

Occupational asthma and rhinitis due to wheat flour: sublingual specific immunotherapy treatment

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ABSTRACT

Background: *There are several potential sensitizers in the bakery environment and wheat flour appears to be the dominant sensitizer in most bakeries. Apart from traditional drug therapy or a change in profession, there are no effective therapies for workers who develop serious respiratory symptoms in the workplace. Objectives:* To describe clinical and laboratory findings in workers with asthma and/or rhinitis induced by wheat flour who underwent sublingual specific immunotherapy (SLIT). **Methods:** *Since drug therapy and prevention strategies were not effective, five bakers were elected to undergo SLIT. A three-year study was led by administering a sublingual wheat flour extract. Questionnaires, allergy and respiratory tests were performed before and after SLIT. Results:* After SLIT an improvement in symptoms is observed in every patient: Asthma Control Test and a quality-of-life questionnaire show higher scores and as a result, workers have reduced the use of drug therapy. We observed significantly reduced exhaled nitric oxide (FeNO) and eosinophil cationic protein (ECP) levels after SLIT, hypothesizing that these parameters may be used to monitor the effectiveness of immunotherapy. The improvement of FEV₁ (forced expiratory volume in 1second) and responsiveness to bronchoprovocative tests with methacholine denotes a possible role of SLIT in treating patients with low-respiratory tract involvement, even though more data are needed. **Discussions:** *This is the first report in the literature on the use of SLIT for baker's asthma and rhinitis. SLIT for occupational wheat flour allergy should be possible and efficient, saving vocational training, professionalism, and avoiding job loss.*

RIASSUNTO

«Asma e rinite professionale da farina di grano: trattamento con immunoterapia specifica sublinguale»
Introduzione: *Nell'ambiente del panificatore ci sono diversi potenziali agenti sensibilizzanti e la farina di grano sembra essere quello dominante. A parte la terapia farmacologica tradizionale o un cambio di professione, non esistono terapie efficaci per i lavoratori che sviluppano gravi sintomi respiratori sul posto di lavoro. Obiettivi:* Descriviamo i risultati clinici e di laboratorio in lavoratori con asma e/o rinite indotti da farina di grano sottoposti a immunoterapia specifica sublinguale (SLIT). **Metodi:** *Poiché la terapia farmacologica e le strategie di prevenzione non erano efficaci, cinque panificatori sono stati sottoposti a SLIT. Uno studio di tre anni è stato condotto somministrando un*

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estratto sublinguale di farina di frumento. Questionari, test allergologici e di funzionalità respiratoria sono stati eseguiti prima e dopo SLIT. Risultati: Dopo SLIT si osserva un miglioramento dei sintomi in ogni paziente: Asthma Control Test e un questionario sulla qualità di vita mostrano punteggi più alti, riducendo l'uso della terapia farmacologica nei lavoratori. Abbiamo osservato una riduzione significativa dell'ossido nitrico esalato (FeNO) e della proteina cationica eosinofila (ECP), ipotizzando che questi parametri possano essere utilizzati per monitorare l'efficacia dell'immunoterapia. Il miglioramento del VEMS (volume espiratorio massimo in 1secondo) e della reattività bronchiale con metacolina indica un possibile ruolo di SLIT nel trattamento dei pazienti asmatici, anche se sono necessari ulteriori dati. Discussione: Questo è il primo studio in letteratura sull'uso di SLIT per l'asma e la rinite del panificatore. SLIT per l'allergia professionale alla farina di grano è pertanto possibile ed efficace, risparmiando professionalità ed evitando la perdita di posti di lavoro.

INTRODUCTION

The baking industry is ubiquitous worldwide and allergy to wheat flour is the main cause of occupational rhinitis and asthma among bakers, with baker's asthma being one of the most common forms of occupational respiratory disease (6, 12). Rhinitis is more common and usually precedes asthma. The incidence of baker's rhinitis ranges between 3% and 12% per year, and of baker's asthma between 0.3% and 4% per year, while the prevalence of rhinitis among bakery workers is estimated to be 15 to 20% and that of asthma is 4 to 13% (5, 20). Occupational exposure to flour dust is positively correlated with sensitization and respiratory symptoms, often associated with conjunctivitis and skin symptoms that may develop after years (26). Atopy has been found to be an important independent risk factor for the development of baker's asthma (26) and a cross-reactivity between wheat flour and grass pollen due to common IgE epitopes has been demonstrated (30). Moreover, the majority of affected individuals have no history of asthma before developing the occupational form of the disease (26).

