

Mite-Allergic Rhinitis: How to Evaluate Clinical Efficacy in Allergen-Specific Immunotherapy Trials?

Oliver Pfaar, MD^{1,3,*}

Roy Gerth van Wijk, MD²

Address

^{1,2}Center for Rhinology and Allergology Wiesbaden, Germany, An den Quellen 10, 65189, Wiesbaden, Germany

Email: oliver.pfaar@allergiezentrum.org

²Section of Allergology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

³Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

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Opinion statement

House dust mite (HDM) allergen exposure is the most important cause of perennial allergic rhinitis and/or asthma. Although allergen-specific immunotherapy (AIT) with HDM is well established, published studies have been characterized by substantial heterogeneity in clinical endpoints. Standardization in measuring clinical efficacy is required. Moreover, when designing an AIT trial with HDM allergens, several considerations have to be taken into account. The history of HDM allergy is less clear cut than the typical history of pollen allergy. In addition, clinical features of HDM allergy may differ from those of pollen allergy. Moreover, although not easily measurable, fluctuation in allergen exposure may cause variation in symptom severity and determine the timing of assessment of clinical effects of HDM AIT.

Key points

1. A combined symptom and medication score (CSMS) is recommended as standard for the primary endpoint in future house dust mite (HDM) allergen-specific immunotherapy trials.
2. The diagnosis of HDM allergy is based on a carefully taken history in combination with sensitization to HDM allergens.
3. Eye symptoms are less prominent in patients with HDM-induced allergic rhinitis. Nasal symptoms, but not eye symptoms, should be included in the CSMS and in symptom scores as well.
4. As methods to determine allergen exposure vary and the efficacy of environmental control

is a matter of debate, a practical approach consists of restraining patients from implementing HDM-reducing measures, such as removing carpets and introducing anti-mite covers, after the start of the study.

5. Efficacy evaluation in the period with the highest exposure to mites is recommended.

Introduction

One of the most relevant groups of indoor allergens in causing perennial allergic rhinitis (AR) and/or allergic asthma (AA) is found in the bodies and feces of house dust mites (HDM), with the two main species being *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [1, 2, 3••]. Besides allergen avoidance as a (secondary or tertiary) preventive treatment, which often lacks sufficient efficacy in domestic settings [4], the treatment of mite allergy is mainly based on antiallergic pharmacotherapy, as well as on allergen-specific immunotherapy (AIT) [3••, 5•, 6]. In a position paper on AIT, the World Health Organization (WHO) clearly highlighted the clinical efficacy of AIT in patients with HDM-induced AR and AA [7]. Within the last two decades, an increasing number of meta-analyses have demonstrated clear evidence of the clinical efficacy of this treatment for both subcutaneous and sublingual AIT (SCIT and SLIT) in HDM allergy [3••, 8–10]. However, in a recently published systematic evidence-based review on the clinical efficacy of HDM AIT, the authors emphasized “marked inter study heterogeneity in terms of primary and secondary efficacy criteria” [3••]. One

reason for this heterogeneity can be seen in specific considerations of HDM-induced allergic diseases that differentiate them from (pollen-induced) seasonal AR and AA.

Various clinical endpoints in published AIT trials for allergic rhinoconjunctivitis (ARC) were recently reviewed in a current position paper from the European Academy of Allergy and Clinical Immunology (EAACI) [11••].

This article aims to (1) review examples of different outcome measures (primary and secondary), as published in the literature on HDM AIT trials (as grouped into seven domains); and (2) discuss general limitations and special considerations for clinical trials in this indication (in contrast to AIT trials in seasonal allergies). The latter include differences in the diagnosis of AR, the clinical characteristics of patients with AR due to HDM allergy, and clinical manifestations of the disease; and limitations in measuring the allergen exposure of the patients, as well as the problem of the timing of clinical assessment of HDM AIT.

Outcome measures in house dust mite allergen-specific immunotherapy trials

Symptom scores

For AR, scoring of symptoms has been determined as clinical endpoint in several HDM AIT trials, both for the subcutaneous route (e.g., see references [12–14]) and for the sublingual route (e.g., see references [15–17]). However, there is a high grade of heterogeneity in the definition of the respective SS throughout the literature. Moreover, in some study protocols, composite-scores with nose- and lung-symptoms were used whereas a few also included conjunctival symptoms (reviewed in [3••]). One recently published trial of sublingual mite-allergen tablets used the Average Adjusted Symptom Score (AAAdSS) as a primary endpoint [18•].

