

Allergen Immunotherapy Outcomes and Unmet Needs: A Critical Review



Davide Caimmi, MD^{a,b}, Moises A. Calderon, MD, PhD^c,
Jean Bousquet, MD, PhD^b, Pascal Demoly, MD, PhD^{a,d,*}

KEYWORDS

- Allergen immunotherapy (AIT) • Allergic rhinitis • Clinical outcomes
- Primary end point • Unmet needs

KEY POINTS

- Allergen immunotherapy (AIT) is a disease-modifying treatment of allergic patients.
- AIT trials do not use a uniformed primary outcome.
- There is a lack of consensus on how to properly evaluate AIT efficacy for all allergic diseases.
- Total combined symptom score could be a standardized tool to evaluate the primary outcome in AIT trials for allergic rhinitis.

INTRODUCTION

Allergen immunotherapy (AIT) is an effective treatment for both adults and children, mainly prescribed for allergic rhinitis, allergic conjunctivitis, and allergic asthma.¹ Although, on one hand, pharmacologic therapies are capable of providing temporary symptoms relief, on the other hand, AIT is the only treatment that can actually modify the atopic march and induce long-term disappearance of the allergic symptoms. For allergic rhinitis, medications (relief therapies) include mast cell stabilizers, antihistamines, glucocorticoids, leukotriene receptor antagonists, and nasal decongestants.^{2,3}

Disclosure: See last page of article.

^a Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud – 34295, Montpellier cedex 5, France;

^b MACVIA-LR, European Innovation Partnership on Active and Healthy Ageing Reference Site, University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud – 34295, Montpellier cedex 5, France; ^c Section of Allergy and Clinical Immunology, Imperial College London, National Heart & Lung Institute, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK;

^d Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, F-75013, 4, Place Jussieu – 75005 Paris, France

* Corresponding author. Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, 371, Av du Doyen Gaston Giraud, Montpellier 34090, France.

E-mail address: pascal.demoly@inserm.fr

Immunol Allergy Clin N Am 36 (2016) 181–189

<http://dx.doi.org/10.1016/j.iac.2015.08.011>

immunology.theclinics.com

0889-8561/16/\$ – see front matter © 2016 Elsevier Inc. All rights reserved.

Intranasal steroids are considered as the most effective treatment to control symptoms and are prescribed as a first-line therapy, very often in association with antihistamines.² Their effects quickly disappear when the treatment is stopped. AIT has, therefore, to be considered as the only real possible disease-modifying treatment of allergic patients.⁴

The two most commonly prescribed routes for aeroallergen AIT are subcutaneous (subcutaneous allergen immunotherapy [SCIT]) and sublingual (sublingual allergen immunotherapy [SLIT]).⁵ The type of prescribed route and the more interest of one over the other is different worldwide, depending on different variables, such as the availability of a regulatory-approved extract, geography, patient preferences, reimbursement policies, and cost both for the local health care system and for patients.⁵

Besides the primary indications mentioned, AIT may be effective in some patients with atopic dermatitis, food allergy, and other allergic conditions^{6,7} (Table 1). Nevertheless, it has to be underlined that, as for food immunotherapy, many issues still need to be clarified in terms of long-term tolerance after discontinuation.^{8,9}

When evaluating the effectiveness of AIT, both statistically significant and clinically relevant outcomes need to be taken into account.¹ Therefore, both clinical trials and daily effectiveness should be considered, even though it is difficult to separate them in research articles. Several issues still need to be addressed in order to properly identify a specific tool capable of predicting the real efficacy of such a treatment. A clinical trial outcome should be a measure allowing one to decide whether the null hypothesis should be accepted or rejected.¹⁰ Classically, there is a differentiation between the *primary outcome*, which usually includes the measurement of symptoms and the use of rescue drugs, and the *secondary outcomes*, which may include the patients' quality-of-life improvement, and several other markers that change from one study to the other.^{3,11} Also, more cost-effectiveness studies are urgently needed.

