

EDITORIAL

IMMUNOLOGICAL TREATMENTS FOR OCCUPATIONAL ALLERGY

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Although avoidance of occupational triggers remains the primary step in the management of work-related allergies, immunological treatments (including biological agents and specific immunotherapy) can be regarded as potential therapeutic options for IgE-mediated diseases; for example, many studies with allergen-specific immunotherapy have been carried out on latex allergy, showing overall favorable results, at least with sublingual immunotherapy. On the other hand, only few case reports have suggested the efficacy of immunotherapy in baker's asthma as well as in laboratory animal-induced asthma. The new technologies, including component-resolved diagnosis and recombinant allergens, are expected to improve the quality and efficacy of specific immunotherapy in the future. Also the use of omalizumab may represent a suitable therapeutic choice in very selected cases of occupational allergy, as well as an approach to reduce side effects of venom immunotherapy in subjects with previous severe reactions to the treatment.

Occupational asthma and rhinitis are defined as respiratory diseases caused by the exposure to agents encountered in the work environment, including highly reactive small molecules, irritants, known immunogens and complex plant and animal products that can stimulate the production of IgE (1). In particular, occupational asthma is one of the most common forms of diseases in many industrialized countries, and occupational allergens are estimated to cause about 1/10 cases of asthma among adults of working age (1). This implies serious health and socio-economic consequences. Two types of occupational asthma can be distinguished: immunologic (due to an IgE-mediated sensitization) and non-immunologic which occurs after acute exposure to high concentration of irritants (2, 3).

Occupational rhinitis is an inflammatory condition of the nose, characterized by intermittent or persistent symptoms due to conditions attributable to a particular work environment and not to stimuli encountered outside the workplace (4). Occupational rhinitis and asthma often coexist (up to 70% of cases in asthma are due to laboratory animals), and also occupational rhinitis may be sustained by IgE or non-IgE-mediated mechanisms.

Allergen specific immunotherapy (SIT) represents a suitable therapeutic option for respiratory allergy (and other IgE-mediated diseases). This is true when allergen avoidance is not feasible/effective and when the IgE-dependent mechanism, and the causal role of the allergen are well ascertained (5). A special indication to SIT is hymenoptera venom

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allergy (HVA), that represents an occupational allergy for beekeepers, gardeners, truck-drivers and other categories of workers. The recent introduction of biological treatments (e.g. omalizumab), and the availability of recombinant allergens, have further enlarged the therapeutic field. The aim of this review is to summarize the studies published to date on the use of SIT and biological treatments in occupational allergy.

ALLERGEN IMMUNOTHERAPY IN OCCUPATIONAL ALLERGIES

Latex allergy

Latex allergy is still a risk mainly for healthcare workers, although its prevalence is declining. In fact, the recent improvements in latex technology have reduced the allergen content of latex-containing devices (e.g. gloves, catheters), and the more appropriate use of those devices has reduced the prevalence of latex allergy (6). Latex avoidance involves the use of non-powdered gloves or non-allergenic gloves and the replacement of all materials likely containing latex. However, complete avoidance is sometimes not feasible. Thus, efforts have been made to obtain standardized latex extracts for diagnosis and treatment.

Following sparse reports, suggesting the clinical efficacy of subcutaneous immunotherapy, (SCIT), three controlled trials were carried out (7-9) (Table I). In the first study, 20 healthcare workers were treated, with a 2-day induction schedule, and with a maintenance dose of 20 mcg/mL of latex protein for one year. Efficacy was assessed by symptom/medication scores and by conjunctival threshold to latex extract. Overall, an improvement of nasal and ocular symptoms was detected as well as a significant increase in specific conjunctival threshold dose. Local reactions were common and 4/9 patients had generalized systemic reactions (7). Another controlled trial, with a standardized extract, involved 24 patients with respiratory and skin symptoms. The efficacy was evaluated by symptom score, glove use test and specific inhalation challenge. The treatment involved a build-up phase of 14 weeks and a maintenance period of six months. After 6 months, an improvement was recorded only in those SCIT patients with cutaneous symptoms, whereas

no effect on respiratory symptoms was seen, except a decrease in bronchial non-specific reactivity. Systemic reactions occurred in 68.7% of patients (8). The third SCIT trial (9) was conducted in 23 healthcare workers with rhino-conjunctivitis and asthma. It failed to detect significant differences in symptom/medication scores between active and placebo groups. The low symptom score at baseline and the low maintenance dose may have accounted for the lack of efficacy. Also in this study, systemic reactions occurred frequently. Due to the unfavorable risk to benefit ratio, SCIT for latex allergy was virtually abandoned.

