

Recent advances in the management of occupational asthma

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Occupational asthma (OA) is the most common occupational lung disease in industrialized countries. This respiratory disorder remains poorly diagnosed and managed, and inadequately compensated for worldwide. The most appropriate treatment for OA remains early removal from exposure to ensure that the worker has no further exposure to the causal agent with preservation of income. However, various studies demonstrate that many workers with OA continue to remain exposed to the causative agent or suffer prolonged work disruption and discrimination, and may face unemployment. Despite removal from exposure, OA frequently turns into a chronic condition and requires intensive medical management, including appropriate pharmacotherapy and patient education and counseling. There are very few studies on allergen immunotherapy in OA. Subcutaneous immunotherapy with latex extract in healthcare workers and with wheat-flour extract in subjects with baker's asthma, at adequate doses, appears to be a useful treatment in reducing cutaneous and respiratory symptoms, but should be considered as a high-risk treatment due to the appearance of systemic reactions.

KEYWORDS: allergen avoidance • allergen immunotherapy • occupational asthma • omalizumab • pharmacotherapy • prognosis

Work-related factors acting through different pathophysiological mechanisms are responsible for various clinical manifestations of asthma [1]. Work-related asthma can be broadly defined as occupational asthma (OA) or asthma caused by specific agents in the workplace, and work-aggravated asthma – that is, pre-existing or coincidental asthma worsened by workplace exposures [2]. There are two major forms of OA:

- Allergic (immunological) asthma, characterized by a latency period required for developing allergic sensitization prior to the development of symptoms;
- Irritant-induced (nonimmunological) asthma, characterized by the onset of asthma following single or multiple exposures to high concentrations of irritant agents.

Occupational asthma is the most common occupational lung disease in industrialized countries and the second most common occupational lung disease reported after pneumoconiosis in developing countries [3]. The median proportion of adult cases of asthma attributable to occupational exposure is between 10–15% [4]. In a longitudinal analysis of the European Community

Health Survey, the population-attributable risk for adult asthma due to occupational exposures ranged from 10 to 25%, equivalent to an incidence of new-onset asthma of 250–300 cases per million people per year [5].

There are substantial legal and economic implications for the worker and their employer with OA and, therefore, early identification and appropriate management are essential. The proportion of subjects with OA who benefit from financial compensation varies from 24 to 87% in European countries [6]. The cost of compensation for OA is largely unknown. Recent data have confirmed that work-aggravated asthma is associated with a similar impact on work productivity and earning capacity as is immunologically-mediated OA [7]. Due to the important economic consequences of work-related asthma, cost–effectiveness analyses should also be considered in the diagnosis [8], surveillance [9] and management of this condition.

The present review focuses on new data concerning the management of OA, including exposure avoidance and pharmacotherapy, and with a special emphasis on innovative approaches such as anti-IgE monoclonal antibodies and allergen immunotherapy.

Exposure avoidance & general measures

Evidence-based guidelines for the management of OA clearly state that the likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent, in workers who have relatively normal lung function at the time of diagnosis and in workers who have shorter duration of symptoms prior to diagnosis or prior to avoidance of exposure [10]. Thus, early diagnosis and early avoidance of further exposure are the cornerstones of patient management for patients with immunological OA. Whenever feasible, the patient should be relocated to a job category without exposure. This may be better achieved in larger companies where relocation is possible, but this seldom happens in smaller companies, where there are no nonexposed roles and, thus, many affected workers choose to either remain exposed or have their employment ended.

Relocation to a nonexposure area may lead to improvement or resolutions of symptoms or prevent deterioration in some workers, whereas ongoing exposure usually leads to worsening of asthma and frequent exacerbations (FIGURE 1). Unlike patients with immunological OA, patients with irritant-induced OA can usually continue to work in the same job, provided that measures are taken to prevent further exposure to high concentrations of irritant agents [11].

The difference in prognosis for workers with OA who remain in the work environment compared with those who completely quit their job and for whom exposure was completely eliminated has been demonstrated in several studies [12].

