

Clinical Management Review

The Role of Immunotherapy and Biologic Treatments in Occupational Allergic Disease

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Occupational exposures are estimated to account for 15% to 25% of all adult asthma in the general population. In some cases, workplace allergen exposures can be reduced but not entirely eliminated. Given the potentially significant impact of job change, some workers may choose to continue working in a job in which there is an ongoing occupational allergen exposure. In these cases, a combined approach including personal safety measures, pharmacotherapy, and allergen immunotherapy may result in the best clinical outcomes. This review presents existing evidence for the use of immunotherapy and biologic treatments in occupational allergic disease for various occupational allergens, including wheat flour, mammalian proteins, natural rubber latex, and Hymenoptera venom. There is increasing but modest evidence on beneficial short-term and long-term effects of allergen immunotherapy and safety in worker populations. Available data suggest that allergen immunotherapy can reduce skin and respiratory symptoms and therefore allow workers to continue their current occupation. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

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INTRODUCTION

Occupational respiratory allergies represent a substantial burden on society, with significant health and financial impacts. Work-related asthma encompasses the entire spectrum of asthmatic conditions related to workplace exposures. Occupational asthma (OA) is a disorder characterized by variable airflow limitation, airway hyperresponsiveness, and inflammation as a result of a particular occupational environment and not to stimuli encountered outside the workplace.^{1,2} Work-exacerbated asthma refers to bronchospasm provoked by triggers at work in workers with concurrent or preexisting asthma. OA and work-exacerbated asthma may coexist in the same patient and are not mutually exclusive. Occupational rhinitis (OR) is an inflammatory disease of the nose, which is characterized by

intermittent or persistent symptoms and/or variable nasal airflow limitation and/or hypersecretion as a result of a particular work environment and not to stimuli encountered outside the workplace.³

The management of occupational allergies usually prioritizes environmental control measures to reduce exposures to relevant workplace allergens. Because environmental interventions are emphasized, this approach may account for the relative paucity of published clinical trials about the efficacy and safety of immunotherapy in occupational respiratory allergies. The cessation or reduction of exposure often leads to negative financial consequences for workers, especially when they have to leave their job.⁴ Therefore, any improvement in treatment that allows workers to continue their current occupational activity is significant.

The pharmacologic treatment of occupational respiratory allergies is not different from that of nonoccupational asthma or rhinitis.^{3,4} Allergen immunotherapy (AIT) is the repeated administration of specific allergens to patients with IgE-mediated disease to provide protection against the allergic symptoms associated with the natural allergen exposure.⁵ AIT should be considered for patients who have symptoms of allergic rhinitis, rhinoconjunctivitis, and/or asthma after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens.⁶ In a systematic review involving 3459 patients with asthma, AIT resulted in significant reductions in asthma symptoms, medication use, and improvement in bronchial hyperactivity.⁷ AIT should not be initiated in patients with poorly controlled asthma symptoms or who have medical conditions or take medications that reduce the ability to survive a systemic allergic reaction or the resultant treatment.

OR often precedes and coexists with OA in workers sensitized with high-molecular-weight allergens. Therefore, offering AIT to a worker with OR may present an opportunity for secondary prevention of OA. AIT may also be considered in symptomatic workers in whom workplace allergen exposures can be reduced but not entirely eliminated. Given the potentially significant impact of job change, some workers may choose to continue working in a job in which there is an ongoing occupational allergen exposure. In these cases, a combined approach including

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Abbreviations used

ADA- Animal dander allergy

AIT- Allergen immunotherapy

NRL- Natural rubber latex

OA- Occupational asthma

OR- Occupational rhinitis

RDBPC- Randomized, double-blind, placebo-controlled

SCIT- Subcutaneous immunotherapy

SLIT- Sublingual immunotherapy

personal safety measures (eg, masks or respirators), pharmacotherapy, and AIT (when appropriate) may result in the best clinical outcomes. At the same time, close medical monitoring is important to ensure that the ongoing exposure does not cause more severe airway obstruction or illnesses.

