

Infrequent Treatments for Occupational Asthma: Immunotherapy and Biological Therapy

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Opinion Statement

Occupational asthma is an important social, health, and economic burden in our society, but its treatment options have not been yet sufficiently explored. Drug therapies do not differ much from ordinary asthma treatments, and avoidance is the main managing option for this condition. However, other therapeutic options like immunotherapy and biological therapies have not been used as in other asthma and rhinitis etiologies. Occupational asthma has different pathomechanisms depending of its triggers, but in immunological IgE-dependent asthma, these therapies can be fairly efficient. Not many immunotherapy studies have been carried out lately on this topic, and its reproducibility might be its biggest disadvantage. Maybe the main existing limitation is the lack of standardized extracts in order to perform this treatment. With no proper extracts, this treatment cannot be implemented, and its tolerance is going to differ depending on the extract used in each specific case. On the other hand, biological treatments are a promising option in the management of severe occupational asthma. Not many studies have been conducted so far in occupational allergy. Nevertheless, these biological treatments are upcoming and evolving therapies, so we expect further studies in a close future, including recently approved therapeutic options such as mepolizumab in eosinophilic refractory asthma. These new treatment possibilities

should enhance their use and empower them also in the occupational field.

The aim of this study is to focus the spotlight in these asthma treatments to encourage the study of its efficacy in occupational asthma, try to optimize the treatment options for this disorder, and bring these infrequent treatments out of the ostracism where they are found nowadays.

Introduction

Allergic respiratory diseases due to occupational exposure to a sensitizing source, such as asthma and rhinitis, represent a social, health, and economic burden for society. Occupational exposure to airborne agents can induce or exacerbate asthma. This is known as work-related asthma (WRA) which is estimated to affect 15–25% of all adult asthmatic patients [1]. Work-related rhinitis (WRR) is often related to WRA, but its prevalence have not been properly investigated. Nevertheless, it is estimated to be similar to WRA [2, 3].

Occupational asthma (OA) is the first occupational lung disease in industrialized countries and the second, after pneumoconiosis, in developing countries [4]. Therefore, its study and classification are important issues. Work-related asthma comprehends OA, which is asthma induced by exposure to the offending sources at the workplace; work-exacerbated asthma where patients with a pre-existing asthma will see their asthma worsened by exposure to their work environment; and variant syndromes such as asthma-like disorders, eosinophilic bronchitis, and potroom asthma. In this classification, OA also can be divided into two groups: immunological and non-immunological [5, 6].

Ordinary drug treatment does not differ from other types of asthma. Nevertheless, treatments such as immunotherapy and biological therapies are not widely used and should be an eligible resource in IgE-mediated immunological OA, where Th2 pathway could be down-regulated [7••]. Avoidance of allergen exposure is still the main objective in OA management, together with an early diagnosis [8]. This allergen avoidance can have

important economic repercussion, especially if leaving the workplace is needed [9] and sometimes cannot be done by the patient. This is the reason why the aim of this paper is to provide a critical overview on these alternative therapies, to optimize these therapeutic options.

This work has been conducted in the form of a systematic review, aiming to analyze the new available treatments in OA. The following steps were followed:

-Preliminary work: firstly search on this topic's scientific literature was undertaken. *Medline*, through the portals *PubMed* (<http://www.ncbi.nlm.nih.gov/pubmed/>) and *SciELO* (<http://www.scielo.br/>), was the chosen bibliographic database; being recent years publications this search spotlight. The following keywords were used, both in English and Spanish: "occupational or work-related asthma and immunotherapy", "omalizumab and occupational or work-related asthma", and "biological treatment and occupational or work-related asthma". Textbooks about the subject were also included to complete this search.

-Study selection: secondly, case reports, case series, and letters to the editor that focused in human and in experimental animal models were selected. Asthma studies were discarded, and only papers focused on OA and occupational rhinitis were taken into account.

-Review: finally, selected results were screened and analyzed by its title and abstracts. Publications meeting the study quality criteria were pointed out and only the ones fulfilling the purpose of the study were thoroughly reviewed.

