

Subcutaneous immunotherapy for allergic rhinitis: an evidence based review of the recent literature with recommendations

Michael T. Purkey, MD¹, Timothy L. Smith, MD, MPH, FACS², Berrylin J. Ferguson, MD³, Amber Luong, MD, PhD⁴, William R. Reisacher, MD⁵, Harold C. Pillsbury III, MD, FACS⁶ and Elina Toskala, MD, PhD^{7,8}

Background: Allergic rhinitis is a common allergic disease with increasing prevalence in Western Societies. Medical therapy is first line treatment, and is aimed at reducing symptoms of immunoglobulin E (IgE)-mediated inflammation of the nasal passages. In patients with disease refractory to medical therapy, subcutaneous immunotherapy is an option. The aim of this study is to update a recent Cochrane review with available level 1 evidence for seasonal and perennial allergic rhinitis.

Methods: A systematic review of the literature was performed from 2006 to 2011 and compared with data from a 2007 Cochrane review on immunotherapy for seasonal allergic rhinitis. We included all studies of level 1 evidence. All forms of single extract immunotherapy were considered. Studies with primary asthma related end-points were excluded. Primary end-points were instruments of clinical efficacy (ie, symptom-medication scores) and adverse events.

Results: We retrieved 12 level 1 studies for review. In total, 1512 patients were randomized into treatment groups, alternative study groups (alternative duration of therapy or sublingual immunotherapy [SLIT]), or placebo. Efficacy was evaluated based on reported symptom and/or medication score, validated quality of life instruments,

immunological assays, challenge testing, and adverse events.

Conclusion: Subcutaneous immunotherapy improves symptom and/or medication scores and validated quality of life measures. In addition, associated changes in surrogate markers of immunologic protection are observed. Subcutaneous immunotherapy is safe when administered to carefully selected patients and in settings capable of responding to systemic reactions. Subcutaneous immunotherapy is recommended for patients with seasonal or perennial allergic rhinitis not responsive to conservative medical therapy, and whose symptoms significantly affect quality of life. © 2013 ARS-AAOA, LLC.

Key Words:

subcutaneous immunotherapy; allergic rhinitis; allergen administration and dosage; desensitization; adverse effects; immunology; pollen; randomized controlled trials; seasonal therapy

How to Cite this Article:

Purkey MT, Smith TL, Ferguson BJ, et al. Subcutaneous immunotherapy for allergic rhinitis: an evidence based review of the recent literature with recommendations. *Int Forum Allergy Rhinol*, 2013; 3:519-531.

Allergic rhinitis (AR) is a common condition characterized by immunoglobulin E (IgE)-mediated inflammation of the nasal passages, with subsequent symptoms of

sneezing, nasal congestion, and rhinorrhea. AR is believed to affect up to 40% of children and up to 30% of adults in the United States.¹ The incidence of AR appears to be increasing, especially in Western societies.² The morbidity of this condition is significant, and affected individuals report

¹Department of Otorhinolaryngology, University of Pennsylvania, Philadelphia, PA; ²Department of Otolaryngology, Oregon Health and Science University, Portland, OR; ³Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA; ⁴Department of Otorhinolaryngology, University of Texas Medical School, Houston, TX; ⁵Department of Otolaryngology-Head and Neck Surgery, Weill Cornell Medical College, New York, NY; ⁶Department of Otolaryngology-Head and Neck Surgery, University of North Carolina, Chapel Hill, NC; ⁷Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA; ⁸Department of Otolaryngology-Head and Neck Surgery, Temple University, Philadelphia, PA

Correspondence to: Michael Purkey, MD, Hospital of the University of Pennsylvania, Department of Otorhinolaryngology, 3400 Spruce St, Philadelphia, PA 19104; e-mail: michael.purkey@uphs.upenn.edu

Potential conflict of interest: None provided.

Received: 12 June 2011; Revised: 22 October 2012; Accepted: 1 November 2012

DOI: 10.1002/alr.21141

View this article online at wileyonlinelibrary.com.

reduction in quality of life measures. In addition, there is a well-documented financial burden to society.³

AR is traditionally classified into 2 different groups: seasonal AR and perennial AR. Seasonal AR or “hay fever” is an IgE-mediated allergic reaction caused by airborne pollens, especially from grasses, trees, weeds, and outdoor molds that demonstrate seasonal and geographic variation due to the presence of environmental allergen. Perennial AR is also an IgE-mediated allergic reaction that is usually caused by domestic allergens such as house dust mites (HDM), animal dander, and indoor molds. Initial treatment of AR is variable and traditionally involves lifestyle changes that prevent antigen exposure, in addition to the combination of medications such as oral antihistamines and intranasal corticosteroids.⁴ Other treatments used include oral or topical decongestants, leukotriene receptor antagonists, cromolyn, and intranasal antihistamines, which are used in specific clinical situations.⁴

Immunotherapy is reserved for patients with moderate to severe AR who do not respond to allergen avoidance and/or medications and who have had significant symptoms greatly affecting their quality of life. Not all sufferers of AR are suitable candidates for immunotherapy. Up to 38% of patients with AR also suffer from asthma,⁵ and this group in particular, has been shown to have a high incidence of adverse reactions related to immunotherapy administration.^{6,7} In properly managed patients with both AR and asthma, however, immunotherapy has been shown to decrease asthma symptoms especially during pollen seasons and to decrease the need for rescue medication and emergency room visits.

Immunotherapy can be delivered in multiple forms: injection or subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), nasal or oral administration.⁸ SCIT delivery strategies usually consist of an escalating series of injections of isolated or mixed allergen extract, given every 1 to 2 weeks to a highest concentration of antigens, known as the maintenance concentration, which is usually given for at least 2 to 3 years.⁹ Variations of this strategy include rush and cluster dosing, which allow clinicians to achieve maintenance dosing in a shorter amount of time.

The mechanism of immunotherapy has been postulated to be related to an effect on T lymphocytes that modulate production of IgE in the presence of antigen, causing a switch from a T helper 2 (Th2) response to a Th1 response. This change results in higher levels of IgG antibodies and reduction of IgE antibodies—the latter responsible for initiating local inflammation and producing the symptoms of allergic disease.

The efficacy and safety of SCIT in sufferers of AR was studied in a 2007 Cochrane Review by Calderon et al.,¹⁰ and was found to significantly reduce symptom and medication scores in suitably selected candidates with minimal adverse events. The purpose of this study will be to update all available level 1 evidence for SCIT in the treatment of AR, summarize the available literature from 2006 to 2011 related to clinical efficacy and safety, and provide up to date information regarding practice of subcutaneous

immunotherapy for the otolaryngologist in the United States.

Methods

As in prior evidence based reviews and recommendations published in the *International Forum of Allergy & Rhinology*,^{11,12} we followed The Clinical Practice Guideline Manual¹³ Conference on Guideline Standardization (COGS),¹⁴ and the Appraisal of Guidelines and Research Evaluation (AGREE) instrument¹⁵ recommendations to improve quality, transparency, and efficient reporting of results in this review. We required studies in this review to have documented objective evidence of AR by positive skin test or elevated levels of allergen-specific IgE on in vitro testing, in addition to clinically significant AR symptoms.

The primary focus of our review was on SCIT for the treatment of AR. We excluded studies whose primary endpoints were asthma-related outcomes. We considered all randomized, double-blind, controlled studies (Level 1b evidence). All forms of single extract immunotherapy were considered, where multiple high doses were administered with no exclusion criteria for rush or cluster induction dosing.

