



The behavior of Italian allergists in prescribing allergen immunotherapy for house dust mites allergy

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The meeting 'Clinical Evidence, Extracts Quality and Biotechnology Innovation in Allergen Immunotherapy' held in Trieste (Italy) on 1 October 2017 concerned the outcomes of a real-world survey conducted on a group of Italian allergists about allergen immunotherapy (AIT) for house dust mites allergy. It pointed out: allergist's confidence that AIT should be prescribed continuously; tablets seem to be well accepted by patients and effective in most subjects with a fast onset of action (3–6 months); combined score for symptom severity and medication use is universally assessed; there is disagreement about the diagnosis of house dust mites allergy, the quote of AIT prescription, the choice for AIT route of administration, assessment of serum IgE and perception of patient's adherence.

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The meeting 'Clinical Evidence, Extracts Quality and Biotechnology Innovation in Allergen Immunotherapy' took place in Trieste (Italy) on 1 October 2017. The meeting involved a group of about 50 Italian allergists particularly expert in allergen immunotherapy (AIT) practice. The main topic concerned house dust mites (HDM) allergy, as it is a very common cause of allergic rhinitis and asthma [1,2]. Actually, HDM allergy is very frequent and represents the main allergen prescribed for AIT in Italy as well as in many other countries [3]. Thus, HDM allergy represents a crucial challenge for the allergist in clinical practice. Specific attention was focused on the analysis of a real-world survey conducted on a group of Italian clinical allergists and concerning the management of AIT in HDM allergic patients.

HDMs belong to the *Arachnidae* family and are worldwide ubiquitous; they preferably grow in humid and warm environments up to 2000 m over sea level. HDMs consist of many species, but the most clinically relevant are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [1,2].

The IgE response to HDM occurs very early in life, reaching a peak during the adolescence-young adulthood and progressively diminishing with aging [4]. The HDM molecular allergen components are well identified and cloned: the major allergens are Group 1 (Der p 1 and Der f 1) and Group 2 (Der p 2 and Der f 2) proteins [5]. HDM allergy is characterized by bothersome symptoms, mainly concerning nasal and bronchial obstruction, and eye itching. Symptoms closely depend on allergic inflammation caused by the allergen exposure. In addition, HDM allergy may have a negative impact on quality of life.

The work-up in patients with HDM allergy deserves careful attention, mainly concerning correct diagnosis and AIT prescription [6,7]. In this regard, it is commonly assumed that HDM allergic symptoms are perennial. However, an Italian study reported that HDM-allergic patients had more symptoms during the fall-winter period [8]. Interestingly, this fall peak of allergic symptoms is concomitant with the so called 'September epidemic' due to viral infections, more evident in allergic children [9]. Actually, the HDM concentration at home is not constant

during the whole year, but may periodically vary with two peaks: fall-winter, the main and spring [1]. Similarly, nasal inflammation seems to be closely related to mite variations, as shown by nasal cytology in HDM allergic patients, that detected a peak in the number of inflammatory cells in the period between October and April [8]. In this regard, mite allergy is frequent in subjects, mainly children, with recurrent respiratory infections. Children with RRI and allergy are an emerging problem for pediatricians and otolaryngologists in clinical practice. The diagnosis of RRI is performed according to the following criteria: >6 RI per year; >1 RI per month involving upper airways from September to April; >3 RI involving lower airways [10]. RRI have a relevant impact on pharmacoeconomy and are a burden for both the family and the society.

Many factors may be involved in promoting and/or causing RRI, including age (for a relative immaturity of the immune system), early attending at nursery school, air and home pollution, passive tobacco smoking, low socioeconomic level and atopy [11]. In particular, allergy plays a crucial role in promoting the RI recurrence as the immune response is impaired in allergic subjects and allergic inflammation favors infections. Actually, allergic subjects have a defect of the type 1 immune response that is appointed to hinder infections producing anti-infective cytokines, namely IFN- γ . In fact, allergic children have more numerous and severe infections than normal subjects [12]. Moreover, allergic subjects typically present the so called minimal persistent inflammation, in other words, mucosal inflammatory cell infiltrate closely associated to allergen exposure [13]. This event may account to sustained susceptibility to infections because of impaired type 1 response, increased ICAM-1 expression (the main rhinovirus receptor) on epithelial cells and local inflammation that represents a *pabulum* for pathogens [14]. Moreover, the virus may promote bacterial superinfection and consequently antibiotic use. As viral infections are frequent in RRI patients, the probability of observing antibiotic resistance is high [15,16]. Another issue is represented by bacterial biofilm that commonly induces antibiotic unsuccess [17].