Biologic therapies can be considered in OA just as with nonoccupational asthma. Omalizumab is an anti-IgE antibody used for the treatment of moderate to severe persistent asthma in patients 6 years and older with a positive skin test result or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. Given the severity of some OA cases, omalizumab has been evaluated as an additional therapy. Recent reports have suggested a beneficial effect of biological treatment with omalizumab in patients with OA who remained exposed to the causal agent.

The objective of this review was to identify and evaluate the existing evidence for the use of immunotherapy and biologic treatments in occupational allergic disease.

DATA SOURCES, SEARCH STRATEGY, AND STUDY SELECTION

Published studies were identified from PubMed and were reviewed by the authors. We used the following keywords search strategy: (work-related OR occupational) AND (asthma OR rhinitis) AND (allergen immunotherapy) AND (omalizumab OR anti-IgE OR biological treatment).

Wheat flour

Bakers and pastry makers often develop OR and baker's asthma due to exposure to wheat flour, which contains high-molecular-weight protein allergens. Rye, barley, rice, oats, and maize may also be causative.⁸ The occupational respiratory allergies are mediated by IgE antibodies specific to cereal flour antigens. The prevalence of baker's asthma is estimated to be 9% among bakery employees, and the incidence of rhinitis is estimated to be 18% to 29%.⁹ Although bakers are most frequently

affected, other workers who are exposed to bakery allergens can develop the disease, including supermarket bakery workers, confectioners, food processors, and flour millers.¹⁰⁻¹²

Despite the significant impact of flour-induced OA, there are few published reports of AIT in the management of the disease (Table I). In the only double-blind placebo-controlled study, 139 patients who worked with wheat flour were evaluated.⁹ Of the 139 subjects, 35 (25%) demonstrated sensitization to wheat via skin prick test or elevated *in vitro* specific IgE. From this sensitized group, 8 patients with asthma were treated for 10 months and 8 for 20 months with wheat flour extract subcutaneous immunotherapy (SCIT). Ten received placebo. Four treated patients discontinued therapy because of a change in job. Treated patients had a significant decrease in wheat flour extract skin prick test sensitivity and in bronchial hyperresponsiveness. By 20 months, wheat flour specific IgE decreased and symptoms improved with exposure. No severe systemic reactions were reported.

Other promising data on the efficacy of AIT in baker's asthma come from case reports and a retrospective study from Italy.^{13,14} In the Italian study, most of the 41 sensitized bakers who were treated with wheat flour extract SCIT for 4 or more years were able to continue their work activity. Benefit continued for several years after stopping treatment.

The use of AIT in the management of baker's asthma has been limited by the lack of standardization and poor quality of allergen extracts. Part of the problem is the uncertainty about which proteins are the major allergens in baker's asthma due to wheat flour exposure.^{10,11} The availability of purified allergens may be helpful for more precise diagnosis and treatment. Although wheat flour extract may be effective in treating baker's asthma, further confirmation is required in larger controlled clinical trials.

Animal allergy (mammalian proteins)

The estimated prevalence of animal dander allergy (ADA) ranges between 11% and 44% of workers.^{15,16} There has been a trend toward a decline in prevalence in the last decades, likely due to the implementation of interventions to reduce exposure to allergens in the workplace.¹⁷⁻²¹ These interventions include education and training of personnel, better local exhaust systems with high-efficiency particulate air-filtered room ventilation, and use of personal protective equipment to limit the inhalation of allergens. In addition, other approaches include surveillance programs with symptoms assessments, skin prick tests for common and occupational allergens, and work practice modifications. Nevertheless, ADA remains an important occupational health problem. The most common allergens related to ADA are

TABLE I. Studies of immunotherapy with wheat flour

Reference	Allergen	Study design	Number studied	Indication	Results	Level of evidence
9	Wheat flour	RDBPC	30	Asthma	-Decreased bronchial hyperresponsiveness -Improvement in symptoms on exposure	A
13	Wheat flour	Case report	1	Asthma	-Decreased asthma symptoms	C
14	Wheat flour	Observational cross-sectional retrospective study	41	Asthma	-Acceptable quality of life -Able to continue working	B

An extract for wheat flour immunotherapy is not commercially available in the United States or Europe.

