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Safe and effective hyposensitization in bakers suffering from year-round allergic rhinoconjunctivitis and allergic bronchial asthma caused by flour dust allergy

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Abstract

Background The inhalation of flour dust increases the risk of allergic obstructive respiratory disease in bakers. Therefore, flour-induced bronchial asthma is one of the most common work-related respiratory diseases, the symptoms of which often lead to disability. **Methods** Since 2002, 39 patients with flour-induced allergic rhinoconjunctivitis and baker's asthma have undergone hyposensitization in the author's department using specific immunotherapy (SIT) with a flour mixture. In addition, 10 cases of treatment failure were treated for a further 5 years with a dual therapy consisting of causal SIT and symptomatic treatment using the anti-IgE antibody omalizumab.

Results SIT- and dual-treated patients showed a marked improvement in nasal, conjunctival, and bronchial symptoms. No severe local or systemic side effects were observed.

Conclusion Both SIT and dual therapy represent an effective and well-tolerated treatment option in flour dust-allergic individuals.

Keywords Flour dust allergy · Allergic rhinitis · Allergic asthma · Nasal provocation · Specific immunotherapy · Omalizumab

Abbreviations

FEV1	Forced expiratory volume in 1 s
IgE	Immunoglobulin E
MAE11	Monoclonal mouse antibody
NPT	Nasal provocation test
rhuMAb-E25	Humanized, monoclonal anti-IgE antibodies
SCIT	Subcutaneous immunotherapy
SIT	Specific immunotherapy
VAS	Visual analog scales

Introduction

Respiratory allergies such as flour-induced rhinitis and bronchial asthma are common occupational diseases [1–5]. According to recent estimates, 15–20% of all bakery workers suffer from “baker's rhinitis” and 5–10% from “baker's asthma.” In addition to bakers, also confectioners, gingerbread bakers, pizza bakers, millers, cereal handlers, and farmers are affected [6].

Altogether, 60% of all flour dust asthmatics suffer from pollinosis due to extensive cross-reactivity between wheat and rye flour antigens and the pollen of grasses and cereals such as barley and oats [7–10]. Non-specific factors such as steam, grease fumes, temperature fluctuations, particulate stimuli, and stress can exacerbate respiratory disease.

Baker's rhinitis and baker's asthma can develop shortly after exposure. However, in many cases, they occur only after years of working in these industries. The inhalation of flour dust initially causes nasal obstruction, rhinorrhea, and sneezing attacks. Lacrimation and conjunctivitis may also be seen. If no preventive measures are taken (avoidance) or causal immunotherapy performed, bronchial asthma can ensue. This is referred to as allergic march. Symptoms recede in most patients during non-working times and only recur in the workplace [11, 12]. Symp-