Sensitization to wheat flour is IgE-mediated, and the sensitizing properties of a number of wheat proteins is well-established (7). In IgE-mediated diseases, immunotherapy can be beneficial, although the literature on immunotherapy for respiratory wheat flour allergy is limited to small studies or case reports with oral or subcutaneous immunotherapy (4, 8, 17, 23, 28). More recently, sublingual

immunotherapy (SLIT) has become an alternative approach with an increased safety profile compared with subcutaneous immunotherapy (SCIT), and it is a safer alternative for patients with asthma (14, 18, 19). In this paper we report five cases of workers who underwent SLIT for wheat flour. To the best of our knowledge, this is the first report in the literature on the use of SLIT for baker's asthma and rhinitis.

METHODS

We examined five workers, four men and one woman (mean age=35.8, median=34, min=32, max=40) suffering from allergic rhinitis and/or asthma to wheat flour. We performed physical examination and skin prick tests (SPTs) to common inhalant, food allergens and occupational allergens (alpha-amylase, yeast, storage mites and different types of flours -wheat, corn, barley, rye, oats-) (Lofarma, Italy, and Stallergenes, France). Serum total IgE and specific IgE (IgEs) versus the five types of flours, yeast, gluten, recombinant proteins of grasses (Phl p 1, Phl p 5b, Phl p 7 and Phl p 12) and wheat (Tri a 14 and Tri a 19 ω -5 gliadin) were determined (ImmunoCAP System, Sweden), and specific IgE over total IgE ratios were calculated. Total IgE level was considered increased when >100 kUA/L and specific IgE level when >0.35 kUA/L, negative when <0.10 kUA/L. We measured eosinophil cationic protein (ECP), cut off 15 μ g/mL (UniCAP, Phadia), and exhaled nitric oxide levels (FeNO), cut

off 25 parts-per-billion (ppb) (NIOX Monitoring System, Aerocrine, Sweden). All patients underwent pulmonary function testing (Vitalograph, UK), anterior active rhinomanometry (Rhinometrics, Denmark), nonspecific bronchial challenge with methacholine (Provocholine, Methapharm, USA) and specific inhalation testing by exposition to wheat flour in an isolation chamber, according to the latest medical consensus (29). The etiological role of sensitization to wheat flour was confirmed by specific respiratory challenges, which are the gold standard for diagnosis of occupational allergies (1). A quality-of-life questionnaire (SF12 standard V1) (13) and the Asthma Control Test (ACT AIFA 2005) (24) were completed.

SLIT with a wheat flour extract (Anallergo, Italy) was administered for three years. An appropriate dose escalation protocol in a supervised setting was led: initially, one drop (400 U.RAST/mL) twice a day, increasing every day with one drop twice a day until reaching the dose of 8 drops twice a day. From day nine, one drop (10.000 U.RAST/mL) a day was administered, increasing one drop a day up to 5 drops a day. Afterward that, patients were taught how to continue the therapy for three years, self-administering 5 drops (50.000 U.RAST/mL daily) 3 times a week.

Periodically, patients were called for a medical check and performed respiratory tests, following the pollen calendar to avoid the influence of seasonal exposure to pollens. Each time, compliance with immunotherapy was assessed.

At the end of the treatment, all tests and questionnaires previously described were performed again.

When necessary, data are expressed as mean \pm SEM. Primary comparisons were analyzed using a non-parametric Wilcoxon test for the monitored parameters before and after SLIT, with $p < 0.05$ considered the threshold to reject the Null Hypothesis (no difference).

RESULTS

All patients shared a long-term exposure to wheat flour on the workplace (10 years minimum), which eventually led to experience both oculorhinitis and

respiratory symptoms at work in 4 of the 5 patients. The symptomatic period before the decision to start SLIT ranged from 3 to 7 years. Only one patient was diagnosed with occupational rhinitis: during specific challenge test with wheat flour, he developed rhinitis symptoms and his anterior nasal resistances showed a significant increase. He did not develop symptoms suspected for asthma and no significant variation in FEV1 was observed.