Moreover, allergic patients with IRR show a Type 2 polarization, reduction of macrophage phagocytosis, reduction of neutrophil chemotaxis and a partial IgA and/or IgG subclasses deficiency [18]. In this scenario, mast cells play a pivotal role, as produce several mediators and cytokines that in turn maintain and amplify Type 2 polarization and consequently allergic inflammation, also minimal [19]. Therefore, mite allergy represents a typical model of persistent inflammation with recurrence depending on seasonal variations of mite concentrations. Thus, mite allergy has a relevant impact on the link between allergy and infection. In addition, mite allergy is also relevant in the pathogenic mechanism of asthma as the persistence of inflammation and the increased susceptibility to viral infections, namely rhinovirus ones, allows to understand the occurrence of asthma exacerbations after respiratory infections. In other words, mite allergy induces an inflammatory cascade and in this scenario overexpression of ICAM-1 on epithelial cells promotes rhinoviral infection susceptibility so patients with mite allergy are more prone to respiratory infections and consequently to present asthma exacerbations. As a consequence, to modify this vicious circle is a challenge for the allergist. AIT is at present the unique causal treatment of allergic reaction. This fact underlines the importance of appropriately prescribe AIT in mite allergic subjects.

Moreover, another relevant issue should be considered, such as the polysensitization: it has always been an obstacle to prescription of AIT. Currently two attitudes are dominant: to renounce to such treatment or to perform it by mixtures of all the allergens that showed a positive result in allergy tests. Both approaches are inappropriate and the latter was demonstrated to be ineffective. The allergy diagnosis is based on the concordance between the positive IgE testing and symptom occurrence after exposure to the sensitizing allergen. This point is crucial as up to 80% of allergic patients are also polysensitized [20]. Moreover, molecular-based allergy diagnostics allow to precisely define and characterize the sensitization profile in order to define genuine sensitization and exclude cross-reactivity [21].

Thus, these concepts could have practical consequence, mainly concerning the AIT schedule. In addition, allergy practice in Italy is characterized by a widespread presence of allergy clinics usually managed by allergists, so currently an adequate care for allergic patients is guaranteed throughout the territory. Moreover, different formulations of AIT are available in Italy for the HDM allergic patients: SLIT solution, SLIT tablets, SLIT lyophilized tablets and SCIT.

Method

On the basis of this background, a web-survey has been conducted on a group of 45 Italian allergists who commonly prescribe AIT in clinical practice. The allergists have been selected based on their primary professional activity, including a large number of allergic patients visited yearly (at least 1000) and a homogeneous geographical distribution over the country. The aim was to discover the current behavior in prescribing and managing AIT in patients with HDM allergy. The survey, rigorously anonymous, has been conducted using the SurveyMonkey

Table 1. Questions of the survey.

Questions	Answer options	Responses
(1) What is your opinion about the criteria to diagnose respiratory allergy to dust mites?	(a) Clinical history and skin tests (b) Clinical history, skin tests and <i>in vitro</i> IgE tests (c) Clinical history, skin tests and molecular diagnostics (d) Consistency between sensitization and occurrence of symptoms	40% 20% 4% 36%
(2) How many patients with certain mite allergy had AIT prescription?	(a) Less than 10% (b) 10–50% (c) 50–80% (d) More than 80%	13% 48% 36% 3%
(3) What is the criterion for choosing the AIT way of administration?	(a) Patient's preference (b) Based on the work of patient (c) Based on the free time of the patient. (d) Previous failure with a given AIT form	15% 20% 57% 8%
(4) What AIT schedule do you use for mite allergy?	(a) Perennial (b) Intermittent (c) Limited to the fall-winter period (d) Depending on single case	81% 10% 9% 0
(5) Concerning patients treated with mite lyophilized tablets, how do you estimate the treatment adherence?	(a) Excellent (b) Good (c) Bad (d) Very bad	40% 60% 0 0
(6) How do you appraise the benefit achieved by mite lyophilized tablets?	(a) Excellent (b) Good (c) Bad (d) Very bad	33% 66% 0 0
(7) Managing mite lyophilized tablets AIT, do you perform specific IgE measurement?	(a) Always (b) Never (c) Sometimes (d) Only in patients with asthma	32% 15% 51% 2%
(8) When do you think that mite lyophilized tablets start to provide a relevant benefit?	(a) After 1 month (b) After 3 months (c) After 6 months (d) After 12 months	12% 51% 34% 3%
(9) What are the criteria that you use to measure response to AIT?	(a) The intensity of symptoms (b) The drug consumption (c) Both (d) Neither	2% 0 98% 0
(10) Do you prescribe drugs during AIT?	(a) As needed (b) Constantly (c) Only for severe symptoms (d) Never	83% 7% 10% 0
(11) What age group is more adherent to mite AIT?	(a) Adolescents (b) 18–25 years (c) 24–40 years (d) More than 40 years	27% 10% 48% 15%
(12) What is your prescribing attitude in mite allergic patients with polysensitization?	(a) The prescription is based on molecular diagnostics (b) The prescription is based on the consistency between clinical history and results of allergy tests (c) I prescribe AIT only for mites (d) I do not prescribe AIT	13% 87% 0 0