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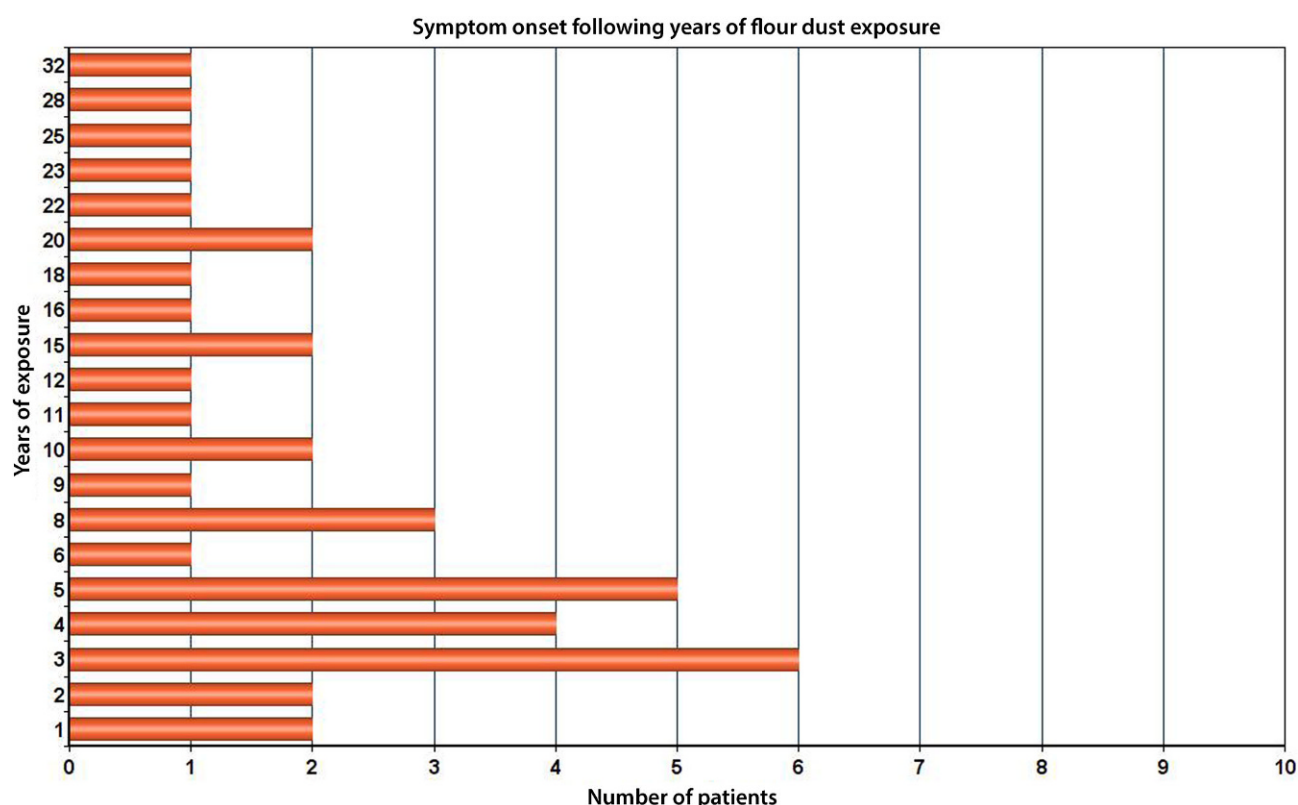


Fig. 1 Symptom onset over the course of working life

toms persist all year round due to constant contact with flour.

The most frequent allergic triggers include the proteins albumin and globulin from rye and wheat flour [13]. Altogether, 90% of all bakers exhibit concomitant sensitization to both types of flour [11, 14]. The main allergens of wheat flour include the microbial enzyme α -amylase and the wheat protein α -purothionin, which are reported to have particularly high allergic potential [15–18]. According to Bauer and Sander [19], immune reactions to wheat and rye flours occupied first place at 59% each, followed by wheat malt (52%) and soy flour (33%). Barley meal and oatmeal are allergenic mainly due to their cross-reactivity. Reactions to α -amylase from *Aspergillus oryzae* were observed in 24% of tests. α -Amylase inhibitors [2] naturally present in flour, baking additives such as starch-degrading enzymes (α -amylase from *Aspergillus oryzae*, amyloglucosidase and hemicellulase from *Aspergillus niger*, thiol reductase, and thioredoxin [20, 21]), impurities caused by storage mites, corn weevils, cockroaches, as well as fungal spores of *Cladosporium*, *Penicillium*, *Aspergillus*, *Rhodotorula* and *Saccharomyces* also have allergenic potential.

The impairments to health caused by permanently high levels of allergen-containing flour dusts in the workplace often lead to occupational disability. As a result, large numbers of bakers need to be retrained at considerable financial cost [22]. Thus, the occupational disease baker's asthma represents a threat to the

livelihoods of those affected, as well as an economic and social challenge. Besides avoidance, specific immunotherapy (SIT) is the only causal treatment for IgE-mediated allergic diseases.

Omalizumab (rhuMAB-E25) is a humanized monoclonal antibody produced using recombinant DNA technology in a guinea pig ovarian cell line (Chinese hamster ovary, CHO) from a murine antibody, MAE11. It binds specifically to free circulating IgE, thereby preventing free IgE from binding to mast cells and thus inhibiting the IgE-mediated allergic reaction. This non-allergen-specific antibody is approved for asthma control in adults and adolescents aged from 12 years.

SIT with a flour mix, as well as dual therapy consisting of causal SIT and symptomatic treatment with the IgE antibody omalizumab, can lead to significant and lasting symptom improvement in flour-induced allergic rhinoconjunctivitis and baker's asthma, thereby maintaining patients' capacity to work.