Level of Evidence: A—Randomized controlled trial; B—Controlled trial without randomization or other quasi-experimental study design; C—Nonexperimental descriptive studies; and D—Expert opinion.

TABLE II. Studies of immunotherapy with animal allergy (mammalian proteins)

Reference	Allergen	Study design	Number studied	Indication	Results	Level of evidence
23	Mouse, rat, rabbit	Unblinded, matched-untreated controls	11	Rhinitis, conjunctivitis	-Decrease in symptoms on exposure	B
24	Rat	Case report	1	Asthma, rhinitis	-Complete symptom relief	C
25	Cow	Case report	1	Rhinitis	-Decrease in symptoms on exposure	C
26	Mouse, rat	Case series	4	Asthma	-Decreased asthma, rhinitis, and cutaneous symptoms	C

Extracts for animal allergy immunotherapy are commercially available in the United States, but not in Europe.

Level of Evidence: A—Randomized controlled trial; B—Controlled trial without randomization or other quasi-experimental study design; C—Nonexperimental descriptive studies; and D—Expert opinion.

dog, cat, rat, mouse, hamsters, guinea pig, gerbil, rabbit, ferret, pig, sheep, goat, and latex. Less common allergens include fruit fly, locust, cockroach, or worm larvae. Most of the mammalian allergens are members of the lipocalin family. These allergens are under the control of androgenic hormones but cross-reactivity is limited.²²

There are relatively few reports of the use of AIT in patients with ADA (Table II). In a study by Wahn and Siraganian,²³ 11 patients with asthma exposed to laboratory animals received AIT with mouse, rat, and rabbit extracts. After AIT, 9 of 11 patients subjectively improved, and all patients had a significant IgG dose-related increase. In another study, a biologist with rhinitis and bronchial asthma due to allergy to rat epithelium received AIT for 18 months with rat epithelium.²⁴ The treatment led to complete rhinitis and asthma symptoms relief and enabled the patient to continue her work. A decrease in specific IgE against rat epithelium during the treatment was observed, being undetectable at the end of the study. In another single case, successful AIT was described in a cow breeder with monosensitization to cow dander with an improvement in rhinitis symptoms.²⁵

In 2016, Goddard and Azar²⁶ described 4 cases of OA induced by mouse and rat. The extracts used were glycerinated extracts of *Mus musculus* and *Rattus norvegicus* (Greer Labs, Lenoir, NC) at 1:20 (wt/vol) concentration. The extract was diluted to 1:100 (wt/vol), and 0.5 mL of this solution was used for maintenance therapy. AIT was started at a 1:1000 (vol/vol) dilution. All patients had a significant, sustained improvement in rhinitis, asthma, and cutaneous symptoms and were able to return to work after AIT.

Occupational allergy to cat, dog, or horse is also frequent in workers related to the care of animals. However, there are no studies of AIT specific to occupational allergies in sensitized workers. Extrapolating results from AIT studies with high doses of standardized extracts of cat and dog allergens, these patients can benefit from AIT for occupational allergic disease.²⁷⁻³⁰

Natural rubber latex

Allergy to natural rubber latex (NRL) has been an important allergic disease. It may still be a health hazard not only for health care workers but also for workers processing latex from rubber trees, in patients with spina bifida, to those who have undergone multiple surgical procedures, and in subjects with certain food allergies.³¹ There has been a noticeable reduction in cases of occupational and nonoccupational NRL allergy in the last 2

decades. The policy of latex-free environments in many institutions and the use of either nonpowdered latex gloves or latex gloves with very low allergen content have helped to reduce the incidence of new cases and to avoid symptoms in sensitized patients. Given availability of specific tests for selection of low-allergen gloves, the use of NRL gloves within the hospital environment may change over time.³²