Immunotherapy

Specific allergen immunotherapy (AIT) is proven to be an effective treatment both for asthma and rhinitis, even been able to prevent the appearance of asthma in patients with allergic rhinitis [10, 11]. This treatment is not only effective, multiple studies show its cost-effectiveness. Thus, even though it still

has improving areas, it is a recommended treatment in allergy consensus documents [12••]. These therapies have demonstrated relevant immunological effects when applied. A dip in mast cell and basophil susceptibility is obtained in an early stage, regardless of the specific IgE levels. IgE levels are not a good effect marker for AIT, because they can even be raised, especially in early stages. However, the ratio between IgE and specific IgG₄ seems to be a more promising parameter in this regard. The subsequent change in the immune system is the appearance of regulatory allergen specific T cells, Treg, and finally an appearance of Breg cells. All these cellular subpopulations redesign will turn out in a downstream change of interleukin production that will end up in suppressing allergic inflammation and creating allergen specific immune tolerance [12••].

In spite of the extensive use of AIT as an asthma and rhinitis treatment in daily practice, it is scarcely used and studied for occupational triggers [9, 13]. Maybe the biggest limitation for the use of AIT in occupational disorders is the lack of good quality standardized extracts [14, 15]. Despite of this absence of available standardized extracts, several studies about the use of AIT in OA have been conducted, and previous reviews have already suggested its usefulness in OA caused by selected high-molecular-weight agents [9, 16, 17].

Cereal grain

The first OA immunotherapy study to be undertaken with a double-blind and placebo-controlled basis was done by Armentia et al. in 1990 [18]. This study opened the path for others to come and suggested this possibility as a feasible treatment. Cereal flour-induced asthma is a very well-studied form of OA. A pretty good number of allergens have been characterized in wheat flour [14, 19••], and even though immunotherapy extracts have not been standardized yet, diagnosis is becoming more accurate with the evolution of diagnostic extracts [20]. This type of OA is relatively common among bakers, but it has also been described in other jobs such as farmers [21], pastry workers [22], or food processors [23]. In these OA cases, wheat is the most common trigger, but other allergens can be found as etiologic causes for these diseases. OA cases have been reported with other cereals such as rice [24], maize [23], or barley [25], among others.

Cereal grain-induced OA has been very well-studied, because it is one of the most common occupational diseases in several European countries. Armentia et al. [18] performed a double-blind placebo study, including 20 subjects receiving AIT and 10 controls. Patients were asthmatic bakers and pastry workers who were treated with a wheat flour extract between 10 and 20 months. Bronchial hyperresponsiveness and skin sensitivity to wheat flour were markedly reduced, accompanied by a subjective symptomatic improvement in all treated patients. Specific wheat flour IgE only decreased in patients who received AIT for 20 months, and none of these parameters changed in the control group.

Due to the importance of this type of OA, not only case reports have been published [26], but bigger studies have been performed. Cirila et al. [27] did a retrospective study where they treated 41 wheat flour-sensitized patients with wheat extract subcutaneous immunotherapy (SCIT) for at least 4 years. Patients

received the SCIT without leaving their workplace, and results were collected between 5 and 10 years after the treatment started by filling out a questionnaire. Patients were divided into two groups by the time of SCIT beginning. Nineteen patients stopped treatment 4–10 years before the data recompilation, and 15 of them were still receiving the final years of their immunotherapy treatment. Out of these 41 patients, 34 achieved a proper desensitization and remained working with a decrease on their symptoms and drug usage. Finally, we would like to underline a study done by Valero et al. in 1988 [28]. They administrated SCIT with a wheat extract to an 11-patient group formed by pastry workers and bakers for a period between 12 and 18 months. Nine out of the 11 patients continued their work activity without problems after the treatment, whereas two of them could not. These two patients had severe asthma, being polysensitized to molds, mites, and flours.

Latex

Latex-induced OA is a big burden for society, especially in certain collectives such as healthcare professionals [29, 30•]. It is a very ubiquitous material; therefore, allergic patients should strictly avoid exposure, not only at their workplaces. Latex is one of the best studied OA triggers, and its extract, with 15 specific known allergens, is the best standardized one among the OA triggers [30•]. This situation makes latex an adequate extract for AIT, and therefore, more studies and immunotherapy options with this allergen are available.

Avoidance is still the best way to manage latex OA, but several AIT studies have suggested that it can be an alternative option when avoidance is not feasible, although its tolerance is still a concern [31, 32••]. Toci et al. [33] published the first latex immunotherapy paper, showing oral desensitization in three patients with good results. Later on, Pereira et al. [34, 35] undertook two different projects. First, they apply an SCIT treatment to a latex allergic radiologist, and secondly, 4 years later, reported the successful immunotherapy treatment in four patients.