Reduction of exposure by appropriate means (relocation to less-exposed jobs, improvement in workplace hygiene, use of modified material and personal protective devices) might be considered as an alternative to complete removal from exposure when this is impractical or unacceptable. However, a comprehensive review of pooled published data showed that reducing exposure is more frequently associated with persistence of asthma symptoms and persistence of bronchial hyperresponsiveness, and with worsening of asthma than complete removal [6]. In latex-induced OA, however, it has been demonstrated that in individuals who reduced their exposure, asthma control and airway hyperresponsiveness improved significantly [13,14]. The use of protective respiratory equipment should not be considered as a substitute for restrictions from exposure to the offending agent [10]. Nevertheless, a helmet respirator has been demonstrated to be partially effective in reducing the consequences of exposure in certain cases. For instance, there is some evidence that respiratory protective equipment may have some role in preventing the induction of sensitization and respiratory allergy to acid anhydrides [15].

Despite exposure avoidance, a significant proportion of patients with OA continue to experience asthmatic symptoms and non-specific bronchial hyperresponsiveness after removal from occupational exposure. Symptoms and nonspecific airway hyperresponsiveness persist in approximately 70% of affected workers [16]. At least 2 years after removal from exposure to the offending agent, approximately 60% of subjects show a decrease in, but a persistence of, specific bronchial responsiveness to high- and

low-molecular-weight agents [17]. The persistence of asthma after cessation of exposure is associated with the presence of airway inflammation [18].

A comprehensive evidence-based review on the diagnosis and management of OA has raised several important questions [19]. The weaknesses associated with the methodological quality of the research evidence in this area were underlined. Most importantly, the interventions were generally divided into removal, reduced exposure or continued exposure; however, the definition of these approaches differed and allocation was nonrandomized. Treatment cointerventions were also incompletely reported in these studies. Nevertheless, some conclusions were drawn based on the evidence. Workers with OA who remained exposed to the workplace asthmagens tended to experience decreased forced expiratory volume in 1 s (FEV₁) over time, increased bronchial hyperresponsiveness and continued to require medications to control their symptoms [19]. Most workers with OA who ceased to be exposed to the workplace sensitizer appeared to experience improved FEV₁ over time and less bronchial hyperresponsiveness. Despite these improvements, many workers will continue to require medications to control their symptoms; some workers with OA can be expected to continue to experience a decrease in their FEV₁ over time, despite ceasing sensitizer exposure [19]. The evidence of outcome for workers who reduced their exposure is insufficient to draw firm conclusions but, from the limited evidence, it appears likely they continue to have ongoing disease [19].

In a recent editorial, Heederik and van Rooy argue that the quality of the exposure information in most studies on the prognosis of OA has not been sufficient to decide whether the exposure

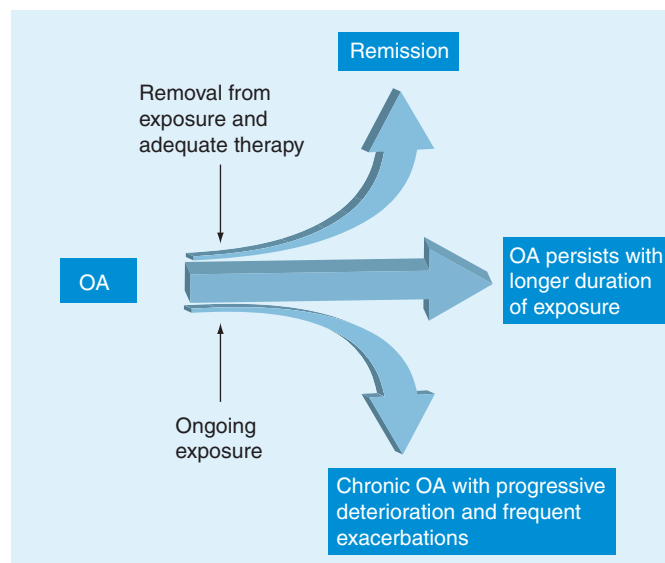


Figure 1. Possible outcomes for workers who have developed OA. These may vary according to the cessation or persistence of exposure to the causative agent. Prognosis is worse among workers with longer duration of exposure after symptom onset, whereas cessation of exposure is associated with a better prognosis. There are scarce data available to infer the probability of each outcome. OA: Occupational asthma.

reduction was present and whether it was sufficient and, therefore, the effect of gradual exposure reductions deserves further research, including good exposure assessment practices [20].