Hevea brasiliensis, the origin of NRL, is the best characterized occupational allergen.³³ Currently, 15 *H brasiliensis* allergens have been identified, Hev b 1-15 (<http://www.allergen.org>). Commercial tests are available in many countries for measuring individual natural latex allergens—Hev b 1 (rubber elongation factor), Hev b 3 (small rubber particle proteins), Hev b 5 (Acidic structural protein), Hev b 6.01 (prohevein), Hev b 6.02 (hevein), Hev b 8 (profilin), Hev b 9 (enolase), and Hev b 11 (class I chitinase). The most important allergens related to occupational allergy are Hev b 5 and Hev b 6.01.³⁴⁻³⁶ To support the diagnosis in patients with suspected IgE-mediated NRL type I allergy, a serological screening with at least 1 cross-reactive carbohydrate determinant and the recombinant allergens rHev b 1, rHev b 3, rHev b 5, and rHev b 6.01 is highly recommended.^{34,37} Nevertheless, in some cases, the use of other latex allergens may be helpful to discriminate between cross-reactivity and cosensitization to latex and fruits.³⁷

Treatment of latex allergy has included prevention measures of avoiding latex-containing products, certain foods, and symptomatic medication. Because complete avoidance of this substance is a difficult task, in the last 20 years an effort has been made to standardize a latex extract to offer other therapeutic alternatives, such as specific immunotherapy. In 2012, Nettis et al³⁸ published a review of available clinical trials on latex immunotherapy, either subcutaneous (SCIT) or sublingual (sublingual immunotherapy [SLIT]). After this date, no further publications on AIT with latex have been published.

The first report was published by Toci et al³⁹ in 1998 using oral immunotherapy in 3 health care workers with latex allergy. All 3 patients were able to tolerate latex exposure after AIT. In 1999, Pereira et al⁴⁰ described the successful use of SCIT in a radiology technician with latex allergy. Two years later, the same authors described the use of subcutaneous IT in 4 patients with latex allergy (3 OA and 1 spina bifida).⁴¹ All 4 patients were treated with specific AIT with aqueous latex extract at a maintenance dose of 0.35 mg/mL of protein. After reaching the maximal dose, all 3 female patients remained asymptomatic at the workplace. The patient with spina bifida was subjected to

TABLE III. Studies with SLIT with NRL

Reference	Study design	Number studied	Maintenance dose (latex protein/ mL) and duration	Age range (y)	Indication	Results	Level of evidence
45	RDBPC	24	300 µg for 3 mo	8-64	Asthma, rhinitis, urticaria	-Glove use, sublingual challenge, and ocular challenge negative -2 local reactions	A
46	Open	26	300 µg for 2.5 mo	15-45	Respiratory symptoms, cutaneous, anaphylaxis	-Significant improvement in glove-use and rubbing test -Systemic reactions 3.6% of doses/46.2% of patients -Local reactions 21.4% of doses/ 88.5% of patients	B
47	RDBPC	40	300 µg for 1 y	18-47	Urticaria, asthma	-Significant improvement in glove use -Side effects in 3 of 35	A
48	RDBPC	20	210 µg for 1 y	4-15	Rhinitis, asthma, urticaria	-Decrease in symptoms at glove- use and rubbing test	A
49	RDBPC	12	300 µg for 1 y	26-32	Urticaria, rhinitis, asthma, systemic	-Improvement at glove use and decrease in symptoms -3 severe systemic reactions	A
50	RDBPC	28	210 µg for 1 y	24-57	Urticaria, rhinitis, asthma, anaphylaxis	-No significant difference after therapy	A

An extract for NRL SLIT is not commercially available in the United States or Europe.