A systematic review of the literature was performed using Medline, and EMBASE from January 2006 to December 2011. A screening literature search was performed to identify randomized studies using the following independent search criteria: (1) MeSH terms: rhinitis, allergic, seasonal/therapy, immunotherapy, immunomodulation, allergens [ad] [im][tu], desensitization, immunologic; and (2) general search phrases: SCIT, allergic, rhinitis, seasonal, hay fever, pollen, SAR, allerg*, season, spring, summer, grass*, birch, ragweed, tree*, and weed*. Included studies were screened against available literature references.

Studies were evaluated and level of evidence was applied based on reported research methodology.¹⁶ After quality evaluation for each study was performed, a summary was produced which includes the aggregate grade of evidence and recommendations based on the American Academy of Pediatrics guidelines.¹⁷ Two authors reviewed the literature (M.T.P. and E.T) and produced the initial manuscript following previously published iterative review guidelines.¹¹ Data was reviewed and debated until a consensus was achieved for validity of evidence related to efficacy and safety. The five remaining authors were responsible for reviewing subsequent iterations of the manuscript, analyzing outcome data, and providing clinical recommendations. Finally, implications of these data and recommendations for clinical use were debated and formulated with consideration of the quality of evidence in addition to the comparison of benefit vs harm. When the level of evidence allowed, clinical recommendations were suggested. Level of bias was assessed and all studies demonstrated a “low risk of bias,” as determined by adequate reporting with respect to concealment allocation, attrition, and detection bias.¹⁰

Primary outcome data for most studies were continuous variables related to symptom or medication use scores. These scales were variable and most frequently employed a system of subject quantification of nasal, ocular, and/or chest symptoms recorded on a daily basis and averaged over a study period. The use of rescue medications (oral antihistamines, nasal sprays, or topical ocular agents) was used frequently. Quality of life measures were used as a primary or secondary end-point in some studies and reviewed as available. Adverse reactions were divided between local and systemic, severity quantified as data permitted, and comorbidities identified when available in an attempt to determine risk factors for severe reactions. Data from 2006 through 2011 was analyzed to supplement the 2007 Cochrane Review of SCIT.¹⁰

Results

There were 12 studies that met inclusion criteria for review (Table 1). Primary outcome evaluations were mostly in the form of symptom scores, medication scores, or a combined symptom medication score. One study used the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) instrument¹⁸ as a primary end-point. Multiple secondary end-points were reported and those included in this analysis were RQLQ evaluations, immunoglobulin assays, challenge tests, and adverse events.

Symptom score or medication score

Three randomized studies assessed primary intervention response with a symptom or medication score alone (Table 2).

Charpin et al.¹⁹ (2007) published a study of 40 patients comparing SCIT using an aluminum adsorbed *Juniperus ashei* extract in patients with allergic rhinoconjunctivitis due to European cypress pollens with placebo to investigate the concept of SCIT treatment with major allergen challenge. A statistically significant improvement in conjunctivitis symptoms (41%, $p < 0.02$) was observed in the first pollen season following therapy. A significant improvement in rhinitis symptoms was also observed in the second season after SCIT (63%, $p < 0.01$). This study also independently analyzed medication scores. Patients were given the same rescue medications and scores were calculated based on the following formula: medication score = $2 \times$ number of cetirizine (10 mg) tablets + $4.5 \times$ number of prednisolone (5 mg) tablets + $1 \times$ number of drops of levocastastine per eye. The total medication score was decreased in the treatment group when compared with placebo. Median values were reduced 49% and 25% in the first and second pollen season, respectively, after initiation of treatment. These results, however, did not reach statistical significance.

Francis et al.²⁰ (2008) studied 18 patients with severe seasonal AR utilizing grass pollen immunotherapy and observed a significant decrease in symptom scores. Mean

scores were 2.42 ± 0.22 for the treatment group and 1.50 ± 0.34 for placebo ($p < 0.05$).

Tahamiler et al.²¹ (2008) performed a study in 193 patients randomized to SCIT ($n \times 96$) or SLIT ($n \times 97$) for treatment of HDM allergy.

Combined symptom-medication score

Seven studies met criteria for inclusion of use of Symptom-Medication Score (SMS) as a primary endpoint for efficacy evaluation (Table 3).

Ceuppens et al.²² (2009) analyzed results from 58 patients receiving glutaraldehyde-modified aluminum hydroxide-adsorbed birch pollen extract to examine the efficacy and safety of these newly available compounds. A combined score was calculated based on a previously published index.²³ There was no difference in SMS between treatment and placebo groups in the first pollen season. In the second season, however, the treatment group experienced a 23% reduction in SMS that approached statistical significance ($p = 0.055$). Further, when the lower airway data was removed and analysis was of only nasal/eye symptoms there was a 32% reduction in SMS that did reach significance ($p < 0.04$).

Riechelmann et al.²⁴ (2010) similarly used the SMS proposed by Bufe et al.²³ to analyze the efficacy of SCIT using glutaraldehyde-modified aluminum hydroxide-adsorbed extract of HDM antigen. Results in this study of 140 patients demonstrated reduced SMS (mean $\pm$ SD) in the treatment group when compared to controls (1.046 ± 0.93 , 0.785 ± 0.69 , $p = 0.048$). Again, the lower airway score was excluded and data from nasal and ocular symptoms also showed improvement in the treatment group that met significance (1.06 ± 0.68 , 0.79 ± 0.70 , $p = 0.039$).

Tabar et al.²⁵ (2011) performed a study in 2011 examining the efficacy of SCIT to HDM allergen in patients treated for 3 or 5 years to examine effect of duration of therapy. Efficacy was analyzed by using a rhinitis severity score proposed by Meltzer. Patients receiving SCIT for HDM allergy for 3 years had reduced rhinitis scores at 3- and 5- year time points (44% and 48%, $p < 0.001$). Patients receiving SCIT for 5 years had reduced rhinitis scores at 3 years and a further reduction in scores at 5 years that reached statistical significance (50%, 69%, $p < 0.001$).

Mauro et al.²⁶ (2007) performed a randomized study comparing SMS for patients receiving SCIT and SLIT for treatment of birch pollinosis. A total of 34 patients (19 SCIT, 14 SLIT) completed the study and there was no difference between SMS between the groups.

Williams et al.²⁷ (2007) performed a follow-up of a 2005 study (Corrigan) examining clinical efficacy of a third year of treatment with aluminum-adsorbed grass pollen SCIT. Findings of the original study demonstrated improved SMS between active and treatment groups at 1 year (26.6%, $p < 0.026$) and 2 years (48.4%, $p < 0.018$). Findings from the 2007 demonstrated further reduction in SMS with a third year of treatment.

