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Allergy to *Parietaria Officinalis* Pollen

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Parietaria pollen allergens (*officinalis*, *judaica*, *lusitanica*, *creatica*) are one of the most common causes of pollinosis in the Mediterranean (Spain, France, Italy, and Croatia). *Parietaria* has very long period of pollination, often reaching peaks of more than 500 grains/m³ of air at the beginning of June, and very strong allergenic properties. There is a significantly positive correlation for the newcomers between the intensity of the skin test reaction and concentration of specific serum IgE with the length of residence in the area, whereas autochthonous patients show a negative correlation between the age and intensity of hypersensitivity. This suggests that the environment encountered at birth may have a decisive role in the development of allergic respiratory diseases. Due to structurally similar pollen antigens in different *Parietaria* species, they are all equally useful in diagnosis and treatment of allergy, regardless of the pollen species to which the patient is sensitive or the prevalent species in the area. In our hands, specific immunotherapy with subcutaneous injections of partially purified, characterized, and standardized pollen extract of *Parietaria* allergen proved effective. It was possible to define an optimal maintenance dose of antigen per injection. During (years of) therapy, we observed an initial increase in total serum IgE concentration and increase in allergen-specific serum IgG blocking antibodies, decrease in allergen-specific serum IgE concentration and amount of histamine released from peripheral blood leukocytes challenged in vitro with the allergen, as well as in symptom and additional medication scores.

Key words: allergens; allergy and immunology; Croatia; desensitization, immunologic; hypersensitivity; hyposensitization, therapy; immunotherapy, allergen; pollen

A member of the Urticaceae family, *Parietaria officinalis* grows in many locations in South Croatia, i.e., the Adriatic coast from Istria to Dubrovnik (1,2). The climate in this region is famous for the mildness of its winters, whose average monthly temperatures do not fall below 10°C. Summer dryness, however, is the most typical feature of the Mediterranean climate. Average temperatures exceed 20°C, whilst dry periods may last three or even four months per year. The flowering season in Southern Croatia is from March to November. *Parietaria* pollen appears first at the beginning of spring, and persists throughout spring and summer (3,4). A second shorter pollination period is observed from the end of August to October. It is generally accepted that wind-pollinated plants are potent allergens in part because of the abundant dispersal of their pollen grains. Most investigations refer to wild plants, which have a dominant impact on the pollen content in the air (5). The *Parietaria* species are an excellent example of plants in both the Mediterranean basin (6,7) and other parts of Europe (8), including Southern Croatia (9-11), and Asian and African countries bordering the Mediterranean sea (12) (Fig. 1). Its distribution is not restricted to the Mediterranean area, since *P. officinalis* and *judaica* have also been identified in the United States (13) and Australia (14). Among 10 or more species, *Parietaria officinalis*, *judaica*, *lusitanica*, and *creatica* are the most common in Croatia (3). The Croatian name is *crkvina*, *drijenak*, *gominjaèa* (see front page of the journal).

Figure Distribution of the *Parietaria* species in the Mediterranean area. [\[view this figure\]](#)
1:

Prevalence

Because of its long pollinating season and high levels of pollination, sensitive patients experience long-lasting symptoms that can be quite severe and difficult to treat. The duration of *Parietaria* pollen season varies with the climate. In Sicily and Southern Italy, this pollen appears first at the beginning of February and persists until December, resulting in almost perennial symptoms. It is responsible for 60%-65% of hay fever pollinosis in Italy: 32% in Central Italy, approximately 8% in Northern Italy, and up to 70% in Liguria (6). According to a survey of 600 atopic children (3-12 years old) made in the area of Naples, 9.9% were sensitive to the pollen of *P. officinalis*; 30.8% of 1,400 atopic adults were sensitive to the same pollen (15). In Naples, the prevalence of sensitivity to *Parietaria* as an isolated