Level of Evidence: A—Randomized controlled trial; B—Controlled trial without randomization or other quasi-experimental study design; C—Nonexperimental descriptive studies; and D—Expert opinion.

TABLE IV. Studies of immunotherapy with Hymenoptera venoms

Reference	Allergen	Study design	Number studied	Indication	Results	Level of evidence
56	Honeybee, <i>Vespula</i> sp. (Rush)	Unblinded, no placebo	97	Anaphylaxis	-Protocol appears safe -No episodes of anaphylaxis	C
59	Honeybee, yellow jacket (rush)	Unblinded, no placebo	101	Anaphylaxis	-Higher rates of systemic reactions with honeybee vs yellow jacket	C
60	Honeybee, yellow jacket (rush)	Unblinded, placebo-controlled	18	Anaphylaxis	-Two field stings without reaction	B
61	Wasp, honeybee (ultrarush)	Unblinded, no placebo	67	Anaphylaxis	-Protocol appears safe -17.5% with mild allergic reaction during treatment	C
62	<i>Myrmecodia pilosula</i> (semirush; ultrarush)	Unblinded, semi-rush vs ultrarush	93	Anaphylaxis	-Higher rate of systemic reactions with ultrarush protocol	B
63	Bumblebee (rush)	Case series	2	Anaphylaxis	-In-hospital sting challenge with local reactions only	C
58	Bumblebee (ultrarush)	Case report	1	Anaphylaxis	-One field sting without reaction	C

Extracts for Hymenoptera venom immunotherapy are commercially available in the United States and Europe.

Level of Evidence: A—Randomized controlled trial; B—Controlled trial without randomization or other quasi-experimental study design; C—Nonexperimental descriptive studies; and D—Expert opinion.

surgical intervention with no allergic reaction. A reduction in skin reactivity to latex was observed in all patients as determined by skin prick testing.

In 2000, Leynadier et al⁴² published a randomized, double-blind, placebo-controlled (RDBPC) trial that evaluated the efficacy and safety of specific SCIT with latex in patients with occupational allergy. Twenty health care workers with symptoms of rhinitis and/or asthma due to latex allergy were included. The extract used was provided by Stallergenes (S. Antony, France), and the maximum maintenance dose was 100 IR (Index Reactivity [arbitrary units used by Stallergenes]), equivalent to approximately 20 µg/mL of latex protein. Patients in the active treatment group had a significantly lower total rhinitis score after 6 ($P < .04$) and 12 months ($P < .05$), conjunctivitis score after 6 months ($P < .02$), and cutaneous score after 12 months ($P < .03$) than in the placebo group. Asthma symptoms after 6 or 12 months of treatment were not significantly different between the 2 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. Concerning safety, almost half the patients receiving active treatment had local reactions, starting

with the first injection. Four of the 9 patients in this group experienced moderate to severe systemic reactions, but none were grade 4 per the World Allergy Organization grading system.

In 2003, Sastre et al⁴³ published a RDBPC study of SCIT with a standardized NRL extract in a population of 24 patients occupationally sensitized to latex who had cutaneous and respiratory symptoms. The extract used was standardized and contained a maximum of 20 µg/mL of latex protein (ALK-Abelló, Madrid, Spain) as a maintenance dose. Systemic reactions were observed in 8% of the doses and in 68.7% of the patients. After 6 months of treatment, patients in the active treatment group had a significant decrease in the skin reactivity to the latex extract and a clear and significant improvement in the rubbing and glove-use test. There were no significant differences between active and placebo groups in symptom score, use of medication, self-assessment, or methacholine challenge test either before or after treatment. Improvement in bronchial symptoms during bronchial specific allergen challenge tests with latex was observed in favor of the active group ($P = .05$). Nasal symptoms also improved but did not reach statistical significance. Tabar et al⁴⁴ published another RDBPC with natural latex extract that included 23 patients. They used the same latex extract used by