PRIMARY OUTCOMES

The European Medicines Agency (EMA) guidance on statistical principles for clinical trials defines the primary variable as the one “capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial.”¹⁰ In 2008, the EMA stated that, so far, no validated symptom and medication scoring method for clinical trials could be clearly used in evaluating AIT effectiveness.³ Nevertheless, the agency pointed out a possible preferred primary outcome measure for AIT clinical trials, the total combined score (TCS), which is the sum of the total symptom score (TSS) and total medication score (TMS).³ The Allergy-Control-SCORE has been actually validated to assess patients' allergy disease severity by recording both symptoms and the concomitant use of symptomatic treatments.¹²

Table 1 AIT indications and other possible uses	
Primary Indications of AIT	Other Possible Uses of AIT
Allergic rhinitis	Atopic dermatitis
Allergic conjunctivitis	Large local venom allergic reaction
Allergic asthma	Food allergy
Hymenoptera venom allergy	Oral allergy syndrome
—	Latex allergy
—	Allergic urticaria/angioedema

Such a score considers the severity of the disease, and the need to consult for the allergic condition and the validated Rhinoconjunctivitis Quality of Life Questionnaire¹³ and is a good method to evaluate respiratory allergy severity in clinical trials.¹² However, very few trials have used this tool.

Regardless, it is important to combine the TSS and the TMS, because the severity of the symptoms and the use of relief medications are 2 interdependent variables that should both be considered when evaluating patients' benefits from such treatment.¹ The use of the TCS has to be considered as the best approach to evaluate the primary outcome of AIT, being able to highlight both the largest effect size and the most efficient (clinically relevant) treatment.¹⁴ Nevertheless, there is no agreed scoring system for TCS yet.¹

In general, to evaluate the TSS, several double-blind placebo-controlled trials have used the patient self-rated Total Nasal Symptom Score (TNSS), assessed over the whole pollen season (with variable definition of the season) or the peak of the pollen season (with variable definition but around 2 weeks in general) for seasonal allergic rhinitis (SAR) and over a 4- to 8-week period for persistent allergic rhinitis (PAR).¹⁵ The TNSS is generally based on 4 symptoms: sneezing, rhinorrhea, nasal congestion, nasal pruritus.¹ The other score that is usually assessed is the total ocular symptom score (TOSS), which is based on the following symptoms: ocular pruritus and watery eyes.¹ Patients record a diary and score their symptoms usually daily, by using a 4-point rating scale ranging between 0 (no symptoms) and 3 (severe symptoms) (Fig. 1).¹⁶

The symptoms may be recorded in the evening in trials for SAR and in the morning in PAR trials.³ A task force by the World Allergy Organization (WAO) has suggested including in the symptoms score lower respiratory symptoms as well (chest tightness, shortness of breath, cough, and wheezing).¹¹

The EMA guidelines recommend that the *"efficacy for the nasal and eye-symptoms should be proven separately"* and *"the overall-effect should be balanced."*³ Nevertheless, clinical trials are different in considering what kind of TSS is used: They may vary from simply TNSS including 4 nasal symptoms,¹⁷⁻²¹ 4 nasal and 3 eye symptoms,²¹ 4 nasal and 2 eye symptoms,²⁰ 4 nasal and one eye symptom,²¹⁻²⁴ or 3 nasal and one eye symptom.²⁵ Some other trials only consider the TOSS as a primary end

Score		0	1	2	3
		No symptoms	Mild, not bothersome, easily tolerated	Moderate, bothersome, but tolerable	Severe symptoms
Nasal symptoms	Sneezing				
	Rhinorrhea				
	Nasal congestion				
	Nasal pruritus				
Ocular symptoms	Ocular pruritus				
	Watery eyes				

Fig. 1. Possible daily symptoms score sheets for patients in AIT trials.

point.^{26,27} On the whole, there is a deep lack of homogeneity in the different AIT trials because of what symptom they focus on.