Patients with OA are usually very sensitive to common stimuli, such as cold air, exercise, dust and irritants. Thus, general measures, such as cessation of smoking and avoidance of exposure to environmental irritants or to common aeroallergens to which the patients may also be sensitized, should always be recommended. Notwithstanding this, in a comprehensive review, Siracusa *et al.* found little evidence to support the view that the risk of OA is increased in workers who are smokers, whereas evidence emerges of an increased risk of occupational sensitization in smoking workers exposed to several high- and low-molecular-weight agents [21].

In the management of OA, it is also important to consider that the majority of patients with this condition also suffer from occupational rhinitis, which most often precedes the development of OA, especially when high-molecular-weight-agents are involved [22]. Occupational rhinitis is associated with an increased risk of asthma, although the proportion of subjects with occupational rhinitis who will develop OA remains uncertain [22].

Exposure control

Identifying all potential inhaled hazards and assessing the associated risk in a particular workplace is of the utmost importance. Despite the fact that enforcing suitable exposure levels to occupational sensitizers is difficult; many countries have implemented legal standards to control exposure to sensitizers. Occupational allergy and asthma to enzymes used in the detergent industry [23] and to platinum salts used in the refining industry [24] have been successfully controlled via the use of preclinical, clinical and industrial hygiene safety programs designed to minimize sensitization and development of disease. Several studies suggest that laboratory animal allergy can be effectively prevented by a targeted program, including education and training, modification of work practices, engineering controls, the use of personal protective equipment and a standardized system of surveillance [25].

The experience of latex allergy is paradigmatic. Available data indicate that preventive measures to avoid occupational latex allergy, mainly the complete replacement of powdered latex gloves with low-protein, powder-free gloves and the use of latex-free materials by sensitized individuals, have led to a decrease of the incidence of latex allergy among healthcare workers [26–28].

Exposure–response relationships have been previously observed in isocyanate spray painters but now for the first time for oligomers and not monomers [29]. Isocyanates have also been demonstrated to trigger innate immune responses that could influence the clinical spectrum of exposure reactions [30]. Prevention strategies have also been found to be effective in isocyanate-induced OA. A study suggested a low rate of sensitization to diphenylmethane diisocyanate (MDI) in a urethane mold plant that had been designed to minimize MDI exposure [31]. A multicomponent, simple control measures surveillance program for isocyanates in an automotive coatings business was successfully implemented [32].

Pharmacotherapy

Pharmacological treatment of OA does not differ from therapy of other types of asthma and should comply with published asthma guidelines [33]. Once the diagnosis of OA has been firmly established, efforts should be made to increase the use of inhaled corticosteroids, which are frequently underutilized in asthma management [34]. In general, the anti-inflammatory agents (i.e., preventers) appear to be an effective short-term therapy for OA; however, limited OA-specific research has been performed [19].

Maestrelli *et al.* demonstrated that inhaled corticosteroids improved airway hyperresponsiveness to methacholine in subjects with toluene diisocyanate (TDI)-induced asthma, but had no effect in reducing bronchial sensitivity to TDI [35]. Thus, pharmacotherapy for OA should never be considered as a suitable substitute for effective exposure avoidance. Malo *et al.* reported that inhaled corticosteroids induce a small but significant overall improvement in the asthmatic condition of individuals with OA caused by high- and low-molecular-weight agents after withdrawal from exposure [36]. The beneficial effect is, however, more pronounced if inhaled steroids are given early after diagnosis.

Marabini *et al.* evaluated the effect of treatment with beclomethasone dipropionate and salmeterol in ten patients with mild-to-moderate OA still exposed to the work environment responsible for their disease [37]. After 3 years, they observed a nonsignificant deterioration in clinical or functional parameters despite persistence of exposure.