TABLE 1. Study summary of the reviewed articles (primary and secondary end-points)

Study	Year	Study design	LOE	Subjects (n)	Study groups	Primary end-point	Secondary end-point
Charpin et al. ¹⁹	2007	RCT	1b	40	1) <i>J. ashei</i> extract AIOH adsorbed IT; 2) placebo	Symptoms score; medication score	Adverse events; NPT; S-IgG and IgE
Mauro et al. ²⁶	2007	RCT	1b	47	1) Birch pollen SCIT: not placebo controlled; 2) birch pollen SLIT	Combined SMS	Adverse events; S-IgG and IgE
Powell et al. ³⁰	2007	RCT	1b	410	1) Grass pollen Alutard SQ maintenance: 100,000 SQ-U; 2) Alutard SQ maintenance: 10,000 SQ-U; 3) Placebo	RQLQ	None
Williams et al. ²⁷	2007	RCT	1b	61	1) Grass pollen allergoid adsorbed to AIOH; 2) placebo	Combined SMS	RQLQ; S-IgG
Tahamiler et al. ²¹	2008	RCT	1b	193	1) House dust mite sublingual IT; 2) House dust mite subcutaneous IT	Symptom score	SPT; NPT
Francis et al. ²⁰	2008	RCT	1b	18	1) Grass pollen extract AIOH adsorbed IT; 2) placebo	Symptom score	Adverse events; SPT; IL production; S-IgG and IgA; IgE response assay
Ceuppens et al. ²²	2009	RCT	1b	62	1) Gluteraldehyde modified birch pollen extract AIOH adsorbed; 2) placebo	Combined SMS	Adverse events; SPT; S-IgG and IgE; Bet v1 basophil activation
Martínez-Cócera et al. ³¹	2010	RCT	1b	46	1) <i>P. preatense</i> extract IT; 2) placebo	S-IgG and IgE	Intradermal skin testing
Höiby et al. ²⁹	2010	RCT	1b	61	1) Depigmented polymerized birch pollen IT; 2) placebo	Combined SMS	Adverse events; S-IgG and IgE; IL production
Riechelmann et al. ²⁴	2010	RCT	1b	140	1) Gluteraldehyde modified house dust mite IT; 2) placebo	Combined SMS	Adverse events; CPT; RQLQ; S-IgG and IgE
Tabar et al. ²⁵	2011	RCT	1b	239	1) House dust mite extract IT × 5 years; 2) house dust mite extract IT × 3 years	Symptom score; medication score	Adverse events; RQLQ; SPT; S-IgG
Pfaar et al. ²⁸	2011	RCT	1b	195	1) Depigmented polymerized grass pollen IT-preseasonal rush schedule; 2) placebo	Combined SMS	Adverse events; RQLQ; S-IgG and IgE

Bet v 1 = major birch allergen; CPT = conjunctival provocation test; IgE = immunoglobulin E; IL = interleukin; IT = immunotherapy; LOE = level of evidence; NPT = nasal provocation test; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; S-IgG = serum immunoglobulin G; SLIT = sublingual immunotherapy; SMS = symptom-medication score; SPT = skin prick test; SQ = subcutaneous; SQ-U = standardized quality units.

TABLE 2. Summary of symptom or medication score studies

Study	Treatment	Conclusion
Charpin et al. ¹⁹ (2007)	Aluminum hydroxide adsorbed <i>J. ashei</i> extract in patients with European cypress allergy	Aluminum adsorbed <i>J. ashei</i> SCIT in patients with allergies to European cypress pollens successfully reduces symptoms scores.
Francis et al. ²⁰ (2008)	Aluminum adsorbed grass pollen SCIT	Grass pollen SCIT reduces symptoms scores in allergic patients.
Tahamiler et al. ²¹ (2008)	HDM SCIT vs SLIT	SCIT may more effectively reduce symptoms scores in house dust mite allergic patients than SLIT

HDM = house dust mites; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

TABLE 3. Summary of SMS studies

Study	Treatment	Conclusion
Mauro et al. ²⁶ (2007)	Birch pollen SCIT vs SLIT	No difference in SMS between SCIT and SLIT
Williams et al. ²⁷ (2007)	Aluminum adsorbed grass pollen SCIT for additional 3rd year	Treatment with one additional year of SCIT improves SMS when compared to 2 years of therapy
Ceuppens et al. ²² (2009)	Glutaraldehyde-modified aluminum hydroxide adsorbed birch pollen vs Placebo	Modified birch pollen SCIT lowers nasal/eye SMS in the second year of treatment
Höiby et al. ²⁹ (2010)	Depigmented polymerized birch pollen extract SCIT	Modified birch pollen SCIT reduces SMS at 18 months follow up
Riechelmann et al. ²⁴ (2010)	Glutaraldehyde-modified aluminum hydroxide adsorbed HDM vs Placebo	Modified HDM SCIT improves SMS
Pfaar et al. ²⁸ (2011)	Pre-seasonal rush SCIT with depigmented polymerized mixed grass pollen	Rush SCIT with modified mixed grass pollen reduces SMS at 2 years follow up
Tabar et al. ²⁵ (2011)	HDM SCIT × 3 years vs HDM SCIT × 5 years	Treatment with 2 additional years of HDM SCIT improves SMS when compared to 3 years of therapy

HDM = house dust mites; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SMS = symptom-medication score.

Pfaar et al.²⁸ (2011) examined 195 patients treated with preseasonal rush SCIT with a depigmented polymerized mixed grass pollen extract over 2 years. Results show reduction of median SMS [interquartile range] at year 2 for the

TABLE 4. Summary of RQLQ studies

Study	Treatment	Conclusion
Powell et al. ³⁰ (2007)	Grass pollen SCIT (100,000 and 10,000 SQ-U) vs placebo	High-dose grass pollen SCIT is more effective in improving RQLQ
Riechelmann et al. ²⁴ (2010)	Glutaraldehyde-modified aluminum hydroxide adsorbed HDM vs placebo	Modified HDM improves RQLQ at 1-year follow-up
Pfaar et al. ²⁸ (2011)	Preseasonal rush SCIT with depigmented polymerized mixed grass pollen	Rush modified grass pollen SCIT improves RQLQ at 1-year follow-up
Tabar et al. ²⁵ (2011)	HDM SCIT × 3 years vs HDM SCIT × 5 years	HDM SCIT improves RQLQ in both 3- and 5-year treatment groups

HDM = house dust mites; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SQ-U = standardized quality units.

treatment group (3.93 [0.77–6.27]), compared to placebo (5.86 [3.11–8.36], $p < 0.01$).

Höiby et al.²⁹ (2010) examined 61 patients receiving SCIT with a depigmented polymerized birch pollen extract. The 18-month median SMS of the treatment group was reduced when compared to placebo (8.0, 12.6, $p = 0.004$).

Rhinoconjunctivitis quality of life questionnaire

Four studies analyzed efficacy of treatment using the RQLQ evaluation tool (Table 4) (Juniper and Guyatt¹⁸ [1991]).

Powell et al.³⁰ (2007) performed a large study of 410 patients using 2 specific doses (100,000 standardized quality units [SQ-U] and 10,000 SQ-U) of grass pollen SCIT compared with placebo. All domains across the RQLQ were improved with the 100,000 SQ-U dosing when compared to placebo ($p < 0.002$), but only 2 of 7 domain scores (ocular symptoms and emotional function) improved significantly ($p < 0.0001$ and $p = 0.02$, respectively) when comparing the 10,000 SQ-U dose to placebo. When comparing the treatment arms, 4 of 7 domain scores (activities, non-nose/eye symptoms, practical problems, and nasal symptoms) were improved in the 100,000 SQ-U group compared to 10,000 SQ-U group ($p < 0.04$).

Riechelmann et al.²⁴ (2010) also compared RQLQ scores between the treatment and placebo groups and found patients in the treatment group had significantly better mean RQLQ scores ($\pm$ SD) after 1 year of treatment (1.30 ± 1.05) when compared with placebo (0.84 ± 1.03 , $p = 0.038$).