Patients

In the period between 2002 and 2010, 180 patients were treated for inhalant flour dust allergy or baker's asthma. Questionnaires completed by 39 patients (10 women, 29 men) aged between 15 and 55 years were evaluated retrospectively. The patient group consisted of bakers exposed to flour dust ($n=28$), confectioners ($n=4$), gingerbread bakers ($n=1$), specialist sales staff ($n=3$), as well as subjects from other

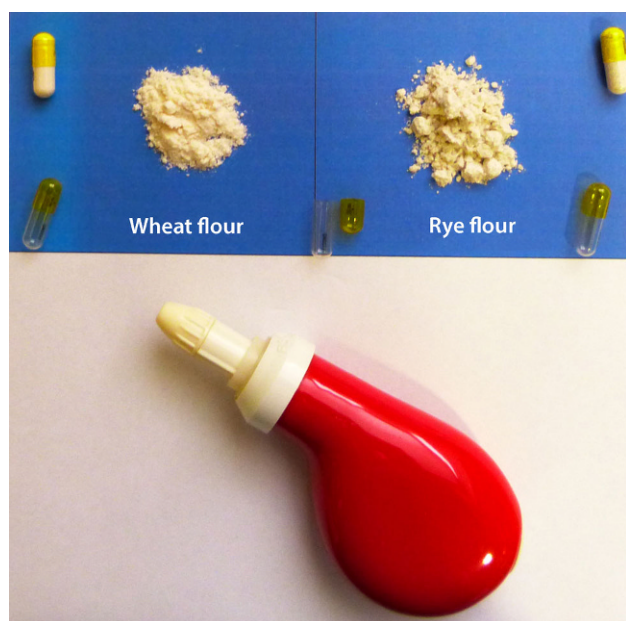
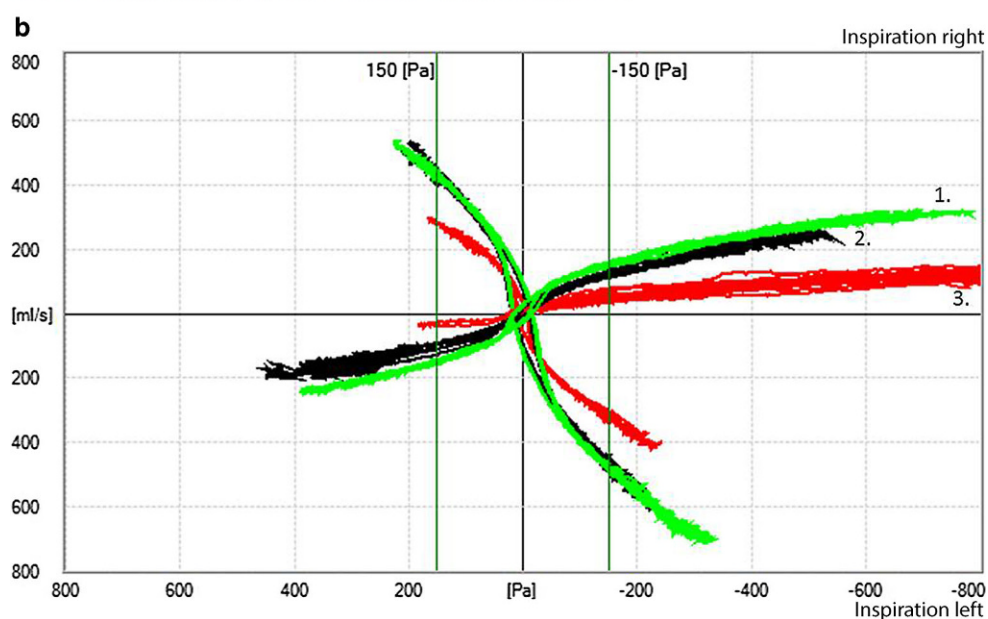


Fig. 2 Flour extracts for prick-to-prick and nasal provocation tests

Fig. 3 Positive nasal provocation test (NPT) using rye flour. **a** Provocation test in practice. **b** 1. Empty curve, 2. solvent curve, 3. provocation curve: bilateral NPT with rye flour, right nostril: 62% drop in flow, positive NPT with 6 points (4 points nasal obstruction, 1 point runny nose, 1 point sneezing attacks)



professions that involve frequent contact with flour ($n=3$). Patients had been exposed to flour dust for 15 years on average. The longest period of exposure was 42 years, the shortest 3 years. Symptom onset occurred following exposure times of varying duration. Some patients perceived symptoms upon first exposure, others only after years or decades. The comparatively high number of patients experiencing symptoms during the first 5 years of flour dust exposure is striking (Fig. 1).