allergen or in association with other allergens is about 80% of all pollinosis patients (16). The prevalence of asthma in patients allergic to *P. judaica* is quite high, approaching 60% in some areas (12,16). Ariano (17) studied pollen counts in the atmosphere of San Remo, Italy, for ten years and compared them to clinical sensitizations in 5,481 patients allergic to pollen; the prevalence of clinical sensitization to *P. officinalis* was 41.8%. In Spain (18) and south of France (7) there is also high prevalence of allergy to *Parietaria*. Patients sensitive exclusively to this pollen have been described, indicating high allergenic specificity of *Parietaria* (18). In our survey of the city of Split and its suburbs population (9), reactions to only *P. officinalis* pollens were positive in 52.5% of hay fever pollinosis patients, whereas 12.5% patients were allergic to both *P. officinalis* and grass pollen. This means that 65% of our population of hay fever pollinosis patients are allergic to the *P. officinalis* pollen. Out of 4,116 atopic patients with respiratory symptoms, 1,600 (38.8%) were allergic to various pollen allergens, and 1,000 (62.5%) of them reacted to *Parietaria* pollen (3).

In the far south of Croatia, in Dubrovnik, the percentage of positive reactions to *P. officinalis* rises to 92.3% (10). This percentage decreases towards the north of Adriatic, reaching 35.1% in Istria (11). There is no information about hypersensitivity to *Parietaria* pollens in the northern part of Croatia.

Course of Sensitization

Most of our subjects with a history of *P. officinalis* hypersensitivity lived in city suburbs. They claimed that *P. officinalis* grew on the walls of their houses and partition walls, and that every harvesting or removal of *P. officinalis* provoked skin, conjunctival, and nasal symptoms, as well as wheezing with cough in some subjects. Most of the symptoms persist 6-7 months of the year, from February or March to June, usually ceasing in July and August, and reappearing during the second shorter pollination period that runs from the end of August to October. We analyzed hypersensitivity in autochthonous subjects and in patients who had been born in inland areas, where the plant does not grow, and later moved to the Adriatic coast where they became exposed to *P. officinalis* pollen and developed hypersensitivity. The newcomers to the area with the plant showed highly significant positive correlations between the length of residence in the area and the intensity of skin test reaction and concentration of specific serum IgE. In contrast, autochthonous subjects showed a negative correlation between their age and intensity of hypersensitivity to *P. officinalis*. This indicates that the environment encountered at birth may have a decisive role in the development of allergic respiratory diseases (19). In this respect, hypersensitivity to pollen allergens, because of the defined flowering periods, can often be correlated with the month of birth as well (20).

Allergen

Different *Parietaria* species crossreact to a great extent, and studies on the crossreactivity among the major allergens of these pollens have been carried out (21). A monoclonal antibody-based ELISA for the quantification of Par j 1 pollen antigen has been developed. The assay detects 0.2 ng/mL of the antigen, and has a high correlation with the allergenic activity of *P. judaica* extracts determined by radioallergosorbent (RAST) inhibition assay. By means of this assay, proteins homologous to Par j 1 were detected in *P. officinalis* and *P. mauritanica*. Par o 1 and Par m 1 proteins were purified by affinity chromatography using the same monoclonal antibody as in the ELISA. Crossed-inhibition experiments demonstrated that Par j 1, Par o 1, and Par m 1, competed for the binding of specific IgE from a serum pool of *P. judaica*-sensitive patients. These results suggest that shared allergenic epitopes are present in the three main allergens investigated, which may simplify the diagnosis and therapy for *Parietaria* allergy (21).

In our study of *P. officinalis* hypersensitivity, pollen was collected during its peak pollination period, i.e., from March to June (22). It was then microscopically checked for purity: there was no contamination with any other pollens, and the contamination with other parts of the flower was less than 5%. The allergen was prepared and standardized according to the method of Pepys et al (23), and adjusted to contain 1,200 protein nitrogen units (PNU) per mL. For the skin prick test, the extract was diluted in glycerol (2:1) to contain 5,000 PNU/mL. RAST-inhibition test was used to determine in vitro allergenic activities. It revealed that 50% RAST-inhibition could be achieved with 1.65 mg/mL of the prepared allergen (22). Titration in international units was not possible because *Parietaria* international reference standard is not available (24).

