

Cost-Effectiveness of Immunotherapy in the Treatment of Seasonal Allergic Rhinitis: Identifying Product-Specific Parameters of Relevance for Health Care Decision-Makers and Clinicians

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Key Words

Seasonal allergic rhinitis · Immunotherapy · Cost-effectiveness · Symptomatic medication

Abstract

Pharmacotherapy is widely used to manage allergic rhinitis (AR), but often does not adequately control symptoms. Allergy immunotherapy (AIT) should be considered for patients who are not adequately controlled on symptomatic treatment. AIT is gaining attention because of its potential to improve symptom relief and quality of life, and to provide sustained effect after the end of treatment by modifying the course of disease. However, evidence of efficacy needs to be shown for each individual AIT product, based on state-of-the-art studies. The majority of products cannot truly claim efficacy and disease-modifying potential, as evidence of such an effect from robust randomized double-blind, placebo-controlled long-term trials is lacking. The potential of a specific immunotherapy product should be evaluated against four levels of benefit defined by the European Medicines Agency (EMA) guideline on clinical development of AIT products. These clearly distinguish between efficacy of symptom relief in the first year, efficacy over 2–3 treatment

years, sustained efficacy and disease modification treatment ends, and sustained absence of allergic symptoms in posttreatment years. The clinician's choice of a specific AIT product should take the level of evidence and risk/benefit into account, as the patient's quality of life and the product's potential long-term effect are important components of its overall cost-effectiveness. Without evidence of maintained clinical benefit and disease modification after the end of treatment, claims of long-term economic benefit of specific AIT products cannot be justified. This paper discusses the evidence that is essential for critical evaluation of product claims in health economic analysis comparing AIT products.

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The Economic Impact of Allergic Rhinitis and Potential Benefit from Allergy Immunotherapy

Allergic rhinitis (AR) has wide prevalence, affecting between 17 and 29% of the population in Europe [1]. It has a measurable impact on society as well as on the individual patient because its impact on sleep [2] and reduction of work performance and quality of life [3] results in

health care costs to both the patient and the health care system [1, 4, 5]. In addition, 40% of patients with AR develop asthma [6], further intensifying these effects and their costs. AR also worsens asthma symptoms and asthma control when the two conditions occur concurrently [6].

The continuing escalation of respiratory allergies causes a substantial direct and indirect economic impact [7, 8]. A recent review has shown that in the EU, avoidable indirect costs per patient insufficiently treated for allergy range between EUR 55 and 151 billion per annum due to absenteeism and presenteeism, equivalent to EUR 2,405 per untreated patient per year [7].

Approximately 15% of Europe's population is receiving long-term symptomatic treatment for allergies and/or asthma, making them the most common reason for a long-term treatment in the pediatric population [9]; however, available treatment options are associated with varying levels of cost-effectiveness. Recent meta-analyses have concluded that both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy drops or tablet products (SLIT) are effective in reducing symptoms of seasonal AR when compared with placebo [10, 11], with a reduction of symptom and medication scores above 20% compared to placebo [8]. SCIT and SLIT are also more effective in the long term than antihistamines and montelukast, and have a comparable clinical impact to corticosteroids [12, 13].

The ARIA guidelines [6] stated clearly that the cost-effectiveness of treatment has to be demonstrated as well as efficacy. The 2010 revision of the ARIA guidelines [14] called for further investigation of the cost-effectiveness of SLIT – a need which has since largely been met.

Current economic evidence supports the cost-effectiveness of allergy immunotherapy (AIT) compared with symptomatic medication [10, 15–17], but published studies evaluating comparator trials are inconsistent in clinical trial design and interpretation of applied methodology [10, 18]. In the most recent study, 23 out of 24 studies examined by Hankin and Cox [14] indicated significant cost savings with AIT (for SCIT and SLIT) compared with symptomatic treatment. In the 6 cases within this analysis which compared SLIT with SCIT, 4 reported more significant cost savings with SLIT [14].

However, the mean efficacy of a product in trials does not necessarily match its efficacy in an individual patient, and the product's cost-effectiveness for the individual may therefore be different from the mean unless there is a good match between the individual's sensitizations and the AIT product selected for treatment. Different treat-

ment choices will be appropriate for individual patients [15]. Few patients are sensitized to only one allergen, although not all sensitizations will be clinically relevant [19]. The European Medicines Agency (EMA) guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases addresses this issue, recommending careful selection of allergenic source (allergen extracts or purified allergens) in relation to the population investigated in AIT clinical trials [19]. The recommendations of the ARIA guidelines [14] are based on all the available evidence, classified into categories according to its quality. One of the criteria for this classification is the extent to which available evidence can be directly applied to target patients, interventions and outcomes.