Pfaar et al.²⁸ (2011) showed a reduction in median RQLQ scores for the treatment group versus placebo group at year 1 (1.93, placebo 2.46, $p = 0.03$) and at year 2 (2.02, placebo 2.30, $p = 0.14$) although the latter did not reach significance.

Tabar et al.²⁵ (2011) found improvement in the domains explored by RQLQ in both the 3- and 5-year treatment

TABLE 5. Studies reporting immunologic assessments

Study	Treatment	Conclusion
Charpin et al. ¹⁹ (2007)	Aluminum hydroxide adsorbed <i>J. ashei</i> extract in patients with European cypress allergy	SCIT raises IgG4 levels
Mauro et al. ²⁶ (2007)	Birch pollen SCIT vs SLIT	SCIT, but not SLIT raises levels of Bet v 1 specific IgG4
Williams et al. ²⁷ (2007)	Aluminum adsorbed grass pollen SCIT for additional 3rd year	SCIT raises IgG4
Francis et al. ²⁰ (2008)	Aluminum adsorbed grass pollen SCIT	Specific IgG4 and IgA are induced at 6–12 weeks and may be required for modulation of IgE mediated events
Ceuppens et al. ²² (2009)	Glutaraldehyde-modified aluminum hydroxide adsorbed birch pollen vs placebo	SCIT raises IgG and IgG4 to Bet v 1 and suppresses Bet v 1 induced basophil activation
Hoöby et al. ²⁹ 2010	Depigmented polymerized birch pollen extract SCIT	SCIT raises IgG1 and IgG4
Martínez-Cócerca et al. ³¹ (2010)	Single species grass pollen SCIT	Single species SCIT raises IgG4 to grass mix
Riechelmann et al. ²⁴ (2010)	Glutaraldehyde-modified aluminum hydroxide adsorbed HDM vs placebo	SCIT raises IgG4
Tabar et al. ²⁵ (2011)	HDM SCIT × 3 years vs HDM SCIT × 5 years	SCIT raises IgG4 at 3 years, which is maintained at 5 years with additional treatment
Pfaar et al. ²⁸ (2011)	Preseasonal rush SCIT with depigmented polymerized mixed grass pollen	SCIT raises IgG4

Bet v 1 = major birch allergen; HDM = house dust mites; IgA = immunoglobulin A; IgG = immunoglobulin G; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

groups when compared to baseline. No difference, however, in RQLQ scores were found between the 3- and 5-year treatment groups.

Immunoglobulin assays

Table 5 contains information on immunoglobulin assays.

Charpin et al.¹⁹ (2007) found mean Juniperus-specific IgG4 levels in the treatment group to be increased from baseline (251.5 g/L) in the first (5771.7 g/L, $p = 0.00001$) and second pollen seasons (11,108.4 g/L, $p = 0.0001$).

Mauro et al.²⁶ (2007) found major birch allergen (Bet v 1) did not increase significantly in SCIT or SLIT treated patients. Levels of Bet v 1 specific IgG4 increased in both treatment groups, but only reached statistical significance with SCIT ($p = 0.001$).

Williams et al.²⁷ (2007) reported increases in specific IgG4 after a third year of short course specific grass pollen immunotherapy.

Francis et al.²⁰ (2008) demonstrated early production of interleukin-10 (IL-10) at low allergen doses coinciding with inhibition of late skin responses at 2 to 4 weeks. Further, specific IgG4, IgA, and inhibitory antibody activity for basophil histamine release and IgE-facilitated allergen binding to B cells occurred later, at 6 to 12 weeks, and preceded inhibition of early skin responses.

Ceuppens et al.²² (2009) reported significant increases in IgG and IgG4 antibodies to Bet v 1 in the treatment group as well as a blocking effect on Bet v 1-induced basophil activation.

Martínez-Cócerca et al.³¹ (2010) reported increases in levels of IgE and IgG4 to grass mix and *Phleum pratense* after treatment with single-species grass pollen SCIT. The levels of IgG4 to Phl p5 and lol p5 were highly correlated.

Richelmann et al.²⁴ (2010) reported significant increases in serum concentrations of IgG4 to *Dermatophagoides pteronyssinus* after SCIT. The change in IgE levels in response to HDM did not differ significantly between groups.

Tabar et al.²⁵ (2011) noted increases in specific IgG4 after 3 years of SCIT. IgG4 levels declined at 5 years of follow up in patients who were treated with immunotherapy for 3 years compared to those who received treatment for 5 years.

Höiby et al.²⁹ (2010) reported mean serum concentrations of specific IgE increased significantly in both treatment and placebo groups. Levels of IgG1 and IgG4 increased significantly in the SCIT group when compared to placebo. These changes were associated with a blunting of the increase in Th2 producing peripheral blood mononuclear cells.

Pfaar et al.²⁸ (2011) reported mean grass-specific IgE decreased in the treatment group (43.3 to 42.9 kU/L) but increased in the placebo group (37.3 to 45.56 kU/L). After the first course of SCIT, grass-specific IgG4 increased from a mean of 186.5 to 996.1 ng/mL in the treatment group and from 195.4 to 205.6 ng/mL in the placebo group. After year 2 of treatment mean concentrations for the treatment group and placebo were 638.6 and 275.7 ng/mL, respectively.

Challenge tests

Table 6 contains information on challenge tests.

Charpin et al.¹⁹ (2007) administered nasal provocation tests to evaluate SCIT efficacy in both treatment groups. Median values of the threshold dose were 100 in the treatment group and 10 Arbitrary index of reactivity (IR)/mL in

TABLE 6. Studies examining challenge tests as a secondary outcome

Study	Treatment	Conclusion
Charpin et al. ¹⁹ (2007)	Aluminum hydroxide-adsorbed <i>J. ashei</i> extract in patients with European cypress allergy	NPT: no statistically significant difference
Francis et al. ²⁰ (2008)	Aluminum adsorbed grass pollen SCIT	SCIT recipients need higher doses of allergen to elicit conjunctival symptoms
Martínez-Cócerá et al. ³¹ (2010)	Single-species grass pollen SCIT	SCIT reduces immediate and delayed cutaneous responses
Riechelmann et al. ²⁴ (2010)	Glutaraldehyde-modified aluminum hydroxide-adsorbed HDM vs placebo	SCIT improves conjunctival provocation test
Tabar et al. ²⁵ (2011)	HDM SCIT ×3 years vs HDM SCIT ×5 years	SCIT did not change skin reactivity to HDM

HDM = house dust mites; NPT = nasal provocation test; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

the placebo group after the first and second pollen seasons; however, this finding did not reach statistical significance.

Francis et al.²⁰ (2008) demonstrated requirement of greater concentrations of *P. pretense* allergen to elicit conjunctival symptoms on provocation testing in the treatment group vs placebo ($32,182 \pm 7432$, 2760 ± 440 SQ-U/mL, $p < 0.05$)

Martínez-Cócerá et al.³¹ (2010) showed diminishment of the immediate and delayed cutaneous responses to both tested grass pollen extracts after SCIT.

Richelmann et al.²⁴ (2010) showed a significant improvement in the conjunctival provocation test at 1 year in patients treated with SCIT.

Tabar et al.²⁵ (2011) did not show any changes in HDM skin reactivity in any group at any time-point.

Adverse events

Table 7 contains information about adverse events.