To limit adverse reactions, aqueous allergen extracts have been modified either to slow systemic absorption or to be less likely to bridge IgE (Table 1). Alum precipitation of allergenic *Parietaria* extracts, either with or without pyridine treatment, makes good "depot" injection, resulting in fewer systemic reactions (24-29). Allergen extracts treated with tyrosine as an adsorbate are commonly used and several trials have shown their efficacy (25,26). Treatment with formaldehyde or glutaraldehyde causes cross-linking of allergenic protein that results in continued immunogenicity but decreased allergenicity. Both have been shown to be effective (25,26). Initial trials of local nasal immunotherapy in patients monosensitized to *Parietaria* and with a clinical history of

rhinoconjunctivitis showed that the use of an macronized powder form of *Parietaria* pollen (4,30) is effective. Rush sublingual immunotherapy in *Parietaria* allergic patients with a clinical history of rhinoconjunctivitis are effective (31,32), too. We applied the more frequently utilized subcutaneous route of administration, using alum-adsorbed, partially purified, characterized, and standardized pollen extract (29). Oral route is very rarely used because of the allergen instability in saliva and gastric juices (33).

Table Modes of allergen immunotherapy for *P. officinalis* pollen. [\[view this table\]](#)
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Pollen Counts

D'Amato (4) performed pollen counts with a VPPS-2000 7-day-recording volumetric spore trap, placed approximately 25 m³ above the ground. The atmospheric presence of *Parietaria* pollen grains was expressed as a daily mean concentration per m³ of air. *Parietaria* pollen reached peak levels of about 500 grains/m³ of air at the beginning of June (4,24). The second, shorter pollination period ran from the end of August to October. The patients whose history included *Parietaria* hypersensitivity alone, confirmed by skin test and allergen specific IgE antibodies, were asked to keep daily diary of symptoms (nasal itching, nasal obstruction, sneezing, running nose, eye irritation and watering, and wheezing with cough) and medication use during the *Parietaria* pollen season. During the peak of the pollen season, the patients recorded a significant increase in symptomatology and symptomatic medication usage (24). The pollen frequently induced severe respiratory symptoms (24).

We used the gravimetric method to estimate the amount of pollen in the air. Glass slides were placed at several locations in the city of Split and its surroundings. They were analyzed weekly from March to June, and the results were expressed as percentage of given pollen among all pollen grains collected (3). *P. officinalis* pollen dominated during the year, both in duration and concentration (up to 20% from April to June), with the peak in 18th-20th week (June) of that year (3). Pollens of *P. lentiscus*, *O. europaea*, *P. helepensis*, *J. oxycedrus*, *Mimosa* and *C. monspeliensis* were found in lower concentrations and for shorter time periods (3).

Our data showed that, at the time of peak *Parietaria* pollen concentration in the air, patients had severe respiratory symptoms; clinically, both symptom and additional medication scores significantly increased (3). Most of the patients were sensitive to *Parietaria* as an isolated allergen (3), which is in accord with the known high antigenic specificity of the *Parietaria officinalis* allergen (3,4,24).

Skin Testing

Since the intracutaneous skin testing is much cheaper than RAST, most allergologists prefer intracutaneous testing as a reference guide in the diagnosis of allergy. This, however, can be done only for well characterized allergens for which a high correlation between skin test and RAST-IgE has been demonstrated. Since we have worked with an allergen for which such correlation is still poorly investigated, we used serum IgE-positive RAST as a reference (22). The three approaches to skin testing were then compared: (a) intracutaneous testing in which the reaction is considered significantly positive when the wheal diameter exceeds negative (buffer) control for at least 6.0 mm (34); (b) method of Bryant et al (35) and Killian et al (36), which assumes that a positive reaction is the one in which the mean wheal diameter exceeds 3.0 mm; and (c) Aas' method (37), for which a significantly positive result is when the reaction is equal to or larger than that induced with 0.1 mg/mL histamine chloride.

The intracutaneous method correlated best with RAST, but it also produced a high number of false-positive results (40%), which actually made it unacceptable. Moreover, some patients had severe and painful local reactions. In contrast, the skin prick method read according to either criterion (35-37) showed significantly less false-positive reactions (none with the Aas' method). However, there were a few false-negative cases, which calls for caution in borderline-negative cases of skin prick test, where rechecking with RAST is required.

The effect of allergen immunotherapy on target organ responsiveness is the closest link to its clinical effectiveness. Accordingly, the results of skin testing change during desensitization immunotherapy. Several reports showed variable reductions of skin test reactivity following courses of immunotherapy, but the degree of reduction did not necessarily correlate with the amelioration of symptoms. Allergen immunotherapy also has an impact on the late-phase skin reaction. After treatment with *Parietaria* pollen immunotherapy, D'Amato et al (24) and Fling et al (38) showed that the suppression of the late-phase cutaneous response correlated with the cumulative dose of the pollen extract, postseasonal levels of specific IgG1 and IgG4, and improvement of symptoms.