Omalizumab is a recombinant and humanized monoclonal antibody that binds to free circulating IgE and partially inhibits the inflammatory cascade. It is approved as add-on therapy for adult and adolescent patients with severe allergic asthma in the EU and moderate-to-severe allergic asthma in the USA. Several randomized, double-blind trials have demonstrated the therapeutic efficacy of subcutaneously administered omalizumab as an add-on therapy in patients with allergic asthma [38]. It has also been demonstrated to have clinical benefit in severe, persistent baker's asthma [39]. Additionally, a study on 16 healthcare workers with occupational latex allergy (rhinitis, conjunctivitis and/or mild-to-moderate asthma) demonstrated that omalizumab had clinically relevant ocular and skin antiallergic activity in workers with occupational latex allergy who were not removed from their work environment [40]. The use of omalizumab in allergic OA and rhinitis deserves further research since, in many instances, these disorders are due to an IgE-mediated mechanism.

Counseling & compensation

Impairment and disability evaluation should be carried out as soon as the asthma is stabilized (temporary) and 2 years later (permanent) and patients should also be counseled regarding compensation [41]. Nevertheless, responsiveness to methacholine continues to improve beyond 2 years following cessation of exposure to agents causing OA [42].

Workers diagnosed with OA should be assisted with relevant compensation claims and rehabilitation. As discussed above, OA may result in serious negative socioeconomic consequences [6,43].

Approximately a third of workers with OA are unemployed up to 6 years after diagnosis and suffer financially [10]. Physicians should support the affected workers in the pursuit of appropriate compensation and should report occupational disease to the corresponding worker's compensation system and occupational health agency. In some countries, work-aggravated asthma may also be eligible for compensation [44].

Box 1 outlines the main steps in the management of OA, which have been slightly modified from the Canadian guidelines [11].

Allergen immunotherapy

Allergen immunotherapy consists of administering gradually increasing quantities of an allergen extract to an allergic patient to ameliorate the symptoms associated with subsequent exposure to the causative allergen [45]. The most common route of administration is by subcutaneous injection but, in the last decade, the sublingual route has increasingly been used. Immunotherapy is accompanied by increases in allergen-specific IgG, particularly the IgG₄ isotype, which blocks not only IgE-dependent histamine release from basophils, but also IgE-mediated antigen presentation to T cells [46]. Allergen immunotherapy acts on T cells to modify peripheral and mucosal Th2 responses to the allergen in favor of Th1 responses. Recent studies have identified increased IL-10 production in peripheral blood and mucosal surfaces after allergen immunotherapy. These IL-10-producing cells might be so-called Tregs and appear to be identified by the CD4⁺CD25⁺ phenotype [46]. Immunotherapy ameliorates both early and late asthmatic responses to allergen exposure. There is evidence that allergen immunotherapy has a long-standing effect on reducing rhinitis and asthma symptoms and the use of medications, and improves bronchial hyperresponsiveness when administered in adequate doses. Immunotherapy is indicated for treatment of IgE-mediated allergic rhinoconjunctivitis and asthma when medications insufficiently control symptoms, in patients who do not wish to receive pharmacotherapy or when it produces untoward side effects and when effective allergen avoidance is not possible.

Box 1. Management of occupational asthma.

Asthma treatment according to published asthma guidelines:

- Assessment and control of nonoccupational sensitizers and other asthma triggers
- Pharmacotherapeutic interventions
- Immunomodulation: omalizumab and allergen immunotherapy (in highly selected cases)
- Patient education

Work exposure:

- For immunological occupational asthma, avoid any further exposure to causative agent(s). If this is not possible, reduce exposure as much as possible
- For irritant-induced occupational asthma, avoid further high-level exposure

Assist patient with relevant compensation claim and rehabilitation
Consider other coworkers affected and notify public-health authorities and the employee's company

Modified from [11].

These indications may be fulfilled in many cases of occupational rhinitis and asthma and allergen immunotherapy can, therefore, be considered for treating occupational allergies, especially when allergens cannot be fully eliminated from the workplace. However, the lack of purified and well-standardized extracts of occupational allergens may restrict its use. There are few reports of allergen immunotherapy for treating occupational rhinitis or asthma and very few controlled double-blind placebo-controlled studies [47].

