse reactions but, in the vast majority of cases, the symptoms are readily reversible if they are recognized early and treated promptly. Some physicians may request that those considered at increased risk of serious systemic reactions outside of the office/medical clinic should carry injectable epinephrine.[155–162]

Because our results suggested that recovery in the immunotherapy group was greater than the placebo group, we recommend to use immunotherapy when needed. Both SCIT or SLIT are safe when performed on selected individuals.

Conclusion

Our meta-analysis showed that the extent of recovery in immunotherapy patients was 53.671-fold greater than that in placebo patients (M-H pooled RR = 53.671; 95% CI, 36.981 to 77.893; z = 20.96; $p < 0.001$).

Acknowledgments

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Appendix 1: Classification of recommendations and evidence[136]

Category of evidence

Ia. Evidence from meta-analysis of randomized controlled trials.
Ib. Evidence from at least 1 randomized controlled trial.
IIa. Evidence from at least 1 controlled study without randomization.
IIb. Evidence from at least 1 other type of quasi-experimental study.
III. Evidence from non-experimental descriptive studies, such as comparative studies.
IV. Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.
LB. Evidence from laboratory-based studies.
NR. Not rated.

Strength of recommendation

A. Directly based on category I evidence.
B. Directly based on category II evidence or extrapolated recommendation from category I evidence.
C. Directly based on category III evidence or extrapolated recommendation from category I or II evidence.
D. Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence.

Appendix 2: Revised grading system for recommendations in evidence-based guidelines

Levels of evidence

1++. High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
1+. Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias.
2++. High quality systematic reviews of case-control or cohort studies *or* High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+. Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2. Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3. Non-analytic studies, eg case reports, case series.
4. Expert opinion.

Grades of recommendations

A. At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or* A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
B. A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from studies rated as 1++ or 1+.
C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from studies rated as 2++.
D. Evidence level 3 or 4 *or* Extrapolated evidence from studies rated as 2+.

References

1. Walker SM, Durham SR, Till SJ, et al. British Society for Allergy and Clinical Immunology. Immunotherapy for allergic rhinitis. *Clin Exp Allergy*. 2011;41:1177–1200.
2. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011:S1–S55. Erratum in: *J Allergy Clin Immunol*. 2011;127:840.
3. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin Ther*. 2000;22:342–350.
4. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007;1:CD001936.
5. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010;8:CD001186.
6. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther*. 2000;22:329–341.
7. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003;4:CD001186.
8. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med*. 1995;151:969–974.
9. Hankin CS, Cox L, Lang D, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol*. 2010;104:79–85.
10. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol*. 2008;121:227–232.
11. Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc*. 2006;27:159–163.
12. Jacobsen L, Niggemann B, Dreborg S, 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.
13. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251–256.
14. Polosa R, Al-Delaimy WK, Russo C, et al. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir Res*. 2005;6:153.
15. Polosa R, Li Gotti F, Mangano G, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy*. 2004;59:1224–1228.
16. Jacobsen L, Nuchel Petersen B, Wihl JA, et al. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. *Allergy*. 1997;52:914–920.
17. Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. 2006;61:198–201.
18. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass polen immunotherapy in children. *Allergy*. 2002;57:306–312.
19. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. *Ann Allergy Asthma Immunol*. 2001;87:43–46.
20. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2001;87:47–55.
21. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol*. 2004;113:1129–1136.
22. Queirós MG, Silva DA, Siman IL, et al. Modulation of mucosal/systemic antibody response after sublingual immunotherapy in mite-allergic children. *Pediatr Allergy Immunol*. 2013;24:752–761.
23. Yukselen A, Kendirli SG, Yilmaz M, et al. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol*. 2013;31:233–241.
24. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. 2014;133:121–129.e2.
25. Moed H, Gerth van Wijk R, Hendriks RW, van der Wouden JC. Evaluation of clinical and immunological responses: a 2-year follow-up study in children with allergic rhinitis due to house dust mite. *Mediators Inflamm*. 2013;2013:345217.
26. Murphy K, Gawchik S, Bernstein D, Andersen J, Pedersen MR. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. *J Negat Results Biomed*. 2013;12:10.
27. Nolte H, Hébert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol*. 2013;110:450–456.e4.
28. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol*. 2013;131:1342–1349.e6.
29. Meyer W, Narkus A, Salapatek AM, Häfner D. Double-blind, placebo-controlled, dose-ranging study of new recombinant hypoallergenic Bet v 1

in an environmental exposure chamber. *Allergy*. 2013;68:724–731.