Immunological Changes

Antibody Responses

Many authors reported that acquired clinical improvement could not be explained by any direct relationship to either reagenic (IgE) or blocking antibody (IgG), although some stated that the IgG/IgE ratio correlated with symptom scores (39). Resta et al (25), Tari et al (27), and our group (29) used Parietaria pollen immunotherapy before the pollen season (from October until March of the following year), and demonstrated a rise in both specific IgE and IgG and suppression of the usual seasonal rise in IgE (Table 2). Specific IgG subclass changed with Parietaria pollen immunotherapy. Both IgG1 and IgG4 levels rose within 8 weeks of the initiation of therapy, with IgG1 peaking at 12 weeks and IgG4 peaking only after two years (27) (Table 2). These changes in antibody production profiles probably reflect the changes in complex interactions between Th1 and Th2 responses, which not only affect antibody production but also alter inflammatory cell recruitment and end-organ reactivity.

Cell Activation and Cytokine Production

Table Humoral and immunological changes in allergen immunotherapy. [\[view this table\]](#)
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Rocklin et al (40) described the development of specific "suppressor" activity during ragweed immunotherapy, which had not been present prior to the initiation of therapy. In comparison to normal subjects, patients with allergic asthma have a heightened activation of T cells when stimulated with allergen, as opposed to nonspecific stimulation with mitogens. Immunotherapy blunts this reactivity, as measured by interleukin-2 (IL-2) levels and soluble or cell-bound IL-2 receptor (IL-2R) (41). Another study (42) assayed the expression of the two components of the high affinity IL-2R, IL-2R-p55 (CD25) and IL-2R-p75 (CD122), on CD4+ and CD8+ T lymphocytes after culture with Dermatophagoides farinae (Df) antigen. A group of mite-sensitive asthmatic children not receiving immunotherapy showed Df-specific CD25 induction on CD4+ cells, but little on CD8+ lymphocytes. The degree of CD4+CD25+ response correlated with the severity of disease. In the immunotherapy group, the increase of the proportion of CD8+CD25+ cells was higher than in the nontreated group or controls. IL-2R-p75 was not induced on either CD4+ or CD8+ cells. The authors attributed the efficacy of immunotherapy to the generation of Df-specific CD8+ lymphocytes.

Plasma levels of platelet-activating factor (43), histamine-releasing factor (44), and eosinophilic cationic protein (28) are higher in asthmatic patients than in healthy controls. Successful immunotherapy causes a decrease in these factors (28,43,44). The production of allergen-induced histamine-releasing factors is significantly decreased after 2 years of immunotherapy and the change correlates with the change in nonspecific histamine responsiveness (44). Alterations in the cytokine milieu are central to the atopic state and the production of increased levels of IgE (41,42). IL-4 enhances the expression of low-affinity IgE receptor (FcεR2/CD23) and the production of IgE by B cells. Soluble FcεR2/CD23 acts as an IgE-binding factor that may, in combination with low levels of IL-4, augment proliferation and IgE production (45). Down-regulation of FcεR2/CD23 on peripheral B cells following successful grass pollen immunotherapy has been documented (45).

Cell Recruitment and Late-Phase Responses

These changes were studied as changes in nasal epithelial metachromatic cells, nasal symptoms, and nasal provocation following specific desensitization immunotherapy. All three parameters were significantly reduced compared to baseline in the patients treated with Parietaria pollen immunotherapy (4,30). Decreased numbers of mast cells were offered as an explanation for the improvement in symptoms (30). Passalacqua et al (30) reported a significant reduction of intercellular adhesion molecule-1 (ICAM-1) expression on epithelial cells after nasal challenge with Parietaria allergen during immunotherapy.

Therapy

Parietaria pollen is an aggressive allergen and the doses tolerated during immunotherapy are less than those achieved with grass pollen, making this particular allergy a treatment challenge. Several research teams carried out extensive studies on the isolation and characterization of pollen allergens (46,47), aiming to obtain, by chemical modifications of pollen allergens, derivatives with reduced allergenic activity but with preserved immunogenic properties of native allergen.