During specific challenge test all patients developed nasal symptoms and signs, followed by an increase of nasal resistance by at least 100% from baseline. Asthmatic patients presented a typical pattern of early reaction with onset of symptoms and fall in FEV1 $> 15\%$ during exposure and recovery in 1-2 hours. None had late or dual reactions.

In all cases, *on - off test* resulted positive, as patients experienced worsen symptoms after exposure to flour dust at workplace.

In asthmatic patients, before starting SLIT, ACT scores were poor, between 10 and 19/25. SPTs showed positive results for grasses (3 over 5 patients) and in one case even to ragweed, whereas all patients resulted positive for wheat. All patients' serum total IgE and FeNO levels were above the normal ranges. IgEs were positive for wheat, barley and rye for all patients, in some cases for corn. IgE against recombinant grass proteins confirmed the environmental etiology of patients with seasonal symptoms. Tri a 14 was negative in all cases, while Tri a 19 ω -5 gliadin tested positive in only one patient without any history of anaphylactic reactions. None of the subjects was positive to alpha-amylase, yeast and storage mites.

Active anterior rhinometry and basal spirometry (FEV₁, % predicted before SLIT 90.5 ± 5.2 liters) were normal, while bronchoprovocative nonspecific test with methacholine showed moderate to severe bronchial hyperreactivity (PD20 before SLIT min=141, max=457, median=309 μ g) in asthmatic patients.

Before SLIT all the patients used oral antihistamines and intranasal corticosteroids as needed, and asthmatic patients used low-medium dose of inhaled corticosteroid (ICS) (fluticasone propionate, daily dose 437.5 ± 62.5 μ g) associated to long-acting beta agonist (LABA). At workplace, asthmatic patients were frequent users of quick-relief inhalers, as reflected in the poor ACT scores.

They were instructed to preventive measures, first of all organizational and technical improvements, and they were advised to avoid direct-exposure tasks such as weighing, mixing, dough-making, rolling and bread-forming. Unfortunately, 4 out of 5 were employed in small or family-run bakeries and could not easily be relocated to a less flour-exposed job. They started to adopt personal preventive measures, such as wearing dust-proof mask and personal protective equipment.

At the end of the three years immunotherapy, 4 out of 5 patients successfully completed the SLIT treatment, while one of them, in agreement with the allergist, suspended immunotherapy 6 months before the end, for either difficulties in adhering to the treatment and because he was reassigned to a different job, reducing the exposure to flour dust.

Starting from 6 months after SLIT, patients reported significant improvements, including the reduction in rhinitis and respiratory symptoms at work, and they were able to gradually reduce medications they were on. In fact, asthmatic patients could step-down inhaled therapy to low dose combination formoterol-ICS (fluticasone propionate, daily dose $212.5 \pm 37.5 \mu\text{g}$) weekly cycles or as needed, and the use of LABA and short-acting beta agonist (SABA) were also reduced in all study participants. According to QoL questionnaires, patients reported to be in good health overall, with reduction of allergy symptoms and improvement in ACT score in all four patients with asthma (Final ACT index $>20/25$ in all patients, average increment: 10.50 ± 1.85). Overall, tests showed significant reductions in total IgE ($p=0.0312$; average reduction: 49.40 ± 18.54 KUA/L) (Figure 1 a), ECP levels ($p=0.0312$; average reduction: 23.32 ± 6.65) (Figure 1 b) and FeNO ($p=0.0312$; average reduction: 12.20 ± 2.44) (Figure 1 c). FEV₁ revealed an increasing trend ($p=0.0625$; average increment: 6.43 ± 1.72), as bronchial responsiveness to methacholine showed a trend in increase of PD20 levels (min=249, max= 1870, median=568), although no difference was found by statistical analysis (Figure 1 d). IgEs for wheat, barley, rye and corn (Figure 1 e) and IgE against recombinant grass proteins also showed no statistical difference. Therefore specific IgE over total IgE ratios were calculated (% before SLIT 2.58 ± 0.52 ; % after SLIT 2.32 ± 0.53),

although no difference was found by statistical analysis.