Cereal flour

The first double-blind, placebo controlled study of allergen immunotherapy in OA was published by Armentia *et al.* in 1990 [48]. A total of 26 asthmatic patients were selected for the study out of 139 bakers and pastry cooks included in a prevalence study of IgE-mediated hypersensitivity to wheat flour demonstrated by skin tests, specific IgE and inhalation challenge to wheat flour. In this trial, 20 patients were treated with an aqueous wheat-flour extract (ALK-Abelló, Madrid, Spain) and ten were given placebo. Patients were treated for between 10 and 20 months. After allergen immunotherapy, the active group showed a significant decrease in skin sensitivity and in airway hyperresponsiveness to methacholine, assessed by a score system. Specific IgE to wheat flour decreased only in patients who were treated with immunotherapy for 20 months. Patients in the active group also reported a significant subjective improvement, whereas patients in the placebo group showed no changes in these variables.

Case reports [49] and retrospective studies [50] have also shown efficacy of wheat flour immunotherapy in baker's asthma. An observational cross-sectional retrospective study was performed on 41 sensitized workers from the same occupational health unit [50]. All underwent subcutaneous specific immunotherapy with the same schedule and the same wheat-flour extract (Lofarma Allergeni, Milan, Italy) for 4 or more years, without avoiding their work activity. The outcome was investigated after 5 or 10 years. Data were collected via a questionnaire. In total, 34 out of 41 subjects were still at work with an acceptable quality of life and a normal working activity, mainly in small enterprises. In the subgroup of 19 patients treated in the past, several bakers still at work had ceased immunotherapy 4–10 years previously. In the subgroup of 15 patients still in treatment, symptoms and drug use during the work activity was reduced or absent in the majority of cases. The authors suggest that allergen immunotherapy with wheat flour may allow relocation in many cases of baker's asthma and may be associated with other environmental interventions in the workplace.

Immunotherapy with cereal flour has several limitations. An important pitfall is the lack of standardized cereal extracts for diagnosis and immunotherapy. Other limitations are the fact that bakers with negative IgE tests to water-soluble wheat extracts might be sensitized to wheat gliadins [51] and that new wheat-flour allergens have been recently identified, making standardization difficult [52,53].

Natural rubber latex

Natural latex is a relatively frequent cause of allergic disease and is still a health hazard for healthcare workers despite improvements in latex glove manufacture and a reduction in the allergen

content of gloves [54]. Other at-risk occupations include workers involved in collecting and processing latex from rubber trees [55] and greenhouse workers [56]. Different proteins present in various latex products have been implicated in causing allergy in distinct risk groups [57].

Treatment of latex allergy includes avoiding latex-containing products and symptomatic medication. Avoidance measures imply the use of nonpowdered and nonallergenic gloves and the replacement of all material likely to contain latex. Since complete avoidance of this substance is a difficult task, other therapeutic alternatives, such as specific immunotherapy, have been evaluated.

Toci *et al.* first reported the use of oral immunotherapy in three health workers with latex allergy with good results [58]. Pereira *et al.* described the successful use of subcutaneous immunotherapy in a radiologist technician with latex allergy [59]. The same authors also described the use of subcutaneous immunotherapy in four patients (three workers and a boy) with latex allergy [60]. All patients had anaphylaxis caused by latex and oral-latex-fruit syndrome and three of them had severe symptoms in the workplace. All four patients were treated with an aqueous extract (ALK-Abelló) administered subcutaneously at the hospital by a modified rush schedule, at a maintenance dose of 0.35 µg/ml of protein. In one patient, a higher dose induced the appearance of a systemic reaction 40 min after administration. After reaching the maximal dose, the three health workers remained asymptomatic at the workplace. A reduction in skin reactivity to latex in all patients by prick tests was observed.