30. Didier A, Malling HJ, Worm M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2013;43:568–577.
31. 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;131:412–420.
32. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy*. 2013;43:242–248.
33. Bonvalet M, Moussu H, Wambre E, et al. Allergen-specific CD4+ T cell responses in peripheral blood do not predict the early onset of clinical efficacy during grass pollen sublingual immunotherapy. *Clin Exp Allergy*. 2012;42:1745–1755.
34. Cox LS, Casale TB, Nayak AS, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol*. 2012;130:1327–1334.e1.
35. Nayak AS, Atiee GJ, Dige E, et al. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. *Allergy Asthma Proc*. 2012;33:404–410. Erratum in: *Allergy Asthma Proc*. 2012;33:499.
36. Baron-Bodo V, Batard T, Nguyen H, et al. Absence of IgE neosensitization in house dust mite allergic patients following sublingual immunotherapy. *Clin Exp Allergy*. 2012;42:1510–1518.
37. Wahn U, Klimek L, Ploszczuk A, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 2012;130:886–893.e5.
38. Klimek L, Schendzielorz P, Pinol R, Pfaar O. Specific subcutaneous immunotherapy with recombinant grass pollen allergens: first randomized dose-ranging safety study. *Clin Exp Allergy*. 2012;42:936–945.
39. Ahmadiafshar A, Maarefvand M, Taymourzade B, et al. Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study. *Iran J Allergy Asthma Immunol*. 2012;11:175–181.
40. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol*. 2012;130:215–224.e7. Erratum in: *J Allergy Clin Immunol*. 2012;130:1224.
41. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717–725.e5.
42. Shamji MH, Ljørring C, Francis JN, et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. *Allergy*. 2012;67:217–226.
43. Valovirta E, Berstad AK, de Blic J, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther*. 2011;33:1537–1546.
44. Kuna P, Samolinski B, Worm M, et al. Sustained clinical efficacy of sublingual immunotherapy with a high-dose grass pollen extract. *Eur Ann Allergy Clin Immunol*. 2011;43:117–121.
45. Didier A, Worm M, Horak F, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol*. 2011;128:559–566.
46. Reich K, Gessner C, Kroker A, et al. Immunologic effects and tolerability profile of in-season initiation of a standardized-quality grass allergy immunotherapy tablet: a phase III, multicenter, randomized, double-blind, placebo-controlled trial in adults with grass pollen-induced rhinoconjunctivitis. *Clin Ther*. 2011;33:828–840.
47. Klimek L, Willers J, Hammann-Haenni A, et al. Assessment of clinical efficacy of CYT003-QbG10 in patients with allergic rhinoconjunctivitis: a phase IIb study. *Clin Exp Allergy*. 2011;41:1305–1312.
48. Panzner P, Petráš M, Sýkora T, et al. Both sublingual and supralingual routes of administration are effective in long-term allergen-specific immunotherapy. *Allergy Asthma Proc*. 2011;32:142–150.
49. Fujimura T, Yonekura S, Horiguchi S, et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clin Immunol*. 2011;139:65–74.
50. James LK, Shamji MH, Walker SM, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol*. 2011;127:509–516.e5.
51. Riechelmann H, Schmutzhard J, van der Werf JF, et al. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy*. 2010;24:e104-e109.
52. Nelson HS, Nolte H, Creticos P, et al. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol*. 2011;127:72–80.e2.
53. Blaiss M, Maloney J, Nolte H, et al. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol*. 2011;127:64–71.e4. Erratum in: *J Allergy Clin Immunol*. 2011;128:436.
54. Mösges R, Graute V, Christ H, et al. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol*. 2010;21:1135–1138.
55. Cortellini G, Spadolini I, Patella V, et al. Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2010;105:382–386.
56. Pfaar O, Barth C, Jaschke C, et al. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study. *Int Arch Allergy Immunol*. 2011;154:336–344.
57. Yonekura S, Okamoto Y, Sakurai D, et al. Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children. *Allergol Int*. 2010;59:381–388.
58. Makino Y, Noguchi E, Takahashi N, et al. Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2010;126:1163–1169.e5.
59. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol*. 2010;21:970–976.
