Allergen-Specific Immunotherapy: Which Outcome Measures are Useful in Monitoring Clinical Trials?

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- Allergen-outcome parameters • Study end points
- Quality of life • Specific immunotherapy • Responder-analysis
- Allergen challenge

Sneezing, rhinorrhea, itching, nasal obstruction, and sleep disturbance are typical symptoms of allergic rhinitis (AR). These symptoms may impair patients' daily abilities as well as their general well-being and work productivity.[1] Current treatments of AR include allergen elimination, pharmacologic treatment, and specific immunotherapy (SIT). A revision of the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline,

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aimed at providing systematically and transparently developed recommendations about the 3 therapeutic options in AR, has been published.[2] Specific subcutaneous immunotherapy (SCIT) and specific sublingual immunotherapy (SLIT) represent the only immune-modifying and causal treatments available for allergic patients.[1,3] The evidence for the effects of SIT is based on controlled and randomized clinical trials using specific primary and secondary outcome measures (end points).[4,5]

Primary end points for evaluating clinical outcome are the severity of symptoms and the need for concomitant medication, and are usually obtained on a daily basis by keeping diaries.[6] Secondary end points may include the specific and general (generic) quality of life (QoL)[7] or impact on work-related abilities,[8] and are usually obtained by questionnaires at follow-up. Some trials have also included allergen provocation tests, allergen chambers, or other surrogate markers such as allergen-specific IgG_4, the ratio of IgE to IgG_4, the IgE-binding capacity of the patient's serum, cytokine analysis, cell-activation markers, the number or differentiation of immune cells, and cell proliferation assays, but these are not considered to be suitable parameters for primary assessment. However, they might be used for investigating the immunologic mechanisms of SIT.[9,10]

This article gives an overview of approved and widely used methods of monitoring the clinical outcome of SCIT and SLIT in both clinical trials and daily routine. In 2000, a draft guidance document on outcome parameters was provided by the US Department of Health and Human Services Food and Drug Administration (FDA).[11] More recently, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical development of products for SIT has outlined recommendations in assessing outcome variables in clinical trials.[12] It must be noted, however, that universally accepted and authoritative national and international guidelines are still lacking with respect to the assessment of the therapeutic effects of SIT.[6]

PATIENTS' SELF-RATED DIARIES: VALUABLE TOOLS IN ASSESSING PRIMARY END POINTS

Successful SIT results in a decrease in both symptom severity and the need for concomitant medication, which can be monitored by daily entries in patients' diaries. In 2007, a task force of the World Allergy Organization (WAO) proposed a model for standardization of SIT clinical trials stipulating that patient-rated scores should be preferred as primary outcome parameters.[6] The individual scores can be recorded instantaneously (ie, an evaluation of symptom severity immediately before the next dose) and reflectively (predefined time period such as 12 hours).

However, this requires a compliant and motivated patient. The design of the diary depends very much on the experience of the allergologist concerned. According to the authors' experience, some practical aspects recommended for a diary to be a reliable and reproducible source of data can be summarized thus[5,13]:

1. Clear and easy to understand instructions
2. Small and handy size to be carried around easily
3. Only one page for each day
4. Large print for elderly patients
5. Waterproofed bindings
6. Multiple-choice questions as well as some space for free text.

As an alternative to paper diaries, electronic tools (eg, handheld computer or Internet-based devices) might be used in clinical trials, with the advantage that timely