Laynadier *et al.* published the first pilot study, a Phase IIb multi-center, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of subcutaneous immunotherapy with latex in patients with occupational allergy [61]. A total of 20 healthcare workers with rhinitis and/or asthma due to latex allergy were included. Treatment started with a 2-day course of rush immunotherapy in the hospital followed by maintenance therapy for 1 year. The extract used was provided by Stallergenes (Antony, France) and the maximum maintenance dose was 100 index of reactivity (IR), equivalent to approximately 20 µg/ml of latex protein. Efficacy was assessed by symptom and medication scores and by variation in the conjunctival reactivity threshold. The safety of the extract was also evaluated. Patients in the active treatment group had a significantly lower total rhinitis score after 6 ($p < 0.04$) and 12 months ($p < 0.05$), conjunctivitis score after 6 months ($p < 0.02$) and cutaneous score after 12 months ($p < 0.03$) than patients in the placebo group. Asthma symptoms after 6 or 12 months of treatment were not significantly different between the two groups after adjustment for baseline values. The global medication score was markedly decreased in the latex-treated group. A significant difference in conjunctival reactivity was observed in favor of the active group ($p < 0.02$). Improvement was more evident after 4 months of therapy. Concerning safety, almost half the patients receiving active treatment showed local reactions starting with the first injection, and four of the nine patients in this group suffered moderate-to-severe systemic reactions.

Sastre *et al.* published a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of subcutaneous immunotherapy with a standardized natural latex rubber extract in a population of 24 patients occupationally sensitized to latex who had cutaneous and respiratory symptoms [62]. To diagnose respiratory allergy, an inhalation challenge was performed in a 7 m³ chamber and, in case of contact urticaria, glove-use and rubbing tests were performed, using a vinyl glove as a negative control. Treatment consisted of a first phase of incremental doses for 14 weeks, with 18 injections, followed by maintenance doses for 6 months. A total of 16 patients received active treatment and eight received placebo. The extract used was standardized and contained a maximum of 20 µg/ml of latex protein or 5 HEP/ml, provided by ALK-Abelló. The average maximum tolerated dose was 11.1 ± 9.3 µg of latex protein. Five patients tolerated less than 1 µg of latex protein, with a cumulative dose of 5.1 ± 3.2 µg; three tolerated between 1 and 10 µg, with a cumulative dose of 58.2 ± 25.3 µg; and eight patients received the maximum dose of 20 µg/ml, which was repeated six- or seven-times, with a cumulative dose of 186.3 ± 14.5 µg of latex protein. Systemic reactions were observed in 8% of doses and 68.7% of patients but no patients dropped out of the study due to systemic reactions or another cause. Systemic reactions occurred in 8.9 and 5.3% of doses during the build-up and maintenance phases, respectively ($p = 0.3831$). Patients with respiratory symptoms had a significant higher rate of immediate systemic reactions than patients with cutaneous symptoms only (8.0 vs 2.7%, respectively; $p = 0.004$). After 6 months of treatment, patients in the active-treatment group had a significant decrease in the skin reactivity to the latex extract along the treatment. Patients in the active group required a concentration of latex extract 12-times higher than previously, in order to induce the same wheal area by prick test. Patients in the placebo group, however, did not show changes in their cutaneous response by skin-prick tests. A clear and significant improvement was found in the active treatment group and in the rubbing and glove use tests. There were no significant differences between patients in the active and placebo groups in symptoms score, use of medication, self-assessment or methacholine test, either before or after treatment. An improvement in bronchial symptoms ($p = 0.05$) during a specific challenge test with latex was observed in the active group. Nasal symptoms also improved but these improvements did not reach statistical significance.

Tabar *et al.* investigated the efficacy and safety of a 12-month subcutaneous latex (Stallergenes, Antony, France) low-dose immunotherapy protocol in 23 patients with latex-induced rhinoconjunctivitis and asthma (the majority of whom were healthcare workers) in a randomized, double-blind, placebo-controlled trial (11 patients in the active group; 12 patients in the placebo group) [63]. Treatment efficacy was assessed by means of symptom and medication scores. Change from baseline of rhinitis, conjunctivitis, skin symptoms, asthma symptoms, medication score and cutaneous reactivity were not significantly different between the two groups. A nonsignificant difference in conjunctival reactivity was observed in favor of the active group ($p = 0.09$). Systemic reactions were much higher in the specific immunotherapy group

than in the placebo group. This study failed to show a significant improvement in symptoms and medication scores, probably because of the low level of symptoms at baseline and the low maintenance dose of therapy, even if allergen-specific conjunctival reactivity decreased in the active group. Moreover, the incidence of systemic reactions was very high in the active group.