Later on, better quality studies were designed. Leynadier et al. [36] carried out a double-blind and placebo-controlled study with 17 latex allergic patients, nine in the active group and eight in the control group. Patients received a 2-day rush induction phase and a 1-year maintenance. After this treatment, conjunctivitis, rhinitis, and skin scores got better, and threshold dose was significantly increased in the active group. Asthma symptoms, which were present in nine patients, did not ameliorate with this treatment. Most of the doses were administrated without side effects, but severe adverse effects like wheezing, hypotension, pharyngeal edema, and urticaria were described on the process. Years later, Sastre et al. [37] performed another double-blind placebo-controlled study, also with SCIT. In this study, 24 patients with asthma and cutaneous symptoms were included, 16 with an active treatment, and 8 with placebo. Both groups underwent an incremental dose phase of 14 weeks with 18 injections and afterwards a maintenance period of 6 months. Improvements in the glove use and rubbing tests, as well as in the bronchial specific challenge with latex were found, but no changes were obtained in methacholine bronchial challenge, asthma symptoms, or the use of medication. On the other hand, an 8% of the injections gave side effects, and a 68.7% of patients were affected by this undesired reactions. Both studies showed some improvement when

immunotherapy was applied, but side effects were frequent or severe, leaving this treatment's tolerance as a big concern.

With this situation over their heads, several groups started to work with sublingual immunotherapy (SLIT). Patriarca et al. [38] performed a study on 12 patients receiving latex SLIT. These patients underwent a 4-day rush hospitalized treatment and continued with a maintenance dose at home. All patients completed the treatment. After 3 months, improvement in mucous and cutaneous symptoms, as well as in nasal and conjunctival challenges was obtained in all patients, having only mild, local, and uncommon side effects. Nucera et al. [39] also performed a study with latex SLIT, where 23 patients were treated with a 2- (10) or 3- (11) day rush dose followed by maintenance. In total, 21 out of the 23 patients completed the study, having two losses for frequent adverse reactions, whereas 70% of patients did not have any adverse reaction. The seven adverse reactions that appeared (three grade 1, two grade 2, and three grade 3) all happened in the 2-day induction group, having no reactions in the 3-day induction group. As a result of this therapy, eight patients (80%) in groups 1 and 8 (73%) from group 2 turned negative their cutaneous tests, and the three patients left in group 2 showed an improvement in symptom scores. Good efficacy results were obtained, and a 3-day rush period seemed better tolerated than the 2-day one. Finally, we would like to highlight a paper by Cistero et al. [40] where latex SLIT was administered to 26 patients with cutaneous symptoms, out of which, 23 had also respiratory ones. The immunotherapy schedule consisted on a 4-day rush phase followed by a 9-week maintenance period. All patients reached maintenance phase, and after finishing it, they showed an improvement in the glove use and rubbing test. An adverse reaction was spotted only in 24.6% of the administered doses, being local reactions in up to 21.4%. These studies showed that efficacy with latex SLIT and SCIT appears to be similar, but tolerance with SLIT is remarkably better than with SCIT. However, more studies are needed both in efficacy and security, and both treatments should still be considered as high risk treatments and be administered in a hospital [40]. Nevertheless, patient numbers in the studies are not high, and the only double-blind placebo-controlled trials were performed with SCIT.

Laboratory animals and others

Other than with this two main allergen extracts, AIT studies for OA with other allergens are especially limited. Hoya asthma, OA due to sea-squirt, is a very common condition in Japan, where it has been properly studied. Jyo et al. started publishing about this topic in 1989 and kept on increasing knowledge on this subject over the years [41, 42]. Three allergens were described in this matter, performing immunotherapy with all of them and observing its efficacy and changes in IgG and IgE titers. Differences between them three were found, been Dilla the less effective one. It was observed that successful treatments raised the IgG titers, while unsuccessful did not, and IgE titers remained unchanged [42]. In the subsequent study, 22 female patients with sea-squirt OA underwent AIT with sea-squirt purified extract. Twenty-one females finished the 2-year treatment. The patient who abandoned the study developed common bronchial asthma; the other 21 remained working normally and stopped having asthma attacks even when shucking oysters at work [42].