One major issue is the recording of the allergen season. In AIT trials, allergen exposure is typically assessed by pollen counts; but these may misrepresent exposure if performed remotely from multiple study centers, because pollen counts vary widely across centers and do not represent the real allergen exposure for individual patients. Moreover, pollen counts may vary daily even during the season. A novel placebo score-based method, which may better reflect the variations in pollen counts, was proposed.²⁸ Electronic-health (e-health) technologies may be used in the future to include a clinical decision support system coupled to cell phones and visual analog scales (VASs) comparing placebo and AIT-treated patients.²⁹

SECONDARY OUTCOMES

Secondary outcome parameters may also be evaluated in AIT trials. These parameters may include several different assessments, as summarized in [Table 2](#).

Evaluations of AIT efficacy may, therefore, include different responder analyses. Only a few studies have used the VAS to estimate the severity and/or control of symptoms.^{30–32} Quality of life has been assessed through a specific questionnaire in several studies in adults^{23,24,33,34} and in children.¹⁷

COST-EFFECTIVENESS OF ALLERGEN IMMUNOTHERAPY

Allergic rhinitis and asthma are among the most common and costliest chronic conditions worldwide.⁵ Data from the Medical Expenditure Panel Survey run in the United States estimated the direct costs of allergic rhinitis to be \$11.5 billion in 2005, with prescription medications (59%).³⁵ When considering the cost associated with over-the-counter (OTC) drugs, another \$1.2 to \$1.7 billion was to be added in a 2008 survey³⁶; this cost is likely to increase in the future, when more medications will become OTC. Moreover, these total costs do not consider lost work productivity due to patients' absence at work.⁵ As for asthma, the total direct and indirect medical care cost in the United States was estimated at \$56 billion in 2007.³⁷ The financial burden of allergic diseases to both society and patients is, therefore, considerable; AIT seems to be associated with a significant cost savings (as high as 80%),⁷ even though these results are based on SCIT studies only and there are only a limited number of studies that have included cost comparisons between AIT and other treatments.⁵ One systematic review highlighted that both SCIT and SLIT are cost-effective compared with other therapies, but this outcome is proven only 6 years after AIT is started.^{38,39}

Table 2 Possible way to assess secondary outcomes in AIT trials		
Rhinoconjunctivitis quality of life	Well and hell days	Allergen challenge chambers
Allergen-specific immunoglobulin G antibodies	Inflammatory parameters	Score in individual symptoms
VASs	Nasal provocation tests	Skin reactivity
Conjunctival provocation tests	Bronchial provocation tests	Functional measures
Generic questionnaires	Disease-specific questionnaires	Others

Once again, there is no homogeneity in the way the economic outcomes are expressed and/or measured.⁵ However, a health technology assessment study funded by the UK National Institute for Health Research Health Technology Assessment program concluded:

A benefit from both SCIT and SLIT compared with placebo has been consistently demonstrated, but the extent of this effectiveness in terms of clinical benefit is unclear. Both SCIT and SLIT may be cost-effective compared with AIT from around 6 years (threshold of £20,000–30,000 per [quality-adjusted life-year] QALY). Further research is needed to establish the comparative effectiveness of SCIT compared with SLIT and to provide more robust cost-effectiveness estimates.³⁸

UNMET NEEDS

Several articles evaluated the efficacy of AIT in patients with allergic rhinitis (AR), but it seems clear that there is no method/end point that is actually universally accepted. In fact, heterogeneous end points have been used in different published trials with a lack of standardization for primary and secondary outcomes. In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) Immunotherapy Interest Group has conducted a task force on “recommendations for the standardization of clinical outcomes used in AIT trials for allergic rhino-conjunctivitis.”²⁹ The position paper is based on EMA guidelines, the American recommendation of the Food and Drug Administration (FDA), already published phase III trials, and expert discussion. The aim of the article was both to highlight and evaluate the current clinical outcomes used in AIT clinical trials and to recommend a consensus position for the best clinical outcomes to consider for future AIT products for allergic rhino-conjunctivitis.²⁹ The EAACI position paper confirms that the TCS should be used as a primary outcome in allergic rhino-conjunctivitis trials, associated nose and eyes symptoms, and the need for concomitant symptomatic therapies. Nevertheless, the TCS is still not validated; there is no strict consensus/direction from the EAACI or regulatory authorities for clinical AIT trials.²⁹ As for AIT trials in asthmatic patients, the position paper does not give recommendations for clinical end points.