Charpin et al.¹⁹ (2007) reported 7 patients in the treatment group and 7 in the placebo group who experienced adverse events mostly in the form of injection site reactions and rhinitis. Three systemic reactions were reported in 2 patients: pneumothorax in 1 patient 1 day after injection 30, and facial urticarial and lip edema in 1 patient 2 days after injection 9. Details of treatment were not provided.

Mauro et al.²⁶ (2007) reported systemic reactions in 16% of SCIT and 0% of SLIT recipients. No data was provided regarding time of onset or treatment.

Ceuppens et al.²² (2009) reported no major adverse events. Local reactions were reported 27 times in the treat-

TABLE 7. Studies reporting adverse effects of treatment

Study	Treatment	Subjects (n)	Conclusion
Charpin et al. ¹⁹ (2007)	Aluminum hydroxide adsorbed <i>J. ashei</i> extract in patients with European cypress allergy	40	3 systemic reactions in 2 patients
Mauro et al. ²⁶ (2007)	Birch pollen SCIT vs SLIT	47	Systemic reactions in 16% SCIT vs 0% SLIT
Ceuppens et al. ²² (2009)	Glutaraldehyde-modified aluminum hydroxide adsorbed birch pollen vs placebo	62	No significant difference in serious adverse effects between treatment and placebo
Martínez-Cócerá et al. ³¹ (2010)	Single species grass pollen SCIT	46	9 SCIT patients with systemic adverse events; 1 episode of anaphylaxis
Riechelmann et al. ²⁴ (2010)	Glutaraldehyde-modified aluminum hydroxide adsorbed HDM vs placebo	140	No significant difference in serious adverse effects between treatment and placebo
Hoöby et al. ²⁹ (2010)	Depigmented polymerized birch pollen extract SCIT	61	30 patients developed systemic reactions, all Grade 1 or 2
Tabar et al. ²⁵ (2011)	HDM SCIT ×3 years vs HDM SCIT ×5 years	239	Systemic reactions in 5.6% of SCIT recipients; 1 episode of anaphylaxis
Pfaar et al. ²⁸ (2011)	Preseasonal rush SCIT with depigmented polymerized mixed grass pollen	195	Local, Grade 1 and 2 systemic reactions were more common in SCIT recipients vs placebo

HDM = house dust mites; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

ment group and 2 times in the placebo. A total of 12 systemic adverse effects occurred in the treatment group and 16 adverse events in the placebo group.

Martínez-Cócerá et al.³¹ (2010) reported 37 adverse events in the treatment group and 0 in the placebo group. Fifteen were related to SCIT. They occurred in 9 patients after 10 doses and during the up-dosing phase. Of the reported adverse events, 2 were described as nonspecific, 7 were local, 4 affected the upper airway, and 1 the lower airway. There was 1 episode of anaphylaxis consisting of asthma and pruritus of the ear canal and oropharynx that required administration of epinephrine and oral corticosteroids. The patient withdrew from the study.

Riechelmann et al.²⁴ (2010) reported a total of 278 adverse events in 88 patients (46 SCIT, 42 placebo). Of these,

59 were thought to be related to treatment. Twenty-five cases observed in 14 patients (6 SCIT, 8 placebo) were systemic and 34 were local. Local reactions were more common in the treatment group when compared with placebo (2.7%, 0.4%). No data were provided regarding time of onset or treatment.

Tabar et al.²⁵ (2011) reported 9 systemic reactions in the treatment groups: 3 nonspecific reactions, 2 rhinoconjunctivitis, 3 asthma attacks, and 1 episode of anaphylaxis (0.07% of all doses administered, and 5.6% of patients receiving SCIT). In the patient who experienced anaphylaxis, symptoms developed 1 minute after administration of the 61st dose of treatment. Administration of subcutaneous epinephrine, intravenous methylprednisone, and nebulized salbutamol resulted in rapid resolution of symptoms. SCIT was discontinued in this patient.

Höiby et al.²⁹ (2010) reported 58 adverse effects in 29 patients (12 SCIT, 17 placebo). Local reactions occurred in 6% of patients receiving SCIT and 13% of the placebo group. Thirty patients in the SCIT group developed systemic reactions (Grade 1 or 2 classification), and none required any specific treatment.

Pfaar et al.²⁸ (2012) reported local injection site reactions in 70.4% of patients for the treatment group and 40% of patients receiving placebo. Systemic reactions occurred 27 times in 16 patients in the treatment group and 7 times in 3 patients receiving placebo. Of these, all were grade 1 and 2 classification. No data on treatment were provided.

Discussion

Immunotherapy for AR is reserved for patients who have failed medical management and whose symptoms greatly affect their quality of life.¹⁰ Medical therapies for AR are numerous and are tailored to individual patients based on several factors including: symptoms, physical examination, response to prior medications, comorbidities, patient and provider preferences, and patient resources. Pharmacotherapy recommendations for the treatment of AR are summarized in Table 8.

When treating patients with AR, a stepwise approach should be applied to medication selection and risk acceptance. Despite optimal pharmacotherapy, some patients with moderate to severe AR will not be adequately controlled. When these patients have exhausted all reasonable medical options, immunotherapy should be considered with attention to the individual's risks and benefits.

Numerous studies with level 1b evidence classification have been performed to evaluate the efficacy and safety of SCIT for the treatment of AR. The Cochrane Review of Allergen Injection Immunotherapy for Seasonal Allergic Rhinitis in 2007¹⁰ analyzed 51 randomized controlled trials from the years 1954 to 2005, and provided a comprehensive picture of the data available at that time. These data provided consistent support that SCIT is effective for seasonal AR based on changes in symptom and/or medication scores, despite limitations in comparing studies with het-

TABLE 8. Pharmacotherapy of allergic rhinitis³²

Medication type	Description
Oral antihistamines	Second-generation oral H1-antihistamines are recommended for the treatment of allergic rhinitis in adults and children
	First-generation oral H1-antihistamines are not recommended when second-generation ones are available, due to safety concerns, primarily sedation and anti-cholinergic effects
Topical antihistamines	Second-generation intranasal H1-antihistamines are recommended for the treatment of allergic rhinitis in adults and children
Intranasal glucocorticoids	Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective approved drugs for the treatment of allergic rhinitis.
Oral or intramuscular glucocorticoids	Intramuscular glucocorticosteroids and the long term use of oral glucocorticosteroids are not recommended due to safety concerns.
Topical cromones	Topical cromones are recommended in the treatment of allergic rhinitis, but they are only modestly effective and require frequent dosing, excellent safety profile.
Leukotriene receptor antagonists	Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 2 years of age, and for perennial allergic rhinitis in patient over 6 months of age.
Intranasal anticholinergics	Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis.
Intranasal decongestants	Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction.
Oral decongestants	Oral decongestants (and their combination with oral H1-antihistamines) may be used in the treatment of allergic rhinitis in adults, but side effects are common

erogeneous, often unvalidated clinical scales. Despite these limitations, the evidence for reduction in symptoms and medication use is uniform and compelling across the literature. Further, these data consistently support improvement in SCIT-treated patient responses to validated quality of life surveys when compared to placebo. With increasing knowledge of the molecular and cellular mechanisms underpinning the pathophysiology of allergic disease, many authors have also demonstrated relevant changes in immunoglobulin classes and cytokine levels that are consistent with measures of SCIT efficacy. These findings are important and may help guide further research to identify novel

surrogate measures of efficacy and/or therapeutic targets. Another important evaluation performed in the Cochrane analysis was assessment of safety. A conservative estimate for epinephrine use for systemic reactions in the treatment group was 0.13% of all injections (compared to 0.01% placebo). This information is important as SCIT will lead to significant adverse events in a small minority of treated patients. It is important to recognize this fact and its implications for patient selection. As of yet, there is no strong data to quantify risk of adverse reactions to SCIT other than limited data and experiential evidence of severe reactions in patients who are highly sensitive to the administered allergen, display severe symptoms, or possess comorbid conditions—specifically uncontrolled asthma and a history of recurrent systemic reactions. Overall, conclusions from this extensive review found that SCIT was an effective and safe therapy for treatment of seasonal AR when administered in an appropriate setting.