AIT: Allergen immunotherapy.

platform and asking 12 questions with multiple answers, reflecting the own usual practice, as reported in Table 1. The questionnaire was administered in Italian and then translated to English in the manuscript.

Results

In regards to question 1, only 36% correctly indicated the consistency between clinical history and HDM-IgE positivity. In fact, the commonest error is to not correlate the symptom occurrence with exposure to the sensitizing allergen. In regards to question 2, considering an appropriate work-up and a correct diagnosis of HDM allergy, 48% of allergists prescribe AIT in 10–50% of patients, 36% in 50–80% of patients. Consequently, AIT is commonly prescribed in half of the HDM allergic patients. In regards to question 3 (concerning the specific characteristics of the patients), 57% answered that the decision is individually-based. In regards to question 4, 81% of allergists

responded they recommend perennial schedule. In regards to question 5, 60% of allergists believe that adherence is good, and 40% excellent. In regards to question 6, 67% of allergists consider the clinical benefit good, and 33% excellent. Regarding the possible answers to questions 5 and 6 (i.e., 'excellent' and 'good', etc.), we deliberately considered these terms leaving the interpretation to the subjective perception of the allergist, as we believe that these issues concern a subjective perception of these questions (similarly to Visual Analogue Scale).

In regards to question 7, concerning on-going AIT treatment, 51% of allergists evaluate serum IgE sometimes, 32% always, 15% never and 2% only in asthmatic patients. In regards to question 8, 51% of allergists believe that the clinical benefit occurs after 3 months, 34% after 6 months, 12% after 1 month and 3% after 1 year. In regards to question 9, 98% of allergists correctly consider the combined score of symptom severity and medication use as the correct criterion. In regards to question 10, 83% of allergists prescribe drugs on demand, 10% if symptoms are severe and 7% continuously. In regards to question 11, based on a simple gut-feeling for which ages of patients are most compliant with AIT, 48% of allergists think that the 25–40-year group has the best AIT adherence, followed by 27% in adolescents, 15% in over-40 and 10% in young adults. In regards to question 12, 87% of allergists consider the consistency between clinical history and sensitization the major factor to decide AIT prescription in polysensitized patients, while 13% use molecular diagnostics.

Discussion

Based on the answers provided by the allergists enrolled in the survey, the results can be summarized as follows: allergists were confident that AIT should be prescribed continuously; allergists perceived that lyophilized tablets are well accepted by patients, effective in most subjects and have a fast onset of action (3–6 months); allergist commonly considered combined score for symptom severity and medication use, prescribed symptomatic drugs on demand and frequently performed an appropriated work-up in polysensitized patients; allergists are not accustomed to certain points, including the diagnosis of HDM allergy, the quote of AIT prescription, the assessment of serum IgE and the perception of patient's adherence to AIT.