The EAACI position paper on clinical outcomes of AIT trials for ARC [11••] recommends a daily symptom score (dSS) in perennial AR caused by HDM, based on four nasal symptoms, as follows: itchy nose, sneezing, runny nose, and blocked

nose, on a scale of 0–3 points (modified from references [19, 20]). Conjunctival symptoms are not included in this recommended scoring of the primary endpoint in AIT trials in HDM-allergic patients [11••] (see also discussion under “[General limitations and special considerations for clinical trials in this indication](#)”).

(Asthma) SS have also been used as a clinical endpoint parameter in several clinical trials of HDM AIT (e.g., see references [21–24], reviewed in reference [3••]). As for AR, differences in asthma SS are found in comparison of these trials, with a lack of harmonized standardization of this endpoint. In the light of the need for comparability of the efficacy of HDM AIT, an international standard for the definitions of asthma SS to be used as clinical endpoints would be preferable in future trials.

Medication scores

In some clinical trials of HDM AIT in AR patients, medication scores (MS) have been used as clinical endpoints (e.g., [13, 15, 18]). As for SS, no definite standard (for both the specific class of pharmacotherapy to be administered as concomitant medication and their scoring for the MS) has been used. The EAACI position paper recommends a stepwise use of antiallergic medication and gives a standardized definition for the daily medication score (dMS) [11••], which is in line with, and is modified from, the World Allergy Organization (WAO) recommendations [19].

Some AIT trials in asthma patients have also used MS as clinical endpoints (e.g., see references [25–28]). Again, heterogeneous use of medication and scoring systems is found in the respective trial protocols, with some of them being related to and modified from a standard published by Dreborg et al. [29].

Combined symptom and medication scores

In AR, one AIT trial on HDM-allergic adult patients [30] has used a combined symptom and medication score (clinical index score [CIS]) as primary endpoint. In principle, combining symptom scores and medication scores in a composite single score as primary clinical endpoint in AIT trials is in line with the European Medicine Agency (EMA) “Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases” [20]. However, there is still a lack of thorough global standardization.

The EAACI position paper highlights for the primary endpoint in future AIT-trials a homogeneous combined symptom and medication score (CSMS) as a simple and standardized method. This score balances both symptoms and the impact of antiallergic medication in an equally weighted ratio [11••].

In AIT trials in HDM-induced AA, composite asthma symptom and asthma medication scores have not been used as primary endpoints (reviewed in reference [3••]). However, in this indication, other endpoints such as controllability of asthma may be preferred as primary outcomes (see “[Control of the disease](#)”).

Control of the disease

As an important alternative to measurements of disease severity (as analyzed, for example, by SS), disease-specific “control” outcome questionnaires have recently been developed and partly validated—e.g., the Control of Allergic Rhinitis and Asthma Test (CARAT) [31•] and the Rhinitis Control Assessment Test (RCAT) [32]. However, the scores from these questionnaires have not been used as clinical endpoints in AIT trials in HDM-induced AR.

However, in a recently published double-blind, placebo-controlled trial of SLIT in patients with HDM-induced AA, well-controlled asthma (WCA), as defined by the Global Initiative for Asthma (GINA; latest revision 2012 [33]), was used as a primary endpoint by Wang et al. [28]. Another example is a randomized, controlled trial in children with HDM-induced AA, which investigated the steroid-sparing effect of SCIT to maintain asthma control [34].

Quality of life

Quality-of-life (QoL) questionnaires were validated more than 20 years ago for both AR [35] and AA [36] in different age groups. Furthermore, a questionnaire evaluating both AR and AA in a composite format has been developed (see reference [37], reviewed in reference [11••]). On this basis, QoL has been evaluated in different AIT trials in HDM-induced AR [30] and AA [28].