Methods

Diagnostic methods

In addition to taking a detailed allergy-specific patient history, scratch testing, and prick-to-prick testing, the diagnostic work-up of occupational flour dust allergy included the determination of total IgE as well as specific IgE antibodies to wheat flour, rye flour, and α -amylase. Lung function (forced expiratory volume in 1 s, FEV1) was determined by means of spirometry. Native flour samples from the patients' bakeries were

Fig. 4 Questionnaire (in German) following specific immunotherapy/dual therapy

Befragungsbogen (nach Dr. B. Hauswald)
nach der spezifischen Immuntherapie (SIT)

Name _____ Datum _____

Geburtsdatum _____

Beschwerdenbesserung in %		Beschwerdenbesserung in %	
0	50	100	Keine Beschw. Zunahme Beschw.
Nase: Obstruktion (zu, verstopft)	☐	☒	☐
Rhinorrhoe (wäss. Sekret)	☐	☒	☐
Niesen / Niesattacken	☐	☒	☐
Auge: Rötung	☐	☒	☐
Juckreiz / Tränen	☐	☒	☐
Lunge: Luftnot / asthmoider Beschwerden	☐	☒	☐
Haut: Juckreiz	☐	☒	☐
Ekzem (Rötung, Quaddeln)	☐	☒	☐

used for skin testing in order to identify the allergenic flour (Fig. 2). Nasal provocation tests (NPT) were also performed using these flours and the allergic reaction measured rhinomanometrically (Fig. 3).

Monotherapy

Patients were subcutaneously administered with a flour mix for 3–5 years (subcutaneous immunotherapy, SCIT). Allergen dose escalation was performed on an inpatient basis in the form of 3-day ultrarush therapy. Subsequently, 100 µg were injected as a depot every 4 weeks (maintenance therapy).

Dual therapy

Patients that continued to exhibit pronounced symptoms despite SIT were treated with a combination of causal SCIT and symptomatic anti-IgE therapy (omalizumab, Novartis). The omalizumab dose was determined on the basis of total IgE and body weight. These injections were also performed subcutaneously, every 4 weeks alternating with SCIT.

Questionnaire

In order to assess clinical symptoms, the questionnaire formulated by Dr. B. Hauswald was collected and evaluated following several years of therapy. As part of this, patients were asked to gauge symptom improvement using a visual analog scale (VAS) (see Fig. 4).

Results

Flour dust allergy was detected in all tested patients using a combination of skin testing (scratch test, prick-to-prick test), specific serum IgE determination, and NPT.

All patients were treated with a flour mix in the context of SIT. SIT resulted in successful hyposensitization in 29 patients.

There was no significant symptom improvement under SIT in 10 patients; as such, the continued practice of their trade remained at risk. Nine of these patients experienced a significant improvement in nasal, conjunctival, and bronchial symptoms under additional symptomatic treatment with the anti-IgE antibody omalizumab. Treatment led to reduced asthma symptoms as well as to a lower frequency and severity of asthma exacerbations. Fig. 5 provides an overview of symptom improvement in the individual symptom areas.