TABLE V. Studies of immunotherapy with other allergens

Reference	Allergen	Study design	Number studied	Indication	Results	Level of evidence
67	Obeche wood	Case series	2	Asthma, rhinitis	-Reduced skin test reactivity -Decreased bronchial hyperresponsiveness	C
70	Sea squirt	Unblinded, no placebo	123	Asthma	-Decreased asthma symptoms -Reduced medication use with exposure	C
69	Sea squirt	Unblinded, no placebo	22	Asthma	-Decreased asthma symptoms	C

Extracts for obeche wood and sea squirt immunotherapy are not commercially available in the United States or Europe.

Level of Evidence: A—Randomized controlled trial; B—Controlled trial without randomization or other quasi-experimental study design; C—Nonexperimental descriptive studies; and D—Expert opinion.

Leynadier et al for 12 months. This trial failed to demonstrate a clinical benefit of latex SCIT, likely due to a low maintenance dose.

Six studies with sublingual AIT have been published between 2001 and 2011 and are summarized in Table III.⁴⁵⁻⁵⁰ In general, SLIT had a better safety profile than SCIT, with overall favorable results in 4 of 5 RDBPC studies. Currently, to our knowledge, there are no commercial subcutaneous or sublingual extracts available for immunotherapy.

Hymenoptera venom

Hymenoptera insect stings are relatively common in the general population, with a prevalence of 56.6% to 94.5%.⁵¹ Recent data suggest that Hymenoptera venom allergy may be responsible for up to one-third of all anaphylactic reactions.⁵² Stinging insect hypersensitivity is an occupational problem for various professions, including farm workers, greenhouse workers, biologists, forest rangers, and beekeepers. Hymenoptera insects in the families Apidae (bees) and Vespidae (wasps) are primarily responsible. Family members include the honeybee (*Apis mellifera*), yellow jacket (*Vespula vulgaris*), wasp (*Polistes annularis*), white-faced hornet (*Dolichovespula maculate*), and yellow hornet (*Dolichovespula arenaria*).⁵³

Several studies show that the rate of systemic reactions in beekeepers is much higher (14%-35%) than in the general population (0.8%-3.3%).⁵⁴⁻⁵⁷ In a study of beekeepers, the number of stings per year correlated with the probability of sensitization.⁵⁴ However, frequent stings appeared to induce tolerance in other studies.^{58,59} Beekeepers with more than 200 stings per year appear to be protected from systemic reactions compared with those stung fewer than 25 times per year (45% with reactions).

The treatment of choice for moderate to severe reactions is SCIT with purified Hymenoptera venoms. In patients with a previous history of anaphylactic reactions, full protection can be achieved in 83% to 95% of patients with the standard maintenance dose of 100 µg administered every 4 to 6 weeks.^{51,57} Four treatment regimens are routinely used to treat patients: (1) conventional (weekly intervals for increasing doses), (2) rush (reaching maintenance dose over 4-7 days), (3) ultrarush (reaching maintenance dose over 1-2 days), and (4) cluster (modified rush with a cluster of injections at the first visit and reaching a maintenance dose within 6 weeks). Given the extensive data available about the efficacy of SCIT with purified Hymenoptera venoms, it appears reasonable to extrapolate data from controlled studies of AIT in nonworker populations to aid in treatment decisions in worker populations.

Several studies demonstrate the efficacy and safety of rush venom protocols, primarily with bee and yellow jacket venom (Table IV).^{56,59,60} Across the 3 studies, 216 patients received treatment, with only 1 patient not reaching maintenance dosing. Most patients had cutaneous reactions at the injection site. Systemic reactions were reported in 0.79% to 1.7% of the bee venom group compared with 0% to 0.12% in the yellow jacket venom group. Systemic reactions were reported at all phases of the protocol. Only 2 severe reactions were reported. In the study of 18 patients, 2 patients had field stings during the study.⁶⁰ One was a beekeeper who was restung several times. Neither patient had a significant reaction.