In our review, we identified studies assessing clinical efficacy of SCIT in patients with seasonal or perennial AR since 2006. We found studies in this review have trended to include multiple analyses of modified seasonal and perennial antigens, comparison of SCIT to SLIT, and studies attempting to elucidate the ideal duration of SCIT therapy for the treatment of AR. It should be noted that multiple studies in the analysis used antigen preparations that have not obtained U.S. Food and Drug Administration (FDA) approval. There are currently no FDA formulations for SLIT therapy (Mauro et al.²⁶ and Tahamiler et al.²¹). Allergoid preparations are used in approximately 20% of SCIT treatments in Europe³³ but currently no FDA preparations are available (Williams et al.,²⁷ Ceuppens et al.,²² Höiby et al.,²⁹ Riechelmann et al.,²⁴ Pfaar et al.²⁸), although clinical trials have been performed in the United States.³⁴ Aqueous or glycerinated extracts are most commonly used, but there are a limited number of depot preparations available (Charpin et al.,¹⁹ Tabar et al.²⁵). It is estimated that approximately 2.5 million Americans are receiving alum-precipitated preparations of aeroallergen extracts.³³ The studies we reviewed were uniform in their assessments that SCIT is effective in reducing symptoms and/or medication use in patients being treated for seasonal or perennial AR. Despite multiple studies using antigen preparations that are not available in the United States, our analysis in conjunction with the 2007 Cochrane review are supportive of SCIT with FDA-approved formulations. We do feel that depot preparations and allergoids will become more commonplace and U.S.-based practitioners should be aware of the data supporting their use. Furthermore, multiallergen therapy is most commonly practiced in the United States while most quality studies in the immunotherapy literature use single-antigen therapy. At this time there is no data to suggest clinical efficacy or risk of adverse events are different when comparing multiallergen to single-allergen therapy, however the data on multiallergen therapy is limited. Figure 1 displays comparative changes in symptom score, medication score, or combined SMS for reviewed studies.

Analysis of aggregate data was not possible due to heterogeneity of outcome measures.

The duration of treatment in our study group ranged from 1 year to 5 years. The optimal duration of treatment with SCIT for allergic disease (including AR) is unknown, and is likely dependent on multiple variables, including dosing of maintenance injections, type of extracts used, and scheduling of administration. No definitive studies examining clinical response and optimal duration for the treatment of allergic rhinitis have been performed. One prospective study of 40 asthmatic patients who were treated with HDM SCIT for 1 to 8 years, demonstrated that those receiving 3 or more years of therapy had a reduced rate of relapse when compared to those who had completed less than 3 years (48% vs 62%, $p = 0.04$).³⁵ What was demonstrated in this review is that additional treatment beyond 2 years for grass pollen SCIT and 3 years for HDM SCIT possesses a measurable clinical benefit (the latter study for rhinitis symptoms alone), and is consistent with findings of immunologic assays. Duration of therapy for SCIT must take into account multiple factors, including relative risk/benefit, tolerance of medications, patient compliance, and costs of treatment in both monetary terms as well as time commitment to therapy. Generally speaking, most clinicians will attempt to treat for a target of 3 years, and then make a biannual assessment of the risks and benefits of continuation of therapy for up to 5 years. The optimal duration of immunotherapy is an important research subject that would benefit from future prospective studies in addition to the identification of surrogate markers that could predict clinical relapse.

Another major challenge facing immunotherapy clinicians and researchers is how to reliably assess for efficacy of treatment. The majority of practitioners are using symptom reporting and use of medications as primary outcome measures. No currently available tool based on allergic symptomatology alone, however, has been validated, and significant heterogeneity exists within the literature, making study comparisons difficult.^{36,37} One validated tool evaluating the effect of allergic disease on quality of life, the RQLQ score,¹⁸ has been proposed as a standardized measure of patient response. In our review, studies demonstrated consistent improvement in RQLQ scores with AR for both seasonal and perennial SCIT, supporting results using other nonvalidated patient questionnaire instruments.

In addition to the use of validated outcome instruments, attempts are being made to identify objective measures of clinical efficacy. This discovery would be a powerful tool for clinicians. Early knowledge of the changes of in vivo or in vitro markers would enable the clinician to not only identify nonresponders and spare them the cost and potential morbidity of therapy, but also provide the opportunity to accurately adjust treatment dosing and duration to maximize clinical efficacy for patients who respond to therapy. Numerous immunologic markers are currently being evaluated in clinical studies. Nonspecific levels of IgE and