Sublingual immunotherapy has also been evaluated in patients allergic to latex. Patriarca *et al.* studied 24 patients allergic to latex with cutaneous and respiratory symptoms. A total of 12 of them underwent a rush (4-day) sublingual desensitization to latex, followed by maintenance therapy, and the other 12 patients were considered to be controls [64]. The sublingual rush desensitization protocol was successfully completed in all patients with no side effects. The extract contained a maximum dose of 50 µg/ml provided by ALK-Abelló. After 3 months of treatment, all patients from the active-treatment group were able to wear latex gloves for 6 h and had an improvement in respiratory, conjunctival and mucocutaneous symptoms as well as in their conjunctival challenge test, this test being negative in 50% of the patients. Patients in the control group did not experience any improvement.

Cisteró *et al.* assessed the tolerability of sublingual rush immunotherapy with latex extract and its effects on skin reactivity [65]. In total, 26 patients with cutaneous and respiratory symptoms due to latex were studied. All underwent rush sublingual therapy (4 days) with a standardized latex extract that contained a maximum dose of 500 µg/ml (ALK-Abelló), followed by a 9-week maintenance treatment course. Skin reactivity to latex was evaluated before, during and at the end of the treatment by the latex glove-use, rubbing and skin-prick tests. All patients reached the maintenance dose. Out of 1044 administered doses, 257 (24.6%) produced adverse reactions, from which 21.4% were local. Only 10.1% of cases required treatment. The glove-use test improved significantly after 5 days and 10 weeks of treatment ($p = 0.003$, $p = 0.0004$, respectively), whereas the rubbing test improved significantly only after 10 weeks of treatment. No change was detected for skin-prick tests. A recent study confirmed the safety of rush induction with latex sublingual immunotherapy, the 3-day protocol being better tolerated than the 2-day scheme [66]. In summary, tolerance of sublingual immunotherapy appears better than tolerance reported for injective therapy with latex extract but, during the build-up phase, systemic reactions with sublingual immunotherapy were also reported in some studies.

The long-term effect of this treatment deserves further investigation.

Laboratory animals

Wahn and Siraganian evaluated the clinical and immunologic response to immunotherapy with laboratory animal allergens in 23 patients; 11 received immunotherapy with 12 different extracts (five mouse, six rat and one rabbit) and 12 were untreated matched patients [67]. Among the treated patients, nine out of 11 subjectively improved with immunotherapy. Treated patients had mean blocking antibody levels significantly higher than untreated patients. The blocking antibody level correlated with both the final weekly allergen dose and also the cumulative allergen dose received during immunotherapy.

Hansen *et al.* described a laboratory worker with severe rhinoconjunctivitis and bronchial asthma due to rat who underwent immunotherapy with a rat extract [68]. Treatment was performed as an in-patient procedure with a rush-immunotherapy protocol. Some months after starting this therapy, the patient felt subjective symptom relief and a decrease in total IgE and specific IgE against rat epithelium was observed. Therapy was continued for 18 months, at which time specific IgE against rat epithelium waned and the patient did not suffer from any allergic symptoms when working in the rat facility any more.

Expert commentary

Evidence-based approaches have recently been undertaken to review the quality of information underpinning medical practice in the field of OA. It might be expected that evidence-based medicine also will change the research agenda in this field. Although this might be problematic for the short term, this is probably positive in the longer term (due to better quality research).

The prognosis of subjects with OA is better if the disease is recognized early and they are removed from exposure quickly, particularly within a year of the onset of symptoms. Thus, early diagnosis and avoidance of further exposure are the cornerstones of management for patients with immunological OA. The use of respirators is of limited value and should not be considered as a substitute to exposure avoidance. Relocation to a nonexposure area may lead to improvement or symptom resolution and prevent deterioration in some workers, whereas ongoing exposure usually leads to worsening of asthma symptoms and frequent exacerbations. The ideal intervention would be to remove the causative agent from the workplace but this approach is not always feasible. The pharmacological management of OA does not differ significantly from the therapy of asthma that is not work-related and should comply with published asthma guidelines. Targeting circulating IgE with omalizumab can be considered as a therapeutic option for patients with severe persistent allergic asthma, but further long-term studies are clearly warranted in patients with allergic OA and occupational rhinitis.