Pharmacotherapy treatment for seasonal AR provides symptomatic relief for most patients in the range of 5–19% over placebo [20], depending on the class of medication; however, the need for multiple medications by the majority of patients clearly points to the insufficiency of this approach in those with a moderate or severe condition. In all cases, relief ends when treatment is discontinued.

Where symptoms are inadequately controlled by pharmacotherapy, the efficacy and longer-term benefits possible through immunotherapy should be considered. Unlike pharmacotherapy, AIT products have been shown to be both an effective symptomatic treatment – relative change versus placebo up to 35% [18] – and also having the potential to convey lasting protection against future response to the specific allergen [9]. The key driver of evidence-based clinical decisions at the point of care is the long-term benefit of sustained disease-modifying abilities of AIT, with the attendant economic advantage of sustained immunogenicity.

Long-term treatment choice for seasonal AR is a more complex decision for the clinician than may be at first apparent, and has health economic implications for both the clinician and health care system. In contrast to symptom management, the optimal aim of immunotherapy is a sustained effect resulting from changes in the immune system of the individual [9]. The decision on a specific product with such benefits must be based on approved indication derived from well-designed clinical trials as recommended by the EMA [19] or adequate national authorities.

However, the current product-specific evidence base is often lacking or limited, and its quality is very variable. Clinical studies may range in quality from study concept and power calculation to reporting. In addition, the dura-

tion of studies ranges from a single pollen season to 3 years or more. Therefore, outcomes published in the literature are the result of heterogeneous clinical trial designs, with varying primary outcome parameters and varying statistical robustness. Some studies combine data from short- and long-term trials or report indirect comparisons, resulting in many studies that are ineligible for inclusion in meta-analysis. Clinical studies of sufficient duration to substantiate long-term claims are rare and cannot be generalized to cover all immunotherapy products. Further, outcomes from trials on adult subjects cannot be assumed to be valid in child subjects, and vice versa.

Interpreting Study Results

The CONSORT statement [21] (Consolidated Standards of Reporting Trials) made the point as far back as 2001 that in order to understand fully the results of a randomized controlled trial (RCT), its design, conduct, analysis and interpretation must be shown with complete transparency from authors. The CONSORT authors continued that despite several decades of educational efforts, the reporting of RCTs still needed improvement, and the CONSORT statement was developed to help in the process through use of a checklist and flow diagram.

The 2011 study of the application of the CONSORT statement to immunotherapy trials [22] assessed the reporting of 46 SCIT and 48 SLIT double-blind, placebo-controlled randomized trials published between 1996 and 2009. Out of these, only 4.2% of SLIT randomized controlled trials met all the criteria of the CONSORT statement on improving the quality of reports of parallel-group randomized trials [22]. Incomplete randomization was found in 33%/32% (SCIT/SLIT); power analysis was only reported in 33%/27% (SCIT/SLIT). Intention-to-treat analysis was only reported in 1 (2.2%) SLIT study and a modified intention-to-treat analysis was used in 1 (2.2%) SCIT study and 2 (4.4%) SLIT studies. The authors concluded that the quality of reporting of most immunotherapy trials is low, and that use of the CONSORT criteria should be encouraged [22].

There are no published and validated values for the minimal clinically important differences for such combined symptom-medication scores in immunotherapy [23]. The threshold for clinical relevance for primary efficacy analysis recommended by the World Allergy Organization (WAO) is 20% above placebo [24], although it must be recognized that a reduction in symptom score of

20% could vary depending on the initial level of symptom severity and the scores and algorithm used to measure severity. In interpreting the results of published AIT trials, careful attention should also be paid to the population analyzed (intention-to-treat, full analysis set vs. per-protocol population [25]), and the presentation of primary end point vs. post hoc analysis. The robustness of studies must depend on the size of the patient sample required to arrive at an outcome with a significance level of, for example, $p > 0.05$.

The resulting evidence needs to be demonstrated for each product, and evidence from one product may not be transferred to others. Proof of the causal role of the allergen in question must be established by appropriate testing (skin prick and allergen-specific IgE) and exclusion of clinically overlapping relevance of any other allergens to which the patient is sensitized before the treatment is conducted. Fulfilment of the above criteria is crucial in order to provide a valid basis on which to carry out cost-effectiveness analysis of an individual product.