Allergen challenge tests

Nasal provocation (NP; e.g., see references [38–40]) or conjunctival provocation (CP; e.g., see reference [30]) have been performed in different trials in HDM-induced AR, whereas bronchial provocation (BP) has been performed in trials in HDM-induced AA (e.g., see references [13, 25, 26]) for analyses of secondary outcome endpoints (reviewed in reference [3••]). However, the different challenge test methods have not been thoroughly standardized and validated, which should be urgently addressed in the future, not only for their clinical implications in HDM-AIT-trials (see details in reference [11••]). Environmental challenge chambers may become promising candidates for allergen provocation if thorough technical and clinical validation can be realized [41].

Well days

In the EMA “Guideline on the Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases” [20], “days with symptom control” with daily symptom scores below a “clinically justified level” are recommended as secondary endpoints for the analysis of clinical efficacy in AIT trials. As an example, one pediatric trial of SLIT in HDM-allergic children with AR used “well days” and “symptom-free days” as secondary endpoints [42]. However, it is questionable if this definition initially developed for intermittent (pollen-induced) AR can be extrapolated to persistent (HDM-induced) allergy.

General limitations and special considerations for clinical trials in this indication

Diagnosis of allergic rhinitis based on house dust mite allergy

The clinical relevance of a history matching HDM allergy is less easy to establish than the typical history of pollen allergy. Therefore, it has been suggested that a positive allergen challenge test should be part of the inclusion criteria for HDM trials [3••]. One problem might be that allergen challenge tests are not standardized. Moreover, the inclusion of nasal challenge tests has been used in a large trial assessing the efficacy of mattress covers [43] in children and adults with HDM allergy, but a subanalysis showed that a positive HDM challenge test did not

substantially change the physician's diagnosis based on symptoms and sensitization to HDM [44]. Therefore, a carefully taken history in combination with sensitization to HDM allergens should be sufficient for establishing the diagnosis.

Clinical characteristics of patients with allergic rhinitis due to house dust mite allergy and the clinical manifestation of the disease

It is generally believed that rhinitis due to HDM allergy is more characterized by nasal obstruction than pollen allergy. Most AIT trials have reported the mean of different nasal symptom category scores, without showing separate nasal SS. In one small SLIT study in HDM-allergic children, low and comparable scores were reported for sneezing, nasal blockage, nasal itching and rhinorrhea [45]. In a study assessing the efficacy of montelukast and antihistamines, patients with HDM allergy reported all nasal symptom categories. Higher scores for obstruction than for sneezing and itching were reported [46]. In another SLIT study in children, rhinorrhea was seen in 89.4 % and nasal obstruction in 82.3 % of patients [47]. In a large study assessing QoL in patients with intermittent and persistent rhinitis, all nasal symptom categories were reported in the majority of patients with persistent rhinitis [48]. Therefore, the use of composite nasal scores is also justified in patients with HDM allergy.

Allergic conjunctivitis is often underestimated [49] and may have an important impact on QoL, even more than nasal obstruction [50]. However, in a subanalysis of children included in a retrospective HDM SLIT study, the frequency of nasal symptoms ranged from 89.4 % for rhinorrhea to 61.7 % for nasal pruritus, whereas the frequencies of ocular pruritus and teary eyes amounted to only 25.7 % and 17.9 %, respectively [47]. In another HDM SLIT study, eye scores were low [42]. In line with this, many randomized, controlled AIT trials have measured only nasal symptoms without taking eye symptoms into account [12–16, 51, 39, 40, 52–55], and fewer studies have included eye symptoms in the assessment of efficacy [18•, 42, 45, 56–59].

The recent EAACI position paper on outcome measures in AIT trials advocates the inclusion of eye scores in trials in rhinoconjunctivitis [11••]. Low eye scores included in composite nasal/eye scores or combined symptom combination scores may, however, influence the effect size of treatment. For that reason, focusing only on nasal symptoms in HDM trials may be justified [11••]. One has to bear in mind that the well-known Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) has been validated for allergic rhinoconjunctivitis [35]. Juniper et al. have also validated an instrument for perennial rhinitis [60].