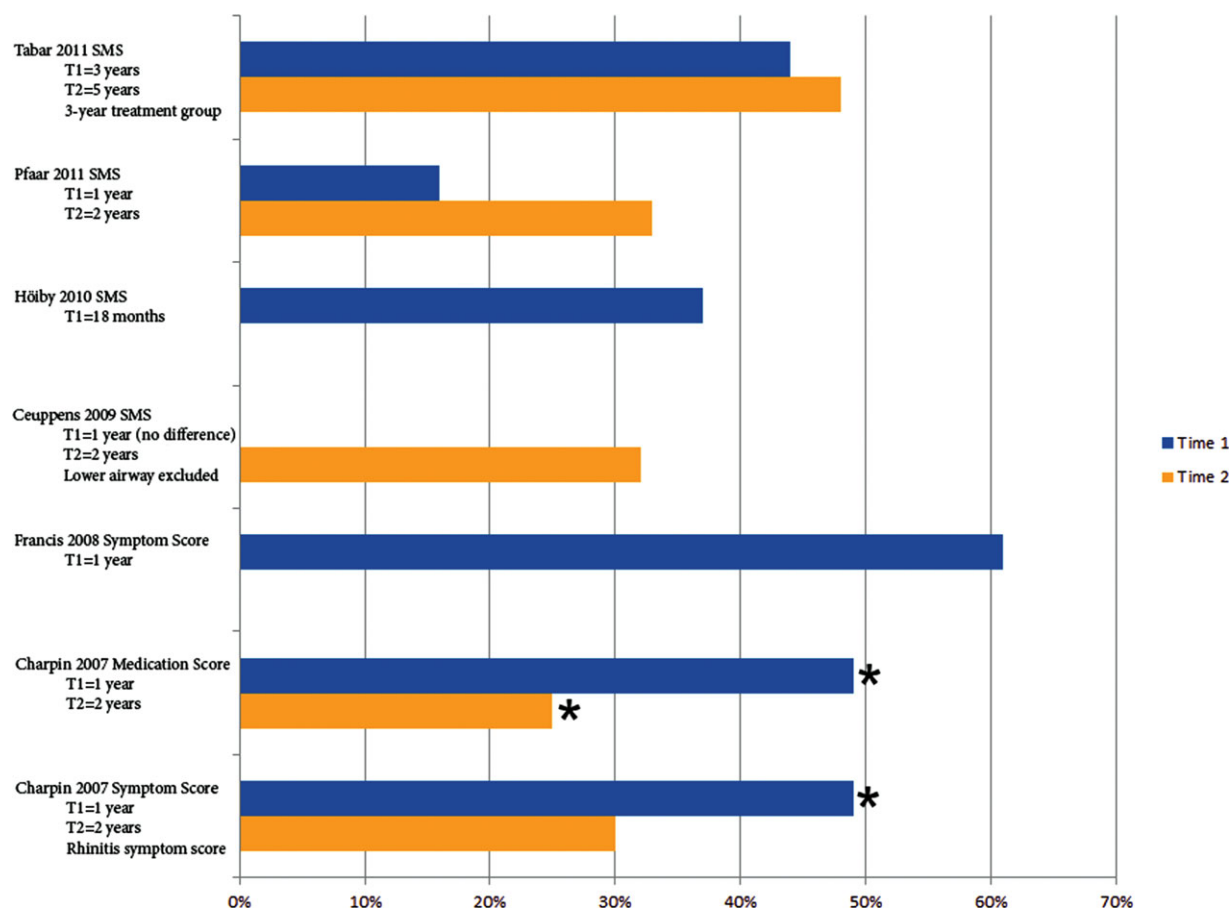


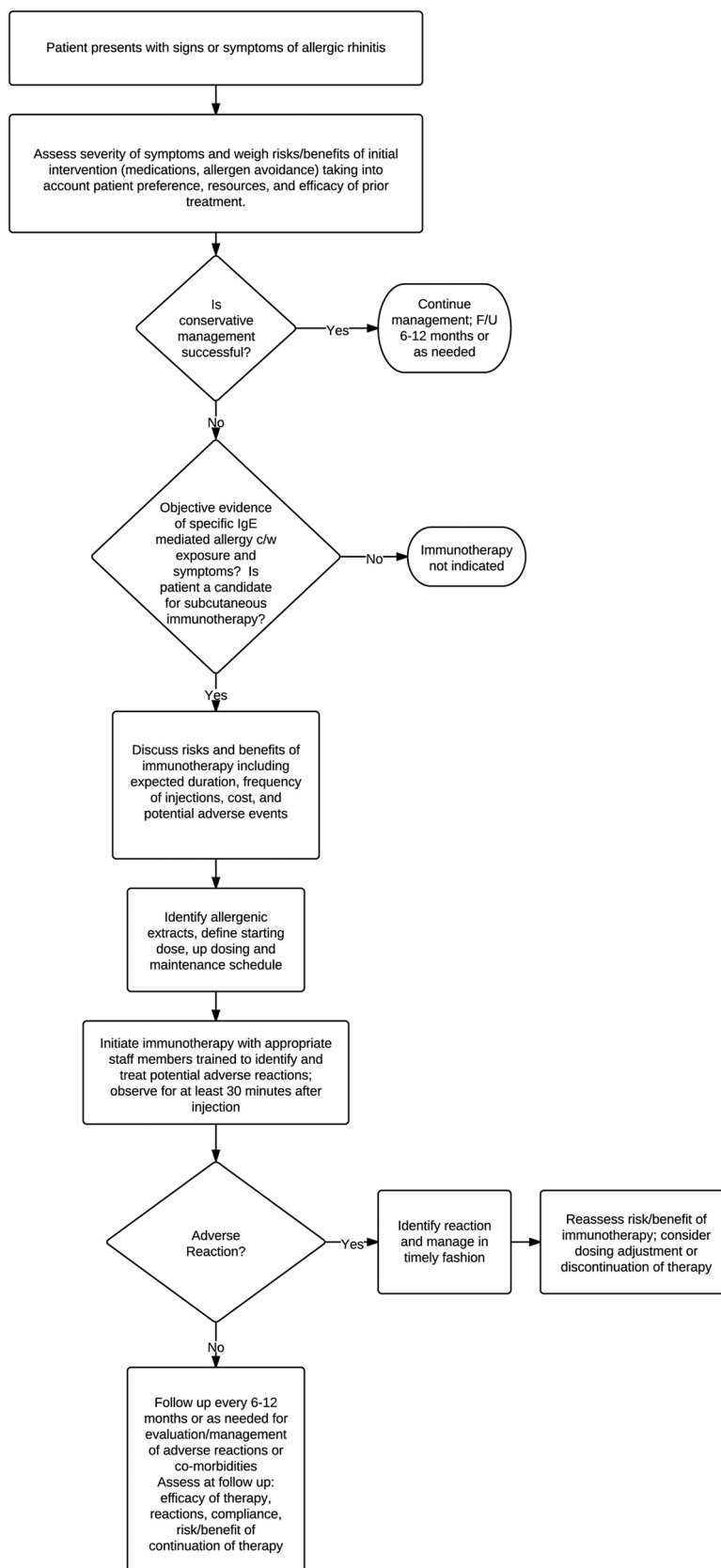
FIGURE 1. Comparative improvements in symptom score, medication score, or combined SMS. *Did not achieve statistical significance. Time 1: data at first follow-up interval (varied by study). Time 2: data at second follow-up interval. Data were omitted when study was not placebo-controlled or reporting did not allow calculation of percent change.

ratios of specific IgE and total IgE have been evaluated with limited success. The most promising marker may be specific IgG4 antibody levels, which correlate with measures of clinical efficacy after SCIT.³⁸ Studies have also examined the possibility of measuring peripheral cytokine production (ie, IL-10) as a marker of a Th1-dominant immune response.³⁷ The studies analyzed in this review consistently showed an increase in allergen-specific IgG4 levels. Further evaluation of immunologic markers of efficacy is warranted and could potentially play a significant role in the way immunotherapy is administered.

Challenge testing is another way clinical efficacy can be measured. Despite their widespread use, challenge tests used for evaluating efficacy of SCIT have many limitations due to confounding factors that may affect the objective result and interpretation. The main problem is the long time period between the baseline and after treatment test. However, challenge tests are well established for diagnosing occupational AR. Skin provocation, primarily, has been shown to be decreased in several studies of SCIT for the treatment of AR.³⁹ However, different extracts have varying potency, which makes comparison between studies difficult, especially in the presence of a negative result. Further, any provocation test depends on a challenge with

a high dose of allergen, which may not be physiologic and has not been shown to accurately predict clinical efficacy. Pollen chambers administered before and after treatment are an innovative solution in provocation assessment, but they are not readily available in most centers. The data from our review is varied regarding challenge testing. SCIT did not uniformly demonstrate a significant change in challenge testing, which these authors attribute to limitations in the outcome measure, not necessarily the treatment. These results further suggest that challenge tests have a very limited role in the evaluation of immunotherapy clinical success. The need for reliable objective measures of clinical response will be instrumental to the future of immunotherapy administration.