60. Höiby AS, Strand V, Robinson DS, et al. Efficacy, safety, and immunological effects of a 2-year immunotherapy with Depigoid birch pollen extract: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. 2010;40:1062–1070.
61. Ciprandi G, Cadario G, Di Gioacchino GM, et al. Sublingual immunotherapy in children with allergic polysensitization. *Allergy Asthma Proc*. 2010;31:227–231.
62. Durham SR, Birk AO, Andersen JS. Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy*. 2011;66:120–123.
63. Campbell JD, Buchmann P, Kesting S, et al. Allergen-specific T cell responses to immunotherapy monitored by CD154 and intracellular cytokine expression. *Clin Exp Allergy*. 2010;40:1025–1035.
64. Gallego MT, Iraola V, Himly M, et al. Depigmented and polymerised house dust mite allergoid: allergen content, induction of IgG4 and clinical response. *Int Arch Allergy Immunol*. 2010;153:61–69.
65. Ceuppens JL, Bullens D, Kleinjans H, et al. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects. *Clin Exp Allergy*. 2009;39:1903–1909. Erratum in: *Clin Exp Allergy*. 2012;42:1543.
66. Kamin W, Kopp MV, Erdnuess F, et al. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol*. 2010;21:e160-e165.
67. O'Hehir RE, Gardner LM, de Leon MP, et al. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional regulatory T cells. *Am J Respir Crit Care Med*. 2009;180:936–947.
68. Nieminen K, Valovirta E, Savolainen J. Clinical outcome and IL-17, IL-23, IL-27 and FOXP3 expression in peripheral blood mononuclear cells of pollen-allergic children during sublingual immunotherapy. *Pediatr Allergy Immunol*. 2010;21:e174-e184.
69. Srivastava D, Singh BP, Arora N, Gaur SN. Clinico-immunologic study on immunotherapy with mixed and single insect allergens. *J Clin Immunol*. 2009;29:665–673.
70. Ventura MT, Carretta A, Tummolo RA, et al. Clinical data and inflammation parameters in patients with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy. *Int J Immunopathol Pharmacol*. 2009;22:403–413.
71. Tsai JJ, Liao EC, Tsai FH, et al. The effect of local nasal immunotherapy in allergic rhinitis: using strips of the allergen *Dermatophagoides pteronyssinus*. *J Asthma*. 2009;46:165–170.
72. Malling HJ, Montagut A, Melac M, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2009;39:387–393.
73. Tseng SH, Fu LS, Nong BR, et al. Changes in serum specific IgG4 and IgG4/ IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. *Asian Pac J Allergy Immunol*. 2008;26:105–112.
74. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2009;123:160–166.e3.
75. Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2008;122:951–960. Erratum in: *J Allergy Clin Immunol*. 2009;123:166.
76. Röder E, Berger MY, de Groot H, et al. Sublingual immunotherapy in youngsters: adherence in a randomized clinical trial. *Clin Exp Allergy*. 2008;38:1659–1667.
77. Panzner P, Petrás M, Sýkora T, Lesná I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med*. 2008;102:1296–1304.
78. Purohit A, Niederberger V, Kronqvist M, et al. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy*. 2008;38:1514–1525.
79. Würtzen PA, Lund G, Lund K, et al. A double-blind placebo-controlled birch allergy vaccination study II: correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation. *Clin Exp Allergy*. 2008;38:1290–1301.
80. Guimarães Junqueir de Queirós M, Oliveira Silva DA, Alves R, et al. Mite-specific immunotherapy using allergen and/or bacterial extracts in atopic patients in Brazil. *J Investig Allergol Clin Immunol*. 2008;18:84–92.
81. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2008;100:256–263.
82. Francis JN, James LK, Paraskevopoulos G, et al. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. *J Allergy Clin Immunol*. 2008;121:1120–1125.e2.
83. Moreno-Ancillo A, Moreno C, Ojeda P, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without updosing. *J Investig Allergol Clin Immunol*. 2007;17:399–405.
84. de Blay F, Barnig C, Kanny G, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol*. 2007;99:453–461.
85. Didier A, Malling HJ, Worm M, 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.
86. Srivastava D, Singh BP, Sudha VT, et al. Immunotherapy with mosquito (*Culex quinquefasciatus*) extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol*. 2007;99:273–280.
87. Powell RJ, Frew AJ, Corrigan CJ, Durham SR. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy*. 2007;62:1335–1338.