Limitations in measuring allergen exposure of patients

In a few studies, measurement of HDM allergens has been performed. Exposure can be measured at baseline. In one study, relatively low levels of the major *D. farinae* allergen Der f 1 were found in the settled dust samples. The levels ranged from non-detectable to 8 µg/g of dust. Mean Der f 1 levels were similar in the active treatment and placebo groups [51]. Exposure may be monitored during the study. In two studies, no change in exposure could be observed [13, 14]. In another study, HDM exposure was expressed in guanine levels in mattresses [53]. After 24 months, the number of patients with class 2±3 guanine levels decreased significantly in both groups ($P=0.01$), while there was a concomitant increase in the number of patients with low guanine levels (class 1), indicating a marked

change in the indoor allergen load [53]. Such a decrease in Der p 1 was also observed in a trial in asthmatics [55]. The latter study included help from an environmental consultant and the introduction of anti-mite mattresses and pillow covers before the start of the study. Although measurement and monitoring of mite allergens for HDM AIT trials have been advocated [3••], one might argue about the added value. Theoretically, a change in allergen exposure during treatment may interfere with the results of AIT. As methods to determine allergen exposure vary and the efficacy of environmental control is a matter of debate [4], a more practical approach consists of restraining patients from implementing HDM-reducing measures, such as removing carpets and introducing anti-mite covers after the start of the study.

Timing of assessment of clinical effects of allergen-specific immunotherapy for house dust mite allergy

Although peak HDM exposures are not as substantial as those seen in pollen allergy, HDM exposure might be relatively high in autumn [61]. In a Polish AIT study, differences relative to placebo were particularly evident in successive heating seasons, which corresponds to the highest period of HDM allergen exposure in Poland [56]. Also, in an Italian study, it was shown that rhinitis and medication scores were significantly lower in the AIT group than in the placebo group in October, November, and December [57]. Lower SS in the AIT group than in the placebo group in most of the winter months ($P=0.05$) were observed in another Italian study [59]. In one study, the diary had to be filled in from November to February, when the exposure to indoor mites is expected to be greater [58]. Also, other studies have taken a specific period of inclusion or efficacy analysis into account [18•, 40, 42, 52, 53, 55]. Therefore, efficacy evaluation in the period with the highest exposure to mites is recommended. Moreover, assessment should always be done at yearly intervals and not at 6-month intervals [16] or 18-month intervals [14, 55].

Compliance with Ethics Guidelines

Conflict of Interest

O. Pfaar (OP) has received research grants for his institution from ALK-Abelló (Germany/Denmark), Allergopharma (Germany), Stallergenes (Germany/France), HAL Allergy (Germany/the Netherlands), Artu Biologicals (the Netherlands), Allergy Therapeutics/Bencard (UK/Germany), Hartington (Spain), Lofarma (Italy), Novartis/Leti (Germany/Spain), GlaxoSmithKline (UK/Germany), Essex Pharma (Germany), Cytos (Switzerland), Curalogic (Denmark), Roxall (Germany), Biomay (Austria), Thermo Fisher (Germany), Circassia (UK), European Union (FP-7-Health-2013 Innovation 1), Biotech Tools s.a. (Belgium), and Meda Pharma GmbH (Germany); and/or he has served as an advisor and on speakers' bureaus for some of the aforementioned companies. OP has received travel grants from HAL Allergy (the Netherlands/Germany) and Allergopharma (Germany), and he is a consultant for Bencard (Germany), HAL Allergy (the Netherlands), Novartis/Leti (Germany), Meda (Germany), ALK-Abelló (Germany/Denmark), Allergopharma (Germany), Biotech Tools s.a. (Belgium), GfK Bridgehead (UK), Navigant Consulting (USA), Sanofi (USA), Guidepoint Global Advisors (USA), Thermo Fisher (Germany) and Stallergenes (Germany/France); he is Scientific Board Member of Mobile Chamber Experts (MCX), a GA2LEN Partner. OP is the current chairman Immunotherapy

Interest Group (IT IG) of the European Academy of Allergy and Clinical Immunology (EAACI) and is the secretary of the ENT section of Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI). He has received grants for the "Spezifische Immuntherapie"-award 2014 and the "Nachwuchsförderpreis"-award 2010 of the DGAKI. He is co-editor and an author of the textbook "Allergien bei Kindern und Jugendlichen" (publisher: Schattauer-Verlag, Germany) and author of different chapters of "Allergologie-Handbuch" (publisher: Schattauer-Verlag, Germany) and has received payment for development of educational presentations from GlaxoSmithKline (Germany), Bencard (Germany), and Novartis (Germany).

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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