Ultrarush protocols have also been evaluated in several studies. In one study of 67 patients, 97.5% reached the maintenance

dose.⁶¹ Side effects were predominantly mild, with 17.5% of patients experiencing allergic reactions. In another study of 49 patients, systemic reactions were seen in 65% of patients.⁶² Severe reactions were observed in 12% of patients. Ultrarush venom immunotherapy initiation appears to increase the risk of systemic reactions.

Bumblebees are generally not very aggressive and allergic reactions are rare. However, with the increased use of domesticated bumblebees for pollination of crops, there has been an increase in the number of reported occupational allergic reactions.⁶⁴ There is a high degree of cross-reactivity between bumblebee and honeybee venom. Therefore, honeybee venom is used for treatment. Case reports indicate that this approach may not always be effective.⁶³ Two patients treated with honeybee venom were stung at work and developed anaphylactic reactions. After repeat bumblebee venom AIT, an in-hospital sting challenge resulted in only a cutaneous reaction. In a case series of workers on a bumblebee farm with anaphylactic reactions to bumblebee venom stings, 7 patients were treated with bumblebee AIT.⁶⁵ During treatment, at least 36 stings were reported without any systemic reactions. Finally, a biologist with a history of anaphylaxis underwent ultrarush bumblebee venom AIT.⁵⁸ Despite a resting, no systemic reaction was reported.

A large study including more than 1532 patients who had received a sting challenge showed a protection rate of 96% for yellow jacket venom IT and 84% for bee venom IT.⁶⁶ Overall, Hymenoptera venom AIT is considered safe and effective treatment for moderate to severe insect sting reactions. It should be considered in all workers with occupational reactions to prevent further allergic reactions to insect stings.

Other allergens

Hinojosa described 2 woodworkers with rhinitis and asthma induced by African maple or obeche wood (*Triplachyton scleroxylon*) who were treated with subcutaneous IT using an aqueous extract of this wood for 24 months (Table V).⁶⁷ After treatment, and while still working, a reduction in skin test reactivity and specific airway responsiveness to this wood (allergen PC20) was observed in both patients.

Asthma because of exposure to sea squirt allergens primarily occurs among Japanese oyster-shucking workers, who continuously inhale the sea squirt antigens in the mist of the body fluid of sea squirts. In 1963, the reported prevalence of sea squirt asthma was 36%.⁶⁸ With industrial hygiene improvements, the reported prevalence of sea squirt asthma has decreased to 8%. In one study, 21 females with sea squirt asthma were treated for 2 years with high-concentration purified sea squirt antigen Ei-M (Table V).⁶⁹ Effects were rapidly observed, with treated patients not developing asthmatic attacks even though they engaged in oyster-shucking work. Furthermore, serum anti-Ei-M IgG antibody was significantly increased after the therapy. No significant side effects were reported. In an uncontrolled study, 123 patients with asthma received SCIT with 1 of 3 known major sea squirt allergens, Gi-rep (n = 47), Ei-M (n = 62), or DIIIa (n = 14).⁷⁰ After 1 year of treatment, 72% of those treated with Gi-rep were able to shuck oysters with minimal or no medications, 90% of patients treated with Ei-M, and 36% of patients treated with DIIIa. Benefit from AIT was maintained over 5 years of treatment. Among Japanese oyster-shucking workers, it has been

reported that a significant number are currently treated or have received therapy in the past with SCIT.⁶⁸

Biologic treatments

Leynadier et al⁷¹ published a unique RBCPC study with anti-IgE in 2004. In this study, 18 patients sensitized to latex were randomly treated with either omalizumab or placebo administered every 2 or 4 weeks for 16 weeks at a dose depending on body weight and total serum IgE level. During the study, patients were working. After 16 weeks, scores were negative in 4 of 7 subjects (57.1%) treated with omalizumab compared with none of the 9 placebo-treated subjects ($P = .019$, Fisher exact test). All subjects were subsequently treated with open-label omalizumab for a further 16 weeks. Eight of 9 subjects (88.9%) previously treated with placebo subsequently achieved negative total scores on the conjunctival challenge test, along with the 3 remaining omalizumab-treated subjects who had positive scores after the first 16 weeks of treatment. At the end of the study, patients treated with omalizumab for 32 weeks exhibited mean relative decreases in skin tests.