The other main immunotherapy area within this minor field is laboratory animals. Even they have not been studied in such a detailed way as sea-squirt OA, this trigger is not local, it is worldwide spread, so its relevance is bigger in a global perspective. Asthma due to exposure to laboratory animals is a common condition among laboratory workers. Several animals have been reported to induce allergy, including rat, mouse, or rabbit [43], but not many AIT studies for this occupational trigger have been carried out. There is a case report showing the efficacy of AIT for rat epithelium [44]. This study showed symptom relief and IgE drop after an 18 months immunotherapy treatment. This patient was able to continue his work afterwards without symptoms with exposures to rat. However, the most interesting and better quality study was designed by Wahn and Siraganian et al. [43], where immunotherapy was prescribed to 11 patients with 12 different extracts (five mice, six rats, and one rabbit), and 12 patients remained as controls. Nine out of 11 patients showed a subjective symptom improvement with this treatment, and blocking antibodies were found significantly high. These blocking antibodies only appeared for the treated extract, and no for others in polysensitized patients, showing that there is not cross-reactivity between them. In four patients, treatment schedule was topped, and the blocking antibodies titers dipped down to pre-treatment levels after 24 months.

Biological treatments

IgE antibodies play a major role in the development of lung inflammation and are associated with hyperresponsiveness to aeroallergens. Bronchoconstriction is induced in Th2 phenotype asthmatic patients. Inflammation in asthma involves a series of inflammatory mediators that recruit and activate various types of immune cells which regulate the migration of inflammatory ones to the lungs [45].

Serum-specific IgE against aeroallergens is the main cause of allergic asthma, causing airways chronic inflammation. This process is induced by effector cells such as basophils, mast cells, and eosinophils, among others, that are activated through high (FcεRI) or low affinity (FcεRII) IgE receptors [46•].

Omalizumab

Omalizumab (anti-IgE monoclonal antibody) reduces free IgE levels by preventing the binding of IgE to FcεRI and therefore the development of an allergic reaction. It binds to IgE at the same site of the cε3 domain defined by the Fc fragment when these antibodies bind to FcεRI and FcεRII. [47]. As a consequence, it inhibits the effector functions of IgE, since the binding of IgE to high affinity receptors on IgE effector cells is blocked, making mast cells and basophils unable to be activated. Omalizumab neutralizes free IgE without affecting other types of antibodies [48].

This treatment obtains a very rapid reduction of free serum IgE and the expression of high affinity receptors, after only 3 months of treatment. Though as soon as the drug is stopped, IgE levels and IgE receptors on the basophils surface return to pre-treatment values within a few months [46].

It has been suggested by Kopp et al. [49] that treatment with omalizumab in allergic asthma should be enhanced by AIT, which is active through the use of other immunological mechanisms.

As said before, OA pharmacological treatment does not differ much from non-work-related asthma therapy and must comply with published asthma guidelines. Therefore, omalizumab can be considered as a therapeutic option for those patients with severe persistent asthma that are not adequately controlled by anti-asthmatic drug therapies [50].

The INNOVATE study was designed to evaluate the efficacy and safety of omalizumab in a population of patients with severe asthma [51]. A total of 419 patients (omalizumab, $n = 209$; placebo, $n = 210$) with severe persistent allergic asthma (GINA 3–4) and ages ranging from 12 to 75 years were included. The primary outcome was the rate of clinically significant asthma exacerbations. Compared to placebo, omalizumab significantly reduced the rate of severe asthma exacerbations (0.24 vs. 0.48, $p = 0.002$) and the rate of total visits to Emergency room caused by asthma (0.24 vs. 0.43, $p = 0.038$). Improvements were also achieved in the Asthma Quality of Life Questionnaire (AQLQ) scores (>0.5 points).