88. Kopp MV, Stenglein S, Kamin W, et al. Omalizumab (Xolair) in children with seasonal allergic rhinitis: leukotriene release as a potential in vitro parameter to monitor therapeutic effects. *Pediatr Allergy Immunol*. 2007;18:523–527.
89. Ibañez MD, Kaiser F, Knecht R, et al. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol*. 2007;18:516–522.
90. Klunker S, Saggar LR, Seyfert-Margolis V, et al. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol*. 2007;120:688–695.
91. Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy*. 2007;62:958–961.
92. Savolainen J, Nieminen K, Laaksonen K, et al. Allergen-induced in vitro expression of IL-18, SLAM and GATA-3 mRNA in PBMC during sublingual immunotherapy. *Allergy*. 2007;62:949–953.
93. Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope*. 2007;117:965–969.
94. Williams A, Henzgen M, Rajakulasingam K. Additional benefit of a third year of specific grass pollen allergoid immunotherapy in patients with seasonal allergic rhinitis. *Eur Ann Allergy Clin Immunol*. 2007;39:123–126.
95. Worm M. Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. *Eur Ann Allergy Clin Immunol*. 2006;38:355–360.
96. Charpin D, Gouitaa M, Dron-Gonzalvez M, et al. Immunotherapy with an aluminum hydroxide-adsorbed *Juniperus ashei* foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol*. 2007;143:83–91.
97. Chakraborty P, Roy I, Chatterjee S, et al. *Phoenix sylvestris* Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. *J Investig Allergol Clin Immunol*. 2006;16:377–384.
98. Vervloet D, Birnbaum J, Laurent P, et al. Safety and efficacy of *Juniperus ashei* sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol*. 2007;142:239–246.
99. Palma-Carlos AG, Santos AS, Branco-Ferreira M, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. *Allergol Immunopathol (Madr)*. 2006;34:194–198.
100. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. 2006;355:1445–1455.
101. Savolainen J, Jacobsen L, Valovirta E. Sublingual immunotherapy in children modulates allergen-induced in vitro expression of cytokine mRNA in PBMC. *Allergy*. 2006;61:1184–1190.
102. Valovirta E, Jacobsen L, Ljørring C, et al. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy*. 2006;61:1177–1183.
103. Larsen TH, Poulsen LK, Melac M, et al. Safety and tolerability of grass pollen tablets in sublingual immunotherapy—a phase-1 study. *Allergy*. 2006;61:1173–1176.
104. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118:434–440.
105. Passalacqua G, Pasquali M, Ariano R, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy*. 2006;61:849–854.
106. Colás C, Monzón S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol*. 2006;117:810–816.
107. Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;117:802–809.
108. Frew AJ, Powell RJ, Corrigan CJ, et al. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;117:319–325.
109. Dokic D, Schnitker J, Narkus A, et al. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Prilozi*. 2005;26:113–129.
110. Marcucci F, Sensi L, Di Cara G, et al. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sublingual immunotherapy. *Pediatr Allergy Immunol*. 2005;16:519–526. Erratum in: *Pediatr Allergy Immunol*. 2006;17:318.
111. Jutel M, Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol*. 2005;116:608–613.
112. Ameal A, Vega-Chicote JM, Fernández S, et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of *Dermatophagoides pteronyssinus* in allergic asthma. *Allergy*. 2005;60:1178–1183.
113. Alvarez-Cuesta E, Aragoneses-Gilsanz E, Martín-Garcia C, et al. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy*. 2005;35:572–578. Erratum in: *Clin Exp Allergy*. 2005;35:1504.
114. Corrigan CJ, Kettner J, Doemer C, et al. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy*. 2005;60:801–807.
115. Bodtger U, Malling HJ, Poulsen LK. Out-of-season recollection of drug use for seasonal IgE-mediated rhinitis: useful but an overestimation. *J Allergy Clin Immunol*. 2005;115:786–790.
116. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2004;93:425–430.
117. Rolinck-Werninghaus C, Wolf H, Liebke C, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy*. 2004;59:1285–1293.
118. Smith H, White P, Annila I, et al. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2004;114:831–837.
119. Mirone C, Albert F, Tosi A, et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy*. 2004;34:1408–1414.
120. Crimi N, Li Gotti F, Mangano G, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect on bronchial hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int*. 2004;19:98–108.
121. Bez C, Schubert R, Kopp M, et al. Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2004;34:1079–1085.
122. Bufe A, Ziegler-Kirbach E, Stoeckmann E, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy*. 2004;59:498–504.
123. Tonnel AB, Scherpereel A, Douay B, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy*. 2004;59:491–497.