Other case reports of use of anti-IgE have been published in patients with baker's asthma with excellent clinical results.^{72,73}

Lavaud et al⁷⁴ described 10 patients with OA induced by high- and low-molecular-weight agents treated with anti-IgE in an open study. Although some environmental interventions were taken to reduce exposure to the causal agent, complete elimination was not possible, and all remained at work. During treatment with omalizumab, the number of severe exacerbations per year decreased in 9 of 10 patients. Five experienced no exacerbation at all. An improvement in FEV₁ was reported in 5 patients. The mean dose of oral corticosteroids decreased by 84%. Three patients discontinued oral corticosteroids. In 4 patients, a reduction in inhaled corticosteroid dose was possible. Seven of 10 workers were able to continue their job without any further environmental intervention. The improvement was observed in patients sensitized to both high- or low-molecular-weight agents.

Concomitant treatment with omalizumab had been demonstrated to be successful in preventing severe anaphylaxis in beekeepers receiving immunotherapy.^{75,76}

It is unknown how many patients with severe eosinophilic OA can potentially benefit from currently available biologic treatment. We performed a *post hoc* analysis (unpublished data, 2019) on a European database of patients with severe OA.⁷⁷ In this study, 162 subjects were classified as having severe OA. On defining uncontrolled patients on the basis of exacerbations, airflow obstruction, high blood or sputum eosinophilia, or high fractional exhaled nitric oxide levels, around 20% to 25% of patients with severe OA were a potential candidate for a currently available biologic drug for asthma (anti-IgE, anti-IL-5/IL-5R, anti-IL-4/13).

CONCLUSIONS

AIT is rarely indicated to treat occupational respiratory allergies. If indicated, AIT should be considered only after reasonable attempts to remove or modify exposure to the offending workplace allergens. When commercial extracts are available to confirm sensitivity by skin test and for treatment, AIT should be considered to modify respiratory allergic symptoms due to workplace exposure to natural protein allergens.

There is increasing but modest evidence on beneficial short-term and long-term effects of AIT and safety in worker populations. The low usage of AIT in OA and OR may be partially due to the lack of standardized extracts for most occupational allergens. Because OR often precedes OA in workers sensitized with high-molecular-weight allergens, there is a potential opportunity for secondary prevention of OA with AIT. Further research is needed to evaluate the efficacy of this secondary prevention approach.

There are many areas of limited data and unmet need in the treatment of occupational respiratory disease with immunotherapy and biologic treatments. There is a lack of standardized extracts for many common occupational allergens. Although some data exist for NRL, understanding of the molecular basis for cross-reactivity phenomena and the ability to resolve low-risk from high-risk markers of clinical expression is limited for most occupational allergens. Lack of commercial availability of immunotherapy extracts limits treatment options. Further well-designed studies are needed to evaluate the efficacy and safety of AIT in occupational respiratory disease. Several studies suggest a beneficial role of treatment with omalizumab in workers with OA who continue to be exposed to the causal agent. Additional studies are needed to evaluate the cost-effectiveness of this treatment when exposure at the workplace cannot be avoided.

Available data suggest that AIT can reduce skin and respiratory symptoms and therefore allow workers to continue their current occupation. It appears reasonable to extrapolate data from controlled studies of AIT in nonworker populations to aid in treatment decisions in worker populations. Compared with SCIT, SLIT with commercially available treatment allergens may potentially be a safer modality for treating appropriately selected workers.

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