Several studies, either open or controlled, were then performed with sublingual immunotherapy (SLIT) (10) in populations, including also, but not only, healthcare workers as summarized in Table I (11-16). Overall, these studies reported favorable results. In summary, a significant improvement was seen in latex glove test, asthma symptoms and urticaria. Also using rush inductions the highest occurrence of local side effects was seen in 25%, with treatment needed in 10% of those, and with one patient needing epinephrine (11). A more recent published trial failed to demonstrate any clinical improvement in adult patients with skin and/or respiratory symptoms after latex exposure. Mild local reactions were also reported in 10% of the SLIT patients (16). An optimal tolerability was reported in an Italian pediatric study, which also demonstrated a long lasting effect (13). Notably, SLIT-induced anaphylaxis was reported in a woman 20 minutes after the highest build-up dose during a rush protocol, requiring treatment in an emergency room (10).

Altogether, these studies underline some uncertainties on the use of SIT in latex allergy. Patients with high sensitivity to latex and severe symptoms seem to have the greatest benefit from SIT, but also seem to be at higher risk of side effects. Patients with mild disease can be easily managed with avoidance measures and SIT seems to be not indicated. Certainly, SLIT is the more suitable option, based on the risk to benefit ratio, although properly controlled studies are needed.

Recombinant DNA technology could achieve a more accurate standardization of extracts in the future, and the possibility of a more detailed

diagnosis, dissecting cross-reacting proteins and genuine sensitizers. Recombinant components are available for the major allergens (Hes b 5 and Hes b 6), which are of relevance in healthcare workers (17).

Cereal flour

Respiratory allergies are common among bakery workers and, although wheat is the most commonly involved cereal, others (rye, barley, rice, maize, and oats) may play a role. The so-called baker's asthma is one of the most common types of occupational allergy and its prevalence does not seem to be on the decline (18). The demonstration of the efficacy of SIT in baker's asthma is essentially based on old studies. The only controlled trial, performed in 1990, was carried out on 30 asthmatic patients treated with an aqueous wheat flour extract up to 20 months (19). After the IT course, actively treated patients showed a significant clinical improvement, an increase in the methacholine threshold provocation dose, and a reduction in specific skin reactivity. Some case reports and a retrospective study seemed to prove the efficacy of IT in baker's asthma (20, 21). However, the lack of standardized extracts is the main drawback of immunotherapy in baker's asthma. This reflects

the uncertainty on the role of the different wheat proteins in causing occupational diseases.

Laboratory animals

Occupational respiratory diseases due to the sensitization to animal allergens are common. The responsible allergens are contained in the urine, saliva and secretions of animals, dried on fur, bedding, or other vectors so that the antigen becomes airborne on particles of different size. Some of these particles are small enough to remain airborne and reach the lower airway. Laboratory animal allergy is the best studied occupational allergy. It is an important occupational health problem, affecting research, pharmaceutical and toxicological sectors and can have a serious impact on employees working in this area. Despite measures to reduce aeroallergen exposure in the workplace, in particular to rodents, there are few signs that this occupational health problem is declining (22). Despite this, only few anecdotal studies have been published to date. In an open study, Whan treated 11 exposed asthmatic subjects with an allergen extract of mice, rat and rabbit, and found 11 actively treated patients showed a significant improvement, and a dose-related increase in IgG.

Table I. Immunotherapy studies carried out in latex allergy to evaluate clinical efficacy.

Author, year (ref)	Patients (A/C)	Study design	Disease	Route	Duration	Main results	Safety
Leynadier, 2000 (7)	9/8	DBPC	A, R, U	SCIT	12 months	Significant improvement in symptom score; increase in specific threshold dose at conjunctival challenge	SRs in 47% of actively treated patients and in 13% of placebo
Sastre, 2003 (8)	16/8	DBPC	R, A, U	SCIT	6 months	No symptom improvement or change in skin reactivity. Decrease in specific bronchial reactivity	SRs in 69% of the active treated group patients
Tabar, 2006 (9)	11/10	DBPC	A	SCIT	12 months	No improvement in clinical scores and in specific conjunctival reactivity	SR in 81 % of active treated patients and 17 % placebo
Patriarca, 2002 (11)	12/12	DBPC	R, A, U	SLIT	3 months	Improvement at the glove test and specific conjunctival challenge	No SRs, only mild LR
Cistero-Bahima, 2004 (13)	26	Open	R, U	SLIT	10 weeks	Improvement at the glove provocation test	SRs in 3.6% doses (46% of patients). LR in 21% doses (88.5% of patients)
Nettis, 2007 (12)	18/17	DBPC	R, U	SLIT	12 months	Improvement at the glove provocation and decrease in skin reactivity and symptoms	0.9 % of active treated patients complained of LRs
Buyukozturk, 2010 (15)	8/4	DBPC	R, A, U	SLIT	12 months	Decrease of symptoms and of glove test	Three severe SRs registered
Gastaminza, 2011 (14)	14/14	DBPC	R, A, U	SLIT	12 months	No change in symptom score, skin reactivity and glove provocation	4 active and 5 placebo treated patients complained of mild SRs
Bernardini, 2006 (16)	12/8 children	DBPC	A, R, U	SLIT	12 months	Improvement in glove test, symptoms and no change in skin reactivity	No SRs or LRs observed

A/C: active/control; A: asthma; R: rhinitis; U: urticaria; LRs: Local Reactions; SRs: systemic reactions; DBPC: double blind placebo controlled

(23). Hansen et al. described a patient with rat allergy who underwent SIT with a rat allergen extract. After 18 months of treatment, the allergy waned and the patient remained symptom-free at the workplace (24). Nonetheless, epidemiological data on allergy to furry animals in occupational environments and its treatment with IT remain scarce, even concerning specific working categories such as veterinaries or pet shop owners.