One unmet need that requires clarification in AIT trials is how to measure the magnitude of clinical efficacy using, for example, effect sizes or a minimal clinically important difference (MCID). MCID is the smallest change in an outcome identified as important by patients. Glacy and colleagues,⁴⁰ from the US Agency for Healthcare Research and Quality, detail the different ways to calculate the MCID. Here as well, there is no consensus regarding the optimal methodology. In contrast to pharmacotherapy trials, AIT field trials allow patients to use rescue drugs, making it impossible to consider the placebo group as “medications free.”⁵ The only setting where patients do not use rescue medications is the environmental exposure chambers,²⁹ but these studies are not accepted as phase III trials.³ The WAO task force has underlined that the effect size of AIT efficacy should exceed 20% of the one recorded in the placebo group,¹¹ without clear justifications for this number. In AIT trials, the placebo group is equivalent to a symptomatic-therapy-alone group.⁵ Even considering this aspect, AIT trials have all demonstrated a significant clinical efficacy of the treatment when compared with placebo both in allergic rhino-conjunctivitis and asthma studies.⁴ The FDA seems to request an effect size of 15% with a lower 95% confidence interval band no smaller than 10% for pollen allergic rhinitis. These numbers are by far greater than what has always been requested for allergic rhinitis pharmacotherapy.

Another interesting point that needs to be clarified is that symptoms, in pollen allergic patients, are obviously more severe during the pollen season. Trials should, therefore, be run during the relevant season; but a standard definition of pollen season and peak pollen season does not really exist and varies from one phase III trial to another. EAACI is currently running a task force to address this issue. As for perennial allergens, such as mites, a higher exposure is highlighted during the fall; choosing the period when the outcomes are measured is crucial. AIT trials take into account this aspect, whereas pharmacologic trials usually do not consider such an increase in allergen exposure, patients being included when they are very symptomatic, meaning very exposed. Also, mite allergic patients are not usually evaluated for ocular symptoms, which might underestimate the presence of allergic conjunctivitis if compared with pollen allergic patients. In mite studies, therefore, eye symptoms often appear as secondary end points, which does not line up with the new recommendations of the EAACI task force.²⁹

However, the future of AIT will be in patient stratification and novel health systems. There is a need to define the patient population that will need AIT and the population that will benefit. This aspect will be the critical issue of AIT in the next 5 years. To help stratifying patients, e-health technology and biomarkers should be combined.²⁹ Biomarkers should define the patients who need to receive AIT (patient stratification), assess the early benefits of AIT after a few months (ie, after the first season for pollens and after a few months for indoor allergens) to decide whether AIT should be stopped or discontinued, determine the long-term benefits of AIT (after 3 years) to decide whether AIT should be continued or can be discontinued, and determine the efficacy of AIT when it is stopped.

Health systems in most countries are based on acute care and severe diseases (eg, cancer). They are often successful in the small proportion of the population needing this type of care. However, chronic diseases and their comorbidities represent the new paradigm of medicine.^{41,42} More than 100 million patients have allergic rhinitis in Europe, and self-management support interventions should be implemented⁴³; integrated care pathways should be developed at the national or regional levels.⁴⁴ The importance of e-health is undisputable. This approach will lead to novel health care models in which AIT should be considered.

All these issues still need to be clarified, validated, and standardized for future AIT trials.