124. van Neerven RJ, Arvidsson M, Ipsen H, et al. A double-blind, placebo-controlled birch allergy vaccination study: inhibition of CD23-mediated serum-immunoglobulin E-facilitated allergen presentation. *Clin Exp Allergy*. 2004;34:420–428.
125. TePas EC, Hoyte EG, McIntire JJ, Umetsu DT. Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals. *Ann Allergy Asthma Immunol*. 2004;92:25–31.
126. Khinchi MS, Poulsen LK, Carat F, et al. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy*. 2004;59:45–53.
127. Pajno GB, Vita D, Parmiani S, et al. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy*. 2003;33:1641–1647.
128. Wüthrich B, Bucher Ch, Jörg W, et al. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol*. 2003;13:145–148.
129. Ascione E, De Lucia A, Imperiali M, et al. Nasal application of immunotherapy. *Chem Immunol Allergy*. 2003;82:89–98.
130. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy*. 2003;33:1076–1082.
131. Radcliffe MJ, Lewith GT, Turner RG, et al. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ*. 2003;327:251–254.
132. Polosa R, Li Gotti F, Mangano G, et al. Monitoring of seasonal variability in bronchial hyperresponsiveness and sputum cell counts in non-asthmatic subjects with rhinitis and effect of specific immunotherapy. *Clin Exp Allergy*. 2003;33:873–881.
133. André C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol*. 2003;131:111–118.
134. Bodtger U, Poulsen LK, Malling HJ. Retrospective assessment of seasonal allergic symptoms: overrating but useful. *Clin Exp Allergy*. 2003;33:496–500.
135. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. *Lancet*. 1999;354:1896–1900.
136. Varney VA, Edwards J, Tabbah K, et al. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo controlled trial. *Clin Exp Allergy*. 1997;27:860–867.
137. Bellinghausen I, Metz G, Enk AH, et al. Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. *Eur J Immunol*. 1997;27:1131–1139.
138. Blaser K, Akdis CA. Interleukin-10, T regulatory cells and specific allergy treatment. *Clin Exp Allergy*. 2004;34:328–331.
139. Francis JN, Till SJ, Durham SR. Induction of IL-101CD41CD251 T cells by grass pollen immunotherapy. *J Allergy Clin Immunol*. 2003;111:1255–1261.
140. Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol*. 2003;33:1205–1214.
141. Savolainen J, Laaksonen K, Rantio-Lehtimaki A, Terho EO. Increased expression of allergen-induced in vitro interleukin-10 and interleukin-18 mRNA in peripheral blood mononuclear cells of allergic rhinitis patients after specific immunotherapy. *Clin Exp Allergy*. 2004;34:413–419.
142. 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*. 2004;172:3252–3259.
143. Niederberger V, Horak F, Vrtala S, et al. Vaccination with genetically engineered allergens prevents progression of allergic disease. *Proc Natl Acad Sci U S A*. 2004;101(Suppl 2):14677–14682.
144. Pilette C, Nouri-Aria KT, Jacobson MR, et al. Grass pollen immunotherapy induces an allergen-specific IgA2 response associated with mucosal TGF-β expression. *J Immunol*. 2007;178:4658–4666.
145. 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*. 2006;97:141–148.
146. Bousquet J, Hejjaoui A, Michel FB. Specific immunotherapy in asthma. *J Allergy Clin Immunol*. 1990;86:292–305.

147. 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*. 1997;7:90–97.
148. Peroni DG, Piacentini GL, Martinati LC, et al. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. *Allergy*. 1995;50:925–930.
149. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Investig Allergol Clin Immunol*. 2005;15:9–16.
150. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy*. 2006;61:1162–1172.
151. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy*. 1999;54:1022–1041.
152. Des Roches A., Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy*. 1996;51:430–433.
153. Durham SR, Emminger W, Kapp A, 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.e7.
154. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy*. 2008;63:374.
155. Lombardi C, Gargioni S, Cottini M, et al. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy*. 2008;63:375–376.
156. Andre C, Fadel R. Anaphylaxis caused by allergen sublingual immunotherapy? *Allergy*. 2007;62:1220–1221.
157. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy*. 2006;61:1235.
158. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy*. 2007;62:567–568.
159. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy*. 2009;64:963–964.
160. Gidaro GB, Marcucci F, Sensi L, et al. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy*. 2005;35:565–571.
161. Cox LS, Larenas LD, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol*. 2006;117:1021–1035.
162. Passalacqua G, Pawankar R, Baena-Cagnani CE, Canonica GW. Sublingual immunotherapy: where do we stand? Present and future. *Curr Opin Allergy Clin Immunol*. 2009;9:1–3.