Other allergens

Some cases of unexpected IgE-mediated allergies, related to the workplace have been described. Workers in oyster farms in Japan have been reported to develop sea quirt (*hoya*)-induced asthma. A group of such patients underwent a 4-year subcutaneous immunotherapy using three different antigens, Gi-rep, Ei-M and DIII. Treatment was considered successful when patients remained asymptomatic when engaged in their oyster shucking work. Interestingly, a significant clinical improvement was associated with the use of Gi-rep and Ei-M. An increase in allergen-specific IgG was also observed in Gi-rep and DIII treated patients, but this did not correlate with the clinical outcome (25). Hinojosa et al. reported the reduction of skin reactivity and an improvement of non-specific bronchial hyperreactivity after a 2-year course of SCIT in two workers allergic to African maple or obeche (*Triplochyton scleroxylon*) (26). According to the paucity of data, no firm conclusion or recommendation can be made on the use of IT in such a rare disease, also because of the poor characterization and standardization of desensitizing vaccines.

Hymenoptera venom allergy

Some categories of workers, spending most of their time outdoors, or working in contact with hymenoptera, are at high risk of being stung by insects and becoming sensitized to hymenoptera venom. Thus, HVA is considered as an occupational disease for beekeepers, fruit sellers, gardeners, farmers, masons and truck drivers (27). Patients showing only local large reactions are prescribed with an emergency kit with oral anti-histamines and corticosteroids, whereas auto-injectable epinephrine is still debated in these cases. Subjects showing systemic reactions are usually treated with SIT

which confers an efficient protection in >80% of cases (28). Bumblebee-induced anaphylaxis is rare, as compared to other HVA, because of the habitat and non-aggressive behavior of these insects. For this reasons systemic allergic reactions occur only in occupational exposed workers such as gardeners (29). In fact, in Europe *Bombus terrestris* have been domesticated and used for more than 20 years to pollinate plants grown in greenhouses, such as tomatoes and sweet bell peppers. About 75% of sera from patients allergic to honeybee react in radio-allergo sorbent test with bumblebee venom and 85% of sera from patients with a positive history of allergy to bumblebee stings show a positive response to honeybee-related venom proteins (30). For these reasons the choice of the extract in bumblebee allergic workers is still a challenging issue, and the common practice of giving honeybee venom IT in bumblebee allergic patients is not universally accepted (28).

Of note, skin lesions caused by processionary caterpillar (*Thaumatopea pityocampa*) are frequent in pinewood areas. Cases of IgE mediated anaphylaxis have been reported in heavily exposed workers, such as foresters (31). Although many relevant allergens have been detected recently, a standardized extract for immunotherapy is not yet available (32).

ANTI-IgE IN OCCUPATIONAL ALLERGIES

Omalizumab, is a humanized monoclonal antibody that binds free-circulating IgE, impeding their engagement with the high-affinity receptor. Omalizumab is indicated in the treatment of severe allergic asthma, and it could be considered a potential option in very selected cases in occupational allergy. Two case reports showed an encouraging clinical effect in severe baker's asthma (33, 34), since a significant improvement in quality of life and a steroid use was assessed in both patients described. Omalizumab was also used in latex allergy, treating 18 health care workers suffering from rhinitis, conjunctivitis and mild asthma. After 16 weeks, an increase in specific conjunctival threshold dose and a reduction in skin reactivity to latex were observed, (35). Finally, concomitant omalizumab treatment was used in three patients allergic to honeybee, who complained of severe reactions to immunotherapy.

Only in two cases the use of omalizumab allowed to reach the maintenance dose, with an efficient protection (36, 37).

CONCLUSIONS

Although occupational allergy is less frequent than in the past, it still remains a public health risk. Avoidance of the occupational trigger is the first mandatory step of treatment of all occupational related conditions, including allergic diseases. However, when complete avoidance is not possible, SIT could be a rational choice in selected IgE-mediated disorders. SIT is the only aetiological treatment available that may affect the natural history of diseases. Criteria for the prescription of SIT to treat allergic rhinoconjunctivitis and asthma are: a) well demonstrated sensitization to occupational allergen(s) b) clear causal relationship with the symptoms; c) avoidance of allergen exposure not feasible or ineffective. This has been well ascertained in HVA, and, to a lesser degree, with latex. Only small studies have been carried out in other sensitizations, including baker's asthma or oyster-induced allergies, and no robust recommendation can be provided in such cases. Further progress in this field necessitates an extensive use of recombinant allergen technology to better identify the allergens involved and therefore to produce standardized extracts. The use of omalizumab, even if shown to be effective, has to be reserved to very selected cases due to the cost of the drug.

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