Omalizumab has been shown to be effective in some cases of OA, as it is the case of bakers allergic to flour. These works from 2008 demonstrate an improvement in the quality of life and in the control of the disease, allowing patients to continue in their usual job [52, 53]. One of the most recent studies from 2013 demonstrated that omalizumab is effective in improving asthma control in patients who remain exposed to the causative agent of either high (HMW) or low (LMW) molecular weight [54]. In this study, 10 patients with uncontrolled OA were recruited and were followed for 6 months to 4 years during treatment with omalizumab. Six patients were exposed to HMW agents and four of them to LMW chemicals. An attempt was made to avoid exposure to the culprit prior to initiate treatment, but it was not possible. During the follow-up period, a reduction in the number of severe exacerbations per year was observed in nine of 10 patients, reaching 0 exacerbations per year in five patients. Pulmonary function improved in half of the cohort, measured by FEV₁. Also, a decrease in oral corticoid consumption was also observed in 84% (from 19 to 3 mg/day at the end of the study). It was also possible to reduce the dose of inhaled corticosteroid by 20% in four patients.

Omalizumab had been shown to have clinically antiallergic activity in occupational latex allergy [55] and also in the prevention of severe anaphylaxis in beekeepers [56, 57].

Mepolizumab

Mepolizumab is a new humanized monoclonal antibody directed against IL-5 [58]. The DREAM study has shown [59••] a significant reduction in exacerbations of severe asthma secondary to a selective inhibition of airways eosinophilic inflammation.

Eosinophilic inflammation as well as IgE production are promoted by Th2-type cytokines such as interleukin 5, 4, or 13. IL-4 and IL-13 are involved in IgE class switching and Th2 differentiation, whereas IL-5 participates in the growth, activation, and survival of eosinophils.

For these effects, it is possible to think that mepolizumab will be postulated as a valid and effective treatment for severe eosinophilic asthma of occupational origin in a close future.

Conclusions

The aim of this paper is to show how, even if allergen avoidance is still the primary objective in OA management, there are other existing tools that can be used for this matter (Table 1). In many situations, avoidance is impossible, or patients might not be willing to cease exposure, because it will mean to lose their job. The ubiquity of some allergens and the economic burden that this allergic disorder carries force us to find ways to optimize our patient's treatments. Both immunotherapy and biological treatments are eligible ways to handle this situation. Immunotherapy has standardized extract lack as its main limitation, but work can be done in this direction to improve the current situation. The other concerning issue with immunotherapy is its security, but this can also be solved with a better quality extract development. On the other hand, biological treatments are only targeting severe asthma, nowadays, so this restricts the target population, limiting its usage. There are also new therapies, and there are newer ones to come, such as mepolizumab, so more studies are

Table 1. Main immunotherapy and biological treatments studies

Authors	Agent	Description
Armentia et al. [18]	Wheat flour	AIT double-blinded placebo-controlled study (20 patients with SCIT and 10 controls)
Cirla et al. [27]	Wheat flour	AIT retrospective study (40 patients with SCIT)
Valero et al. [28]	Wheat flour	AIT study (11 patients with SCIT)
Toci et al. [33]	Latex	AIT study (3 patients with oral AIT)
Pereira et al. [35]	Latex	AIT study (4 patients with SCIT)
Leynadier et al. [36]	Latex	AIT double-blinded placebo-controlled study (9 patients with SCIT and 8 controls)
Sastre et al. [37]	Latex	AIT double-blinded placebo-controlled study (16 patients with SCIT and 8 controls)
Patriarca et al. [38]	Latex	AIT study (12 patients with SLIT)
Nucera et al. [39]	Latex	AIT study (23 patients with SLIT)
Cistero et al. [40]	Latex	AIT study (26 patients with SLIT)
Jyo et al. [41, 42]	Sea-squirt	AIT study (22 patients with SCIT) and 3 allergens described
Wahn and Siraganian [43]	Animal extracts	AIT study (11 patients) with 12 different extracts
Olivieri et al. [53]	Omalizumab	Observational study
Lavaud et al. [54]	Omalizumab	Observational study (10 patients)
Leynadier et al. [55]	Omalizumab	Observational study (18 patients)

expected to come that will open a new perspective for these treatments. In summary, these are useful therapies that cannot be abandoned; in fact, they should be further explored in OA.

Compliance with Ethical Standards

Conflicts of Interest

Manuel Rial declares that he has no conflict of interest. Ignacio Esteban-Gorgojo declares that he has no conflict of interest. Joaquín Sastre reports having served as a consultant to Thermofisher, MSD, Novartis, Gennetech, Sanofi, Leti, Roche, FAES FARMA, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, LETI, and FAES FARMA; as well as having received grant support for research from Thermofisher.

Human and Animal Rights and Informed Consent

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

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