Based on these outcomes, it seems that there is the need of providing further information to clinical allergists concerning the relevance of molecular allergy diagnostics in clinical practice, as it could better define the allergy diagnosis. Moreover, we have the conviction about the importance of AIT prescription in a greater number of patients, as there is evidence that early intervention may guarantee optimal success [22,23]. In fact, although drug treatment can help reduce the incidence and severity of symptoms, only AIT can modify the course of the disease, providing immediate, long-term and preventive immunological and clinical effects in patients with AR [24,25]. Both types of AIT, subcutaneous and sublingual immunotherapy (respectively SCIT and SLIT), function through multiple mechanisms, including regulating-T and -B cell responses, changing antibody isotypes and decreasing mediator release and migration of eosinophils, basophils and mast cells to affected tissues [26]. In the process of immune tolerance induction, allergen-specific T-regulatory cells (Tregs) have a pivotal role in the downregulation of the Th₂ response [27]. This appears to be one of the milestones in the development of peripheral tolerance to allergens. Naturally occurring FoxP3⁺ CD4⁺CD25⁺ Treg cells and inducible type 1 Treg (Tr1) cells contribute to the control of allergen specific immune responses in several major ways, mediated by cytokine signaling of IL-10 or TGF- β : suppression of DCs that support the generation of effector-T cells; suppression of effector-Th₁, -Th₂ and -Th₁₇ cells; suppression of allergen specific IgE, and induction of IgG₄; suppression of mast cells, basophils and eosinophils and suppression of effector T-cell migration to tissues [26]. Moreover, an observation from a single study has demonstrated a significant correlation between improvement of symptoms and the increase in Treg cell numbers during immunotherapy [28].

Recent SCIT trials using allergen derivatives have shown that SCIT is an active vaccination which induces a new immune response in patients [29]. This response includes not only the induction of an allergen-specific IgG₄ response, but also IgG₁ [30]. This IgG response highly correlated with the reduction of allergic symptoms and a reduction of skin sensitivity to the allergen, suggesting that allergy vaccination induced allergen-specific IgG antibodies block the IgE recognition of allergens and the subsequent allergic reactions [30].

Conclusion

A considerable group of Italian allergists considers AIT for HDM allergy a valid therapeutic option, but some uncertainty still persists. Thus, there is the need of providing diffusely accurate and correct information about AIT in clinical practice, according to the current guidelines on mite AIT. In particular, it has to underline that AIT is the only treatment for allergic disorders that exerts effects both on the allergic inflammation and the natural history of

allergy. Really, AIT reduces the inflammatory events consequent to allergen exposure. Thus, AIT-responder subjects may have a benefit also concerning respiratory infections and asthma exacerbations. On the other hand, AIT may prevent the onset of asthma in patients with allergic rhinitis. Therefore, AIT should be prescribed in the majority of allergic subjects to obtain long-standing outcomes.

Future perspective

The current survey provided the opportunity to define some issues that could modify the clinical approach to AIT for mite allergy in next future. Molecular diagnostics will have a pivotal role in the work-up of patients with mite allergy as it will allow to characterize the sensitization profile in polysensitized patients: it is the basis of the Precision Medicine. Therefore, a precise diagnosis represents the correct premise for the Personalized Medicine. AIT tablets could be an optimal choice in patients with mite allergy as they are comfortable to be taken at all ages and are very manageable. In addition, allergist should be aware about the relevance of knowing the exact mechanisms of action of AIT, the criteria for defining AIT responder, and the potential side effects. Finally, a crucial challenge for the allergist will be the patient engagement in the management of mite allergy. Actually, the persuasion and the involvement of patients with chronic disorders are the basis of a fruitful therapeutic pathway and an adequate adhesion.

Executive summary

Background

- Mite allergy is very common and allergen immunotherapy (AIT) is the only causal treatment.
- AIT management is still debated, so a group of Italian allergists discussed the results of a web-survey.

Outcomes

- This group of Italian allergists is confident that AIT should be prescribed continuously.
- These allergists believe that AIT tablets are usually well accepted by patients, and are effective in most subjects with a fast onset of action (3–6 months).
- Combined score for symptom severity and medication use is commonly used by these allergists for assessing AIT response.
- These allergists disagree about: the diagnosis of HDM allergy; the quote of AIT prescription; the choice for AIT route of administration; the assessment of serum IgE; and the perception of patient's adherence to AIT.

Future perspective

- Molecular diagnostics will have a pivotal role in the work-up of patients with mite allergy in the next future.
- AIT tablets will represent an interesting therapeutic option.
- Patient engagement will contribute to enhance the adhesion to AIT.

Conflict of interest

The authors have no relevant conflict about the current paper.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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