One patient developed specific IgE versus Tri a 14, which was negative before SLIT. In the patient positive, Tri a 19 ω -5 gliadin showed a reduction after SLIT. Skin reactivity to either grasses or wheat was largely unchanged.

DISCUSSION

In this article, we describe some unique cases of workers with asthma and/or rhinitis induced by wheat flour and treated with sublingual immunotherapy. The diagnosis was determined by clinical examination, SPTs, IgEs and respiratory challenges, which are the gold standard for diagnosis of occupational asthma and rhinitis (1). Apart from traditional drug therapy or a change in profession, there are no effective therapies for workers who develop serious respiratory symptoms in the workplace. In some cases, biological therapy has been tried with some success (16), and standard SCIT has been reported to be effective in a few cases of baker's asthma (3, 8, 10). In contrast with SCIT, SLIT has a greater rate of compliance and a safer profile thanks to its convenience and ease of administration with fewer risks, and the independence that provides to the patient (18). Therefore, SLIT is an attractive and reasonable therapeutic option. Moreover, all our patients had previously undergone standard drug therapy with partial effectiveness, revealing the need for an integrated multidisciplinary approach (25).

In our study, after three year of SLIT symptoms became milder and workers needed less treatment, reflecting the potential effectiveness of this immunotherapy. We observed an improvement in asthma symptoms in every patient, with scores ranging from totally under control to acceptably controlled (ACT index $>20/25$).

We observed significantly reduced FeNO and ECP after SLIT, hypothesizing that these parameters may be used to monitor the effectiveness of immunotherapy, as it is well-known for specific immunotherapy with environmental allergens (21) and it has been recently proved for occupational exposures (2, 11, 15). In our study we also observed the decline in serum total IgE, but no significantly reduction of