Results of the allergen immunotherapy are rather diverse due to the use of unstandardized allergen extracts, poor study design, and small number of patients, and the risk of adverse effects is still relatively high. On the other hand, the incidence of hypersensitivity, its chronicity, unpleasant symptoms, and relative ineffectiveness of the generally accepted treatments stimulate the search for more etiological and effective treatments for the disease, thus turning the problem back to the procedures of immunotherapy. Abramson (48) published a meta-analysis of 32 asthma immuno-

therapy randomized controlled trials. The combined odds ratio for clinical improvement for any allergen was 3.2 (95% confidence interval [CI]); reduction in medication after mite therapy was 4.4 (95% CI); and for combined reduction in bronchial hyperresponsiveness was 6.8 (95% CI). Immunotherapy caused the improvement in the forced expiratory volume in 1 second (FEV₁) with a mean increase of 7.1% of the predicted value (95% CI). The conclusion of the meta-analysis was that allergen immunotherapy was a treatment option in highly selected allergic asthmatic subjects. During the last decade, numerous studies have been published about clinical and laboratory effects of specific subcutaneous (24-29,49), local nasal (4,30), and rush sublingual immunotherapy (31,32) in *Parietaria* pollen-sensitive patients with nasal symptoms. Many authors recorded a significant reduction in the use of medication and reduction of symptoms scores (4,24-32). Lessening of the reduction of nasal inspiratory peak flow after metacholin and/or specific allergen challenge was also associated with the immunotherapy, indicating a reduction in nasal inflammation (4,30). Immunotherapy also caused the reduction of expression of intercellular adhesion molecule-1 on epithelial cells after nasal challenge with metacholin or allergen (30) (Table 3).

Table Efficacy of allergen immunotherapy. [\[view this table\]](#)
3:

We studied the effects of specific immuno- therapy during three years of treatment of 40 patients with *P. officinalis*-sensitive seasonal rhino- conjunctivitis (29). The patients were treated with subcutaneous injections of a partially purified, characterized and standardized pollen extract of *P. officinalis* allergen (alum-absorbed depot preparation). The treatment was applied preseasonally and clinically assessed during the plant flowering season. Allergen-specific IgE antibodies decreased, specific IgG increased, and histamine release from peripheral blood leukocytes challenged in vitro with the allergen decreased during the three years of the treatment. Clinically, both symptom and additional medication scores significantly decreased in the treated patients and also in comparison to patients treated with ketotifen. In our hands, high doses of the allergen were much more effective than low doses. This is typical for high-quality extracts that have been well characterized. Immunotherapy with small allergen doses does not differ from placebo. Allergen immuno- therapy can induce a variety of local and systemic side effects of patients. Local wheal and flare reactions at the site of injection were common, in 37.5% patients in our study (29), although they may herald the onset of a systemic response (50). Systemic responses usually start within minutes of the treatment and may be organ specific (29) or generalized (29,50). It is strongly recommended to respect a waiting period of 20 minutes for all patients after the injections and longer periods for high-risk patients (asthmatic patients). Local nasal immunotherapy with *Parietaria* pollen macronized powder (4,30) or allergoid (25,26), showed no side effects. In our study, four patients with *Parietaria* pollen-sensitive rhinitis, treated subcutaneously, developed anaphylaxis during the second or third treatment in the first year.

Conclusions and Recommendations

Parietaria pollen allergens are one of the most common causes of pollinosis in the Mediterranean area and the major one in South Croatia. Among various *Parietaria* species, *Parietaria officinalis* is the most common in South Croatia. Successful immunotherapy of *Parietaria*-induced allergic symptoms would have a significant clinical impact. Future developments may include the production of pure allergens by molecular cloning and the development of peptide fragments of allergen that induce unresponsiveness in Th2 cells (46,47). Duro et al (46,47) and D'Abusco et al (51) showed that the antibody response induced by natural exposure to the pollen of *Parietaria* appears to be highly focused on a single linear antigenic determinant of the major allergens, which may play a relevant role in the development of clinical allergy. Other new approaches include use of allergen-antibody complexes and the development of non-activating IgE humanized monoclonal antibodies that may prevent allergen-induced activation mast cells (29,50). Whether these novel approaches will result in safer and more effective immunotherapy remains to be determined; none of them has been effective in clinical asthma so far.

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