SUMMARY

Several articles have been published over the years on AIT treatments and efficacy. Prevention of both asthma and the appearance of new sensitizations in patients with allergic rhinitis are crucial objectives of AIT⁴⁵ and not yet demonstrated for the newly developed products. However, registration is a stepwise process, starting with the demonstration of short-term (1 year) efficacy and safety. Primary end points are not homogeneous throughout publications, and secondary end points vary from one article to the other.⁴⁶ The main unmet need for all AIT trials is to find a validated and uniform primary end point for all studies. This consistency would allow clinicians to decide in a standardized manner whether AIT is an appropriate therapy for their patients¹ and indirectly compare products. Nevertheless, even if the total combined symptoms score seems to be a proper tool for a primary end point evaluation, and it would make trials as close as possible to real-life circumstances, its validation is still missing.⁴⁶ Also, international guidelines should identify both at what time, in relation with the pollen season or the allergen peak,

the clinical significance of AIT should be evaluated and what exact magnitude of treatment efficacy should be considered over the placebo group. Once these issues are solved, AIT trials will be uniform and a real comparison between results and treatment efficacy will be possible.

DISCLOSURE

D. Caimmi has nothing to disclose. M.A. Calderon has received consulting fees, honoraria for lectures, and/or research funding from ALK, Stallergenes, Merck, Allergopharma, and HAL. J. Bousquet has received honoraria for scientific and advisory boards: Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; lectures during meetings: Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; and board of directors: Stallergenes. P. Demoly is a consultant (and a speaker) for Stallergenes, Circassia, ALK, DBV, and Chiesi and was a speaker for Merck, Astra Zeneca, Pierre Fabre Médicaments, Menarini, Allergopharma, Allergy Therapeutics Ltd, ThermoFischer Scientific, and GlaxoSmithKline.

REFERENCES

1. Makatsori M, Pfaar O, Calderon MA. J Allergen immunotherapy: clinical outcomes assessment. *J Allergy Clin Immunol Pract* 2014;2:123–9.
2. 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:S8–160.
3. European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP). Guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis (CHMP/EWP/2455/02). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003554.pdf. Accessed June 7, 2015.
4. Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013;131:1288–96.
5. Cox L. Allergy immunotherapy in reducing healthcare cost. *Curr Opin Otolaryngol Head Neck Surg* 2015;23:247–54.
6. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol* 2013;131:295–9.
7. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. *Immunotherapy* 2012;6:1–16.
8. Pajno GB, Cox L, Caminiti L, et al. Oral immunotherapy for treatment of immunoglobulin E-mediated food allergy: the transition to clinical practice. *Pediatr Allergy Immunol Pulmonol* 2014;27:42–50.
9. Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? *J Allergy Clin Immunol Pract* 2014;2:97–8.
10. European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP): ICH topic E 9. Statistical principles for clinical trials. Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf 1998. Accessed June 7, 2015.

11. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) task force. *Allergy* 2007;62:317–24.
12. Hafner D, Reich K, Matricardi PM, et al. Prospective validation of 'Allergy-Control Score™': a novel symptom-medication score for clinical trials. *Allergy* 2011;66: 629–36.
13. 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.
14. Clark J, Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. *Allergy* 2007;62:1023–8.
15. US Department of Health and Human Services. Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER): guidance for industry. Allergic rhinitis: clinical development programs for drug products. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf>. Accessed 2000.
16. Pfaar O, Kleine-Tebbe J, Hörmann K, et al. Allergen-specific immunotherapy: which outcome measures are useful in monitoring clinical trials? *Immunol Allergy Clin North Am* 2011;31:289–309.
17. Potter P, Maspero JF, Vermeulen J, et al. Rupatadine oral solution in children with persistent allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Pediatr Allergy Immunol* 2013;24:144–50.
18. Ciebiada M, Gorska-Ciebiada M, Barylski M, et al. Use of montelukast alone or in combination with desloratadine or levocetirizine in patients with persistent allergic rhinitis. *Am J Rhinol Allergy* 2011;25:e1–6.
19. Meltzer EO, Lee J, Tripathy I, et al. Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. *Pediatr Allergy Immunol* 2009;20:279–86.
20. Sastre J, Mullol J, Valero A, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo in the treatment of perennial allergic rhinitis. *Curr Med Res Opin* 2012;28:121–30.
21. Meltzer E, Ratner P, Bachert C, et al. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int Arch Allergy Immunol* 2013;161:369–77.
22. Marmouz F, Giralt J, Izquierdo I. Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial. *J Asthma Allergy* 2011;4:27–35.
23. Rogkakou A, Villa E, Garelli V, et al. Persistent allergic rhinitis and the XPERT study. *World Allergy Organ J* 2011;4:S32–6.
24. Hashemi SM, Okhovat A, Amini S, et al. Comparing the effects of botulinum toxin-A and cetirizine on the treatment of allergic rhinitis. *Allergol Int* 2013;62:245–9.
25. Guilemany JM, Garcia-Pinero A, Alobid I, et al. The loss of smell in persistent allergic rhinitis is improved by levocetirizine due to reduction of nasal inflammation but not nasal congestion (the CIRANO study). *Int Arch Allergy Immunol* 2012;158:184–90.
26. Keith P, Lee LA. Fluticasone furoate nasal spray is the only intranasal corticosteroid to reduce the ocular symptoms of seasonal allergic rhinitis consistently. *J Allergy Clin Immunol* 2011;127:288–9.
27. Prenner BM, Lanier BQ, Bernstein DI, et al. Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2010;125:1247–53.