EMA Guidance and Pharmacoeconomics

The EMA concurs that long-term strategies including AIT have an important role in the treatment of AR alongside symptomatic pharmacotherapy. Its guidance [19] makes detailed stipulations on the design of trials, including the diagnosis of patients with a history of IgE-mediated diseases such as AR/rhinoconjunctivitis or allergic asthma covering at least 2 consecutive years for seasonal allergies and 1 year for perennial allergies. Testing for specific allergens is specified with the aim of exclusion of multiple sensitizations as far as possible. Patients with comorbidity of AR and allergic asthma should be excluded from efficacy studies on asthma [19].

The trial strategy should include early determination of irritancy in healthy individuals and preliminary investigation of safety and tolerability, followed by dose-finding studies, tests to determine immunological changes and confirmatory studies. Appropriate primary and secondary end points are specified in detail [19].

While the EMA acknowledges that significant results on efficacy of specific immunotherapy in AR/rhinoconjunctivitis may be obtained after the evaluation of a single pollen season or one or two control periods for perennial allergies, it holds that the main aim of specific immunotherapy is a persistent effect due to changes in the immune system, which can only be demonstrated in long-term studies [19]. Most importantly, the EMA holds that

the following different claims are possible, but that they depend on the duration of the study:

- 1 Treatment of allergic symptoms: efficacy in the first pollen season
- 2 Sustained clinical effect: maintenance of efficacy during 2–3 treatment years
- 3 Long-term efficacy and disease-modifying effect: sustained efficacy in posttreatment years
- 4 Curing allergy: sustained absence of allergic symptoms [19]

Therefore, in order to prove long-term efficacy and a true disease-modifying effect, data is required that covers more than 1 posttreatment year.

While Cochrane meta-analyses have confirmed the efficacy and safety of sublingual drops or tablets for seasonal rhinitis [26] and conjunctivitis [27], clinical development strategies in use do not consistently align with the EMA guidelines and there is a great deal of heterogeneity of results due to different inclusion criteria, outcomes, doses and duration of trials [28–30].

Additional difficulties in comparing the evidence presented by clinical trials have been enumerated recently by Calderon et al. [31] in a study of randomized, double-blind, placebo-controlled trials for SLIT on seasonal AR, conducted between 2009 and 2013. The study found that large variations are possible in the maximum daily symptom score, simply on the grounds of the number of symptoms assessed and their definition. Methods of allocating daily medication scores depend on which medications are allowed, and their relative weighting. Trial scoring methods also vary, as do trial designs and analysis methods [31].

The consequence of this heterogeneity is that not every product has the same level of efficacy according to the EMA efficacy claims. It is therefore important for the clinician to critically evaluate the efficacy as per label of the individual product.

Cost-effectiveness analyses currently use a 9-year time horizon in the evaluation, thus long-term studies are more appropriate for extrapolation as they provide additional data including implications of a disease-modifying effect on health care budgets. Comparing cost-effectiveness between products, attention should be paid to the approved product indication, usually reflecting the level of clinical evidence. Disease-modifying long-term effects have been demonstrated for few products only. To draw valid conclusions, it is necessary to be aware of these issues in order to differentiate between products that only provide symptomatic relief and products that provide disease-modifying long-term effect [23, 32–34].

What Does This Mean to the Health Care Provider with Respect to Treatment Options?

Economic evaluations support the use of AIT to complement symptomatic treatment in patients with seasonal allergy that is severe or uncontrolled by symptomatic treatment alone. However, the lack of studies for many products and variation in the methodology and quality of health economic models used with different products makes direct comparison challenging. All four efficacy stages defined by the EMA provide a valid basis for a product-by-product basis evaluation of exactly which claims are valid in relation to long-term patient benefit and cost-effectiveness.

In selecting treatment options for uncontrolled or severe AR, clinicians need to balance the background of health care payers' budget restrictions against the additional long-term benefit of disease-modifying treatment to both patient and payers. Prescribing decisions should be based on valid evidence of the actual long-term benefit of the various treatment options, and the acknowledged potential of products to offer symptomatic relief and/or disease modification. As more studies are completed, it is anticipated that standards of design and conduct of trials will become more homogeneous, enabling more effective treatment. Meanwhile, clinicians and payers are encouraged to consult appropriate product-specific studies to demonstrate efficacy according to the four efficacy stages defined by EMA.