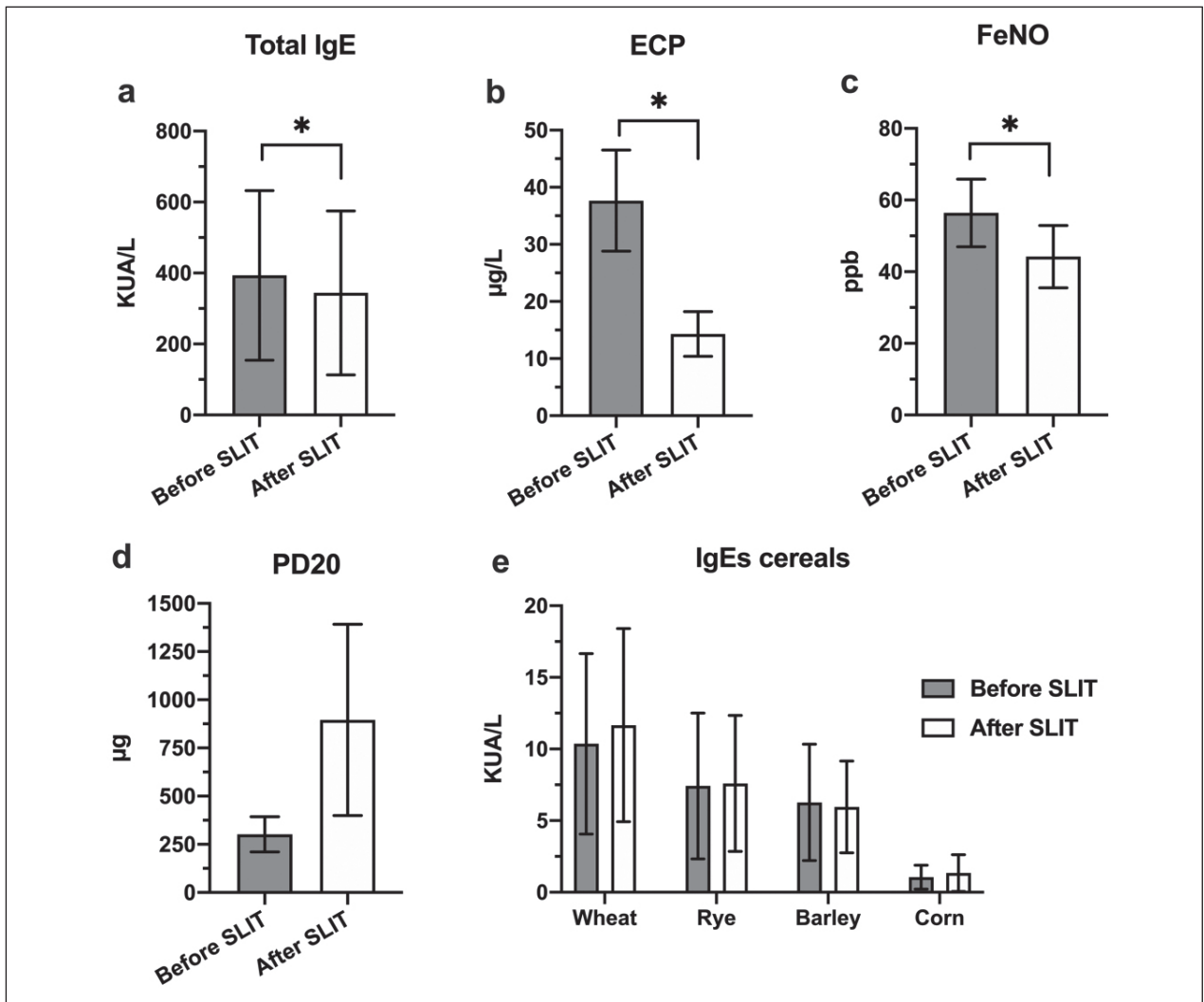


Figure 1 - Parameters monitored in workers before and after three-year SLIT with wheat flour extract. Figure 1 a: serum total IgE. Figure 1 b: eosinophil cationic protein. Figure 1 c: exhaled nitric oxide. Figure 1 d: nonspecific bronchial challenge with methacholine. Figure 1 e: serum specific IgE versus four types of flours. * $p=0.0312$.

Figura 1. Parametri monitorati nei lavoratori prima e dopo tre anni di SLIT con estratto di farina di grano. Figura 1 a: IgE totali sieriche. Figura 1 b: proteina cationica eosinofila. Figura 1 c: ossido nitrico esalato. Figura 1 d: test di provocazione bronchiale aspecifico con metacolina. Figura 1 e: IgE specifiche sieriche versus quattro tipi di farine. * $p=0.0312$.

specific IgE or of the ratio of specific IgE to total IgE (27). Our results are comparable with observations reported in the literature in subjects treated with injection immunotherapy (8). FeNO measures were all above the normal cut off and remained high after SLIT. Patients were not steroid-naïve at the beginning of SLIT due to the severity of symptoms, but inhaled therapy was reduced at the end of SLIT. Persistent high level of FeNO could be associated to supposed high allergen exposure levels.

The improvement of FEV₁ and responsiveness to bronchoprovocative tests with methacholine could imply a role of SLIT also in treating patients with low-respiratory tract involvement: to prove this hypothesis, though, more data are needed.

Moreover, immunotherapy for respiratory wheat flour allergy seems to improve even seasonal symptoms due to grass pollen-induced rhinitis and asthma, possibly because wheat flour and grass pollen share common IgE epitopes (9).

Since this is a limited cohort, it is difficult to evaluate compliance and the overall effectiveness of SLIT. However, specific immunotherapy and job reassignments can contribute synergistically to the health of subjects with occupational allergies, by both reducing the immune response to allergen stimulation and by reducing occupational exposures.

There are several potential sensitizers in the bakery environment, despite the observation that wheat flour appears to be the dominant one in most bakeries. In our opinion, the best approach to flour allergy in bakers is an integrated multidisciplinary therapy, combining clinical and organizational approaches, i.e. favoring drug therapies, immunotherapy or both, choosing the most suitable modality of immunotherapy according to the patient compliance and reassessing the workplace and/or the job activities.

In the future, we will see the improvement of new technologies, including component-resolved diagnosis and recombinant allergens, for the betterment of the quality and efficacy of specific immunotherapy (22).

This is the first report in the literature on the use of sublingual specific immunotherapy (SLIT) for baker's asthma and rhinitis. The present report highlights for the first time the potentially useful therapeutic use of SLIT in patients with occupational asthma and rhinitis due to wheat flour.

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NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED BY THE AUTHORS