Adverse reactions and their management are a primary consideration in the administration of immunotherapy. Although there is a low risk of systemic reactions with SCIT, anaphylaxis and fatal reactions do occur. The overall risk of systemic reactions in patients receiving SCIT ranges from <1% with the use of conventional schedules to as high as 34% in patients receiving rush up-dosing, which is usually performed in a hospital setting.^{40–43} A 15-year retrospective review of the SCIT systemic reaction rate by Cox et al.⁴⁴ found the percentage of systemic reactions per injection

**FIGURE 2.** Key decision points in the administration of SCIT.⁴⁶

with conventional dosing was approximately 0.2%. A 2006 survey of American Academy of Allergy, Asthma, and Immunology (AAAAI) members administering SCIT did note 41 fatalities for the period of 1990 to 2001, equating to approximately 3.4 deaths per year over that time period.⁴⁵ The 2007 Cochrane review found a conservative estimate of epinephrine use (marker of severe systemic reaction) to be approximately 0.13% of patients undergoing SCIT. Of note, no fatalities were reported in any of the studies reviewed. Review of our smaller data set demonstrated more frequent systemic reactions in SCIT-treated groups than placebo or SLIT-treated groups. There were 2 episodes of anaphylaxis, 1 each in studies using grass pollen and HDM allergen. Relative contraindications to initiation of SCIT include severe, uncontrolled, or labile asthma because this group has been shown to have an increased risk of adverse events. Further, patients who have significant comorbidities such as autoimmune disease, pregnancy, malignancy, or a condition that would impair their ability to survive a severe systemic reaction, such as severe cardiopulmonary disease, should be evaluated with caution. Patients who are receiving beta blocker therapy are also at increased risk for systemic reactions that may be treatment resistant and initiation of SCIT in this population should also be approached with caution. Once the decision to proceed with SCIT has been made, it is the responsibility of the clinician to educate the patient on potential risks and benefits including rare, but serious systemic reactions that have in some cases lead to death. Further, one must provide a clinical setting where prompt recognition and treatment of severe systemic reactions is ensured.

Practice parameters for immunotherapy have been developed by multiple international organizations. The Joint Task Force representing the AAAAI, along with the American College of Allergy, Asthma and Immunology, and

the Joint Council of Allergy, Asthma, and Immunology have produced a comprehensive practice guideline now in its third update. The American Academy of Otolaryngic Allergy (AAOA) was invited to review these guidelines and supports them as a good evidence-based document. However, the AAOA has maintained its position that these guidelines do not encompass all of the options and evidence-based techniques available for immunotherapy. While not considered official practice guidelines, the AAOA has also produced the Scope of Knowledge for Allergy and recommendations concerning optimal dosing schedules for SLIT. The authors encourage all otolaryngologists performing immunotherapy to review these recommendations and keep up to date with allergy-based and otolaryngology-based best practices literature. Figure 2 outlines key decision-making points for the administration of SCIT therapy.

Summary: SCIT for seasonal and perennial AR

Aggregate quality of evidence: A (Level 1b: 12 studies).

Benefit: Improvement in symptom and/or medication scores and validated quality of life measures. Associated changes in surrogate markers of immunologic protection.

Harm: Local and systemic reactions (rare but with significant morbidity/mortality if they occur).

Cost: Moderate in both monetary cost and time commitment.

Benefits-harm assessment: Preponderance of benefit over harm in appropriately selected patients.

Value judgments: none.

Recommendation level: Recommend subcutaneous immunotherapy for patient with seasonal or perennial allergic rhinitis not responsive to conservative medical therapy and whose symptoms significantly affect quality of life. 

References

- Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. *Allergy Asthma Proc.* 2001;22:185-189.
- Sly RM. Changing prevalence of allergic rhinitis and asthma. *Ann Allergy Asthma Immunol.* 1999;82:233-248; quiz 248-252.
- Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. *Ann Allergy Asthma Immunol.* 2011;106(2 Suppl):S12-S16.
- Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol.* 2010;126:466-476.
- Aberg N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy.* 1989;19:59-63.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol.* 1987;79:660-677.
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol.* 1993;92(1 Pt 1):6-15.
- Toskala E. A contemporary review of sublingual immunotherapy. *Laryngoscope.* 2009;119:2178-2181.
- Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. *BMJ.* 1993;307(6909):919-923.
- Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev.* 2007(1):CD001936.
- Rudmik L, Soler ZM, Orlandi RR, et al. Early post-operative care following endoscopic sinus surgery: an evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2011;1:417-430.
- Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol.* 2011;1:431-437.
- Rosenfeld RM, Shiffman RN. Clinical practice guideline development manual: a quality-driven approach for translating evidence into action. *Otolaryngol Head Neck Surg.* 2009;140(6 Suppl 1):S1-S43.
- Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med.* 2003;139:493-498.
- Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care.* 2003;12:18-23.
- Center for Evidence-Based Medicine (CEBM). Levels of Evidence, March 2009. <http://www.cebm.net/index.aspx?o=1025>. Accessed December 20, 2012.
- Classifying recommendations for clinical practice guidelines. *Pediatrics.* 2004;114:874-877.
- Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy.* 1991;21:77-83.
- Charpin D, Gouitaa M, Dron-Gonzalez 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.
- 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.
- Tahamiler R, Saritzi G, Canakcioglu S, Ozcora E, Dirican A. Comparison of the long-term efficacy of subcutaneous and sublingual immunotherapies in perennial rhinitis. *ORL J Otorhinolaryngol Relat Spec.* 2008;70:144-150.
- Ceuppens JL, Bullens D, Kleinjans H, van der Werf J. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects. *Clin Exp Allergy.* 2009;39:1903-1909.
- 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.
24. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy*. 2010;24:e104–e109.
 25. Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol*. 2011;127:57–63, 63.e1–63.e3.
 26. Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. *Eur Ann Allergy Clin Immunol*. 2007;39:119–122.
 27. 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.
 28. Pfaar O, Urry Z, Robinson DS, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. *Allergy*. 2012;67:272–279.
 29. Hoöby AS, Strand V, Robinson DS, Sager A, Rak S. 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.
 30. 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.
 31. Martínez-Cócerca C, Sastre J, Cimarra M, et al. Immunotherapy with a *Phleum pratense* allergen extract induces an immune response to a grass-mix allergen extract. *J Invest Allergol Clin Immunol*. 2010;20:13–19.
 32. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160.
 33. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103:451–459; quiz 459–461, 495.
 34. 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.
 35. 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.
 36. Burton MJ, Krouse JH, Rosenfeld RM. Extracts from The Cochrane Library: allergen injection immunotherapy for seasonal allergic rhinitis (review). *Otolaryngol Head Neck Surg*. 2007;136:511–514.
 37. Senna G, Calderon M, Makatsori M, Ridolo E, Passalacqua G. An evidence-based appraisal of the surrogate markers of efficacy of allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2011;11:375–380.
 38. Gehlhar K, Schlaak M, Becker W, Bufe A. Monitoring allergen immunotherapy of pollen-allergic patients: the ratio of allergen-specific IgG4 to IgG1 correlates with clinical outcome. *Clin Exp Allergy*. 1999;29:497–506.
 39. Loureiro G, Tavares B, Chieira C, Pereira C. Effect of Dermatophagoides specific immunotherapy on cutaneous reactivity. *Eur Ann Allergy Clin Immunol*. 2007;39:5–8.
 40. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy*. 1994;73:409–418.
 41. Windom HH, Lockey RF. An update on the safety of specific immunotherapy. *Curr Opin Allergy Clin Immunol*. 2008;8:571–576.
 42. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol*. 2010;104:530–535.
 43. Bousquet J, Hejjoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol*. 1989;83:797–802.
 44. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol*. 2010;125:569–574, 574.e1–574.e7.
 45. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol*. 2006;117:169–175.
 46. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 Suppl):S1–S55.