28. Frew AJ, Dubuske L, Keith PK, et al. Assessment of specific immunotherapy efficacy using a novel placebo score-based method. *Ann Allergy Asthma Immunol* 2012;109:342–7.
29. Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI position paper. *Allergy* 2014;69:854–67.
30. Demoly P, Bousquet PJ, Mesbah K, et al. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy* 2013;43:881–8.
31. Wu KG, Li TH, Wang TY, et al. A comparative study of loratadine syrup and cypromheptadine HCL solution for treating perennial allergic rhinitis in Taiwanese children aged 2–12 years. *Int J Immunopathol Pharmacol* 2012;25:231–7.
32. Mehuys E, Gevaert P, Brusselle G, et al. Self-medication in persistent rhinitis: overuse of decongestants in half of the patients. *J Allergy Clin Immunol Pract* 2014;2:313–9.
33. Bautista AP, Eisenlohr CP, Lanz MJ. Nasal nitric oxide and nasal eosinophils decrease with levocetirizine in subjects with perennial allergic rhinitis. *Am J Rhinol Allergy* 2011;25:383–7.
34. Bousquet J, Zuberbier T, Canonica GW, et al. Randomized controlled trial of desloratadine for persistent allergic rhinitis: correlations between symptom improvement and quality of life. *Allergy Asthma Proc* 2013;34:274–82.
35. Soni A. Allergic rhinitis: trends in use and expenditures, 2000 to 2005. Statistical brief #204. Bethesda (MD): Agency for Healthcare Research and Quality; 2008.
36. Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc* 2010;31:375–80.
37. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol* 2011;127:145–52.
38. Meadows A, Kaambwa B, Novielli N, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess* 2013;17:vi, xi–xiv, 1–322.
39. Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol* 2014;14:363–70.
40. Glacy J, Putnam K, Godfrey S, et al. Treatments for seasonal allergic rhinitis. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013. Available at: <http://effectivehealthcare.ahrq.gov/ehc/products/376/1588/allergy-seasonal-report-130711.pdf>.
41. Bousquet J, Jorgensen C, Dauzat M, et al. Systems medicine approaches for the definition of complex phenotypes in chronic diseases and ageing. From concept to implementation and policies. *Curr Pharm Des* 2014;20:5928–44.
42. Grover A, Joshi A. An overview of chronic disease models: a systematic literature review. *Glob J Health Sci* 2015;7:210–27.
43. Franek J. Self-management support interventions for persons with chronic disease: an evidence-based analysis. *Ont Health Technol Assess Ser* 2013;13:1–60.
44. Bousquet J, Addis A, Adcock I, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). *Eur Respir J* 2014;44:304–23.
45. Verheggen BG, Westerhout KY, Schreder CH, et al. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. *Clin Transl Allergy* 2015;5:1.
46. Calderon MA, Eichel A, Makatsori M, et al. Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials. *Curr Opin Allergy Clin Immunol* 2012;12:249–56.