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References

- 1 Bachau V, Durham SR: Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758–764.
- 2 Léger D, Annesi-Maesano I, Carat F, et al: Allergic rhinitis and its consequences on quality of sleep: an unexplored area. *Arch Intern Med* 2006;166:1744–1748.
- 3 Demoly P, Allaert FA, Lecasble M; PRAGMA: ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. *Allergy* 2002;57:546–554.
- 4 Schoenwetter WF, Dupclay L Jr, Appajosyula S, et al: Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004;20:305–317.

- 5 Hellgren J, Cervin A, Nordling S, et al: Allergic rhinitis and the common cold – high cost to society. *Allergy* 2010;65:776–783.
- 6 Bousquet J, Khaltaev N, Cruz AA, et al; World Health Organization; GA(2)LEN; AllerGen: 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.
- 7 Zuberbier T, Lötvald J, Simoons S, et al: Economic burden of inadequate management of allergic diseases in the European Union: a GA²LEN review. *Allergy* 2014;69:1275–1279.
- 8 Pfaar O, Bachert C, Bufe A, et al: Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. *Allergo J Int* 2014;23:282–319.
- 9 Calderon MA, Demoly P, Gerth van Wijk R, et al: EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. *Clin Transl Allergy* 2012;2:20.
- 10 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.
- 11 Nelson HS: Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective? *J Allergy Clin Immunol Pract* 2014;2:144–149; quiz 150–151.
- 12 Matricardi PM, Kuna P, Panetta V, et al: Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol* 2011;128:791–799.e6.
- 13 Devillier P, Dreyfus JF, Demoly P: A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014;12:71.
- 14 Hankin CS, Cox L: Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol* 2014;14:363–370.
- 15 Brozek JL, Bousquet J, Baena-Cagnani CE, et al: Allergic Rhinitis and Its Impact on Asthma (ARIA) 2010 revision. *J Allergy Clin Immunol* 2010;126:466–476.
- 16 Cox L: Allergy immunotherapy in reducing healthcare cost. *Curr Opin Otolaryngol Head Neck Surg* 2015;23:247–254.
- 17 Scadding GK: Optimal management of allergic rhinitis. *Arch Dis Child* 2015;100:576–582.
- 18 Canonica GW, Cox L, Pawankar R, et al: Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6.
- 19 European Medicines Agency: Committee on Medicinal Products for Human Use Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases. CHMP/EWP/18504/2006. London, EMA, 2008.
- 20 Wilson AM, O'Byrne PM, Parameswaran K: Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116:338–344.
- 21 Moher D, Schultz KF, Altman DG; CONSORT Group: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–1194.
- 22 Bousquet PJ, Calderon MA, Demoly P: The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA²LEN) article. *J Allergy Clin Immunol* 2011;127:49–56.e1–11.
- 23 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
- 24 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) taskforce. *Allergy* 2007;62:317–324.
- 25 Bousquet J, Schunemann HJ, Bousquet PJ, Bachert C, et al: How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA(2)LEN statement. *Allergy* 2011;66:765–774.
- 26 Radulovic S, Wilson D, Calderon M, Durham S: Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011;66:740–752.
- 27 Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S: Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev* 2011;7:CD007685.
- 28 Calamita Z: Evaluation of meta-analyses about sublingual immunotherapy in allergic respiratory diseases. *J Allergy Clin Immunol* 2010;125:508; author reply 509–510.
- 29 Calderon MA: Meta-analyses of specific immunotherapy trials. *Drugs Today (Barc)* 2008;44:31–34.
- 30 Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G: Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol* 2012;130:1097–1107.e2.
- 31 Calderon MA, Bernstein DI, Blaiss M, et al: A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. *Clin Exp Allergy* 2014;44:1228–1239.
- 32 Summary of Product Characteristics, GRAZ-AX[®] 75,000 SQ-T Oral Lyophilisate. Horsholm, ALK, 2014.
- 33 Summary of Product CHARACTERISTICS, Oralair[®] 100 IR & 300 IR Sublingual Tablets. Antony, Stallergenes SA, 2013.
- 34 SQ 200 Grass Mix and Rye/ALK-Depot SQ 231 Rye/ALK-depot SQ 299 Grass Mix. Package Leaflet and Summary of Product Characteristics. Horsholm, ALK, 2013.