Since complete allergen avoidance is not always feasible and pharmacological treatment does not always resolve respiratory symptoms, a treatment such as allergen immunotherapy might be considered, provided an IgE-mediated mechanism to high-molecular-weight antigens is demonstrated. The best documented use of allergen immunotherapy in OA corresponds to latex allergy in healthcare workers. Subcutaneous immunotherapy with latex extract, at adequate doses, appears to be a useful treatment in reducing cutaneous and respiratory symptoms, but systemic reactions induced by this treatment may occur. At present, subcutaneous immunotherapy with latex extract can only be considered as almost experimental and must be administered by experienced allergists in a hospital setting. A few studies have also demonstrated some clinical efficacy of subcutaneous immunotherapy with wheat-flour extract in sensitized bakers with asthma. The use of standardized extracts and at appropriate doses is highly recommended.

Further clinical trials are needed to assess the efficacy, safety and long-term effectiveness of immunotherapy, and in addition, add-on studies with pharmacologic agents or anti-IgE monoclonal

antibodies in IgE-mediated OA could be carried out. A possible modification of the natural history of allergic sensitization from rhinitis to asthma is another interesting effect to be demonstrated with immunotherapy.

Five-year view

There are few high-quality systematic reviews in OA since it is usually not ethical or feasible to carry out randomized trials of diagnostic tests or therapeutic interventions. However, in the last few years, evidence-based guidelines for the prevention, identification and management of OA have been published in the UK by the British Occupational Health Research Foundation [10,33] and by independent researchers [19], and a systematic review has also been released in Spain [69]. These guidelines stress the need for early diagnosis and quick removal from exposure once the diagnosis of OA has been objectively made. They also highlight the important role of physicians to assist their patients with appropriate compensation claims and to establish links with appropriate agencies to ensure that other coworkers are

considered when a diagnosis of OA is made, since this should be considered as a sentinel event. Such notification may enhance preventive measures in that workplace, help to consider other possible coworkers who may also be at risk and enable detection of any factors that may have contributed to sensitization and OA. As noted in these guidelines, current areas of particular interest for research and future developments include identifying new causative agents, mechanisms of sensitization and the health effects associated with complex multiple exposures, encompassing 'mixed' environments and the possible synergistic effect of irritants and sensitizers.

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Key issues

- Occupational asthma (OA) is the most common occupational lung disease in industrialized countries but it remains poorly diagnosed and managed, and inadequately compensated for worldwide.
- The symptoms and functional impairment of OA caused by several agents may persist for years after avoidance of further exposure to the causative agent.
- The likelihood of improvement or resolution of symptoms, or of preventing deterioration, is greater in workers who have no further exposure to the causative agent. On the contrary, ongoing exposure to the causative agent is associated with poor asthma control and frequent exacerbations.
- Complete avoidance of exposure is the most effective treatment of immunological OA and should be strongly recommended for affected workers.
- Relocation of the worker with OA or substitution of the causative agent offers the best chance for recovery.
- The outcome of OA does not differ according to the molecular weight of the causal agent.
- The pharmacological treatment of asthma is identical to that of nonoccupational asthma, with inhaled corticosteroids being the cornerstone of therapy.
- Immunomodulatory treatments, such as anti-IgE monoclonal antibodies, can be considered in the management of selected cases of severe IgE-mediated OA.
- Immunotherapy may also be of value in the small proportion of patients with allergic OA caused by high-molecular-weight agents, whose symptoms remain uncontrolled on maximum drug therapy and who remain exposed at work.
- Workers with OA are more likely to be unemployed after diagnosis and, therefore, suffer financially.
- Patients with OA should be assisted with their relevant compensation claim and rehabilitation.

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