On the basis of the questionnaire, clinical symptoms affecting the nose, eyes, and skin improved by 83.4% on average. The most pronounced symptom improvement was seen in ophthalmological symptoms, such as redness, itch, and lacrimation, at 91.3% on average. With good tolerability, no local or systemic side effects were observed, with only one exception. In this particular case, omalizumab therapy was discontinued at the patient's request after 24 months due to recurrent upper respiratory tract infections approximately 1 week following injections. Therapy was discontinued in another patient due to new-onset uterine cancer. No causal relationship has been demonstrated as yet. The remaining pa-

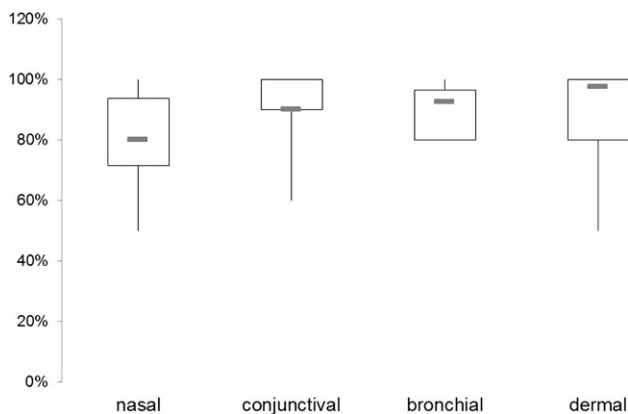


Fig. 5 Symptom improvement following dual therapy

tients continued to receive symptomatic therapy with omalizumab.

Omalizumab treatment discontinuation was attempted in four patients (1 woman, 3 men) after an average of 4.25 years. Omalizumab was reinstated in two patients 4 months following treatment discontinuation due to the recurrence of progressive symptoms.

All patients retained their capacity to work.

Discussion

Allergies cause significant impairment to the quality of life of those affected [23]. For many flour dust-allergic individuals, the question arises as to the impact allergies have on their continued ability to practice their trade. In some cases, entire family-run businesses are jeopardized. As a result, strict avoidance is only rarely possible. Preventive measures such as extraction systems [11] or the use of low-dust, hydrothermally treated release flours [24] to reduce flour dust emissions are able to reduce, at best, the allergic risk potential [25]. This makes it all the more important to provide affected individuals with a reliable diagnosis and to initiate SIT.

The diagnosis of allergic rhinitis in the case of sensitization to flour dust is generally confirmed by NPT and skin prick tests using extracts from individual flour samples [6, 26, 27]. Tasman et al. consider the complex production of these flour extracts to be justified in the interest of diagnostic safety and due to the significance of flour dust allergy in terms of labor laws [10]. Therefore, the discontinuation of flour extract production by the manufacturer should be viewed critically.

At an incidence of 25%, allergic rhinitis is one of the fastest growing IgE-mediated inhalant allergies [28]. Without appropriate treatment, more than 40% of allergic rhinitis patients develop bronchial asthma within approximately 8 years [29]. Since 1911, allergen-specific immunotherapy, SIT, has been the only causal treatment option in allergic rhinitis besides avoidance [29–31]. Studies have demonstrated an

improvement in nasal and conjunctival symptoms as well as in bronchial asthma symptoms under SIT [32, 33]. Hyposensitizations such as rush or ultrarush protocols can be associated with a high rate of side effects [34]. With the exception of mild localized reactions, the patients in this study did not experience any severe adverse side effects such as respiratory, gastrointestinal, cardiovascular, or life-threatening systemic effects. In line with the findings of the present study, Cirila et al. showed in their retrospective study specifically of bakers that 34 of 41 bakers were able to continue work without interruption after at least 4 years of SCIT with wheat flour extract. The reduced drug use in a subgroup of 15 patients is also consistent with the observations made in this study [35].

The therapeutic [12, 36] and economic benefits [37] of omalizumab has been evidenced in proven cases of severe, uncontrolled baker's asthma (posing a threat to livelihood) and the need for treatment throughout patients' professional lives. The results presented here for dual therapy confirm earlier studies that reported a significant clinical benefit from combined omalizumab and immunotherapy in the treatment of persistent allergic rhinitis and accompanying asthma [38].

Conclusion

Both SIT and dual therapy represent an effective and well-tolerated treatment option in flour dust-allergic individuals. Dual therapy consisting of causal SIT and symptomatic treatment with the anti-IgE antibody omalizumab offers those in whom SIT therapy has failed extremely good tolerability and increased protection against anaphylactic reactions, alongside a strong symptomatic effect. As such, not only can quality of life be improved, but jobs also maintained.

Conflict of interest B. Hauswald, M. Cuevas, J. Boxberger and T. Zahnert declare that they have no competing interests.

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