Clinical and Molecular Profiles in Patients Allergic to Amaranthaceae

Agulló-García A[1,2], Colás Sanz C[1,2,3], Martínez-Lostao L[4], Salamanca Fernández G[5], Ferrer Clavería L[1,2], Cubero Saldaña JL[1,2], Lozano Andaluz SV[1], Carbajo Martínez E[1], Villalba Díaz MT[6]

[1]*Allergy Department, University Hospital Lozano Blesa of Zaragoza, Zaragoza, Spain*
[2]*Aragon Institute for Health Research (IIS Aragon), Zaragoza, Spain*
[3]*Faculty of Medicine, University of Zaragoza, Zaragoza, Spain*
[4]*Immunology Department, University Hospital Lozano Blesa of Zaragoza, Zaragoza, Spain*
[5]*Medical Affairs & Clinical Department, LETI Pharma, Tres Cantos, Madrid, Spain*
[6]*Department of Biochemistry and Molecular Biology, Faculty of Chemical Sciences, Complutense University of Madrid, Madrid, Spain*

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Recent studies have revealed a mismatch between the air pollen concentration and clinical symptoms among patients monosensitized to Amaranthaceae pollen [1]. The long symptomatic period affecting most patients can be explained by the duration of the flowering period for Amaranthaceae species (May to October) [2]. This botanical family is more likely to adapt to climate change than others. Therefore, a better understanding of its behavior is increasingly interesting owing to a probable growth in the number of sensitizations and allergic respiratory symptoms in the near future.

Few studies have examined the allergenic and clinical relevance of the various Amaranthaceae species, with only *Salsola kali, Salsola oppositifolia*, and *Chenopodium album* pollen available for the diagnosis and treatment of patients.

S kali pollen is a complex allergen source containing numerous Sal k 1 isoforms [3,4] and other allergens, with variable cross-reactivity [5-9]. Only 1 recombinant Sal k 1 isoform is currently available for molecular diagnosis, and this is clearly insufficient for a complete evaluation of hypersensitivity to this pollen.

The aims of our study were to establish the clinical profiles of patients with relevant symptoms to Amaranthaceae pollen and to correlate them with their molecular sensitization profiles.

The study was approved by The Ethics Committee of Aragón (CEICA), Zaragoza, Spain. All patients signed an informed consent document to participate.

Fifty patients sensitized to *S kali* with symptoms compatible with respiratory allergy during the pollination period of Amaranthaceae species from Zaragoza (Aragón, Spain) were included. Blood samples were drawn, and serum samples were used for the in vitro study. Symptoms appearing from April to October 2018 were assessed subjectively using a visual analog scale (VAS).

SDS-PAGE (Online supplement, figure 1), immunoblotting, and ELISA were performed for qualitative and quantitative studies of *S kali* allergens. Allergens were identified using immunodetection, while indirect ELISA assays were used for quantification of specific IgE (sIgE) in the case of previously identified allergens.

The PSPP statistical program was used to distribute patients into clusters, and mean symptom curves were obtained for each group (Online supplement, figure 2). These mean curves were compared graphically with the flowering curves of species of Amaranthaceae obtained in a previous study [2], and 3 associations (clusters) were obtained (Figure). Statistical analysis methods are given in the online supplement (File 1).

Therefore, the 50 patients were classified into 3 groups according to this statistical association, with specific differences seen in terms of intensity and temporality of the symptoms for each of the clusters (Online supplement, figure 3).

Group 1, formed by 13 patients, correlated with the *S kali* flowering season (R=0.92; PSPP was also used to calculate these correlations) and presented symptoms of low intensity and a peak between the end of July and the beginning of August. The mean global VAS was 4.46 (1.42). All 13 patients had allergic rhinitis, which was associated with conjunctivitis in 77% and asthma in 54%. In this group, 92% of patients recognized Sal k 1, 23% Sal k 4 (profilin), 15% Sal k 5 (Ole e 1–like), and 15% Sal k 6. However, the panallergen Sal k 7 (polcalcin) was not recognized by any patients. One of the patients who recognized Sal k 4 (profilin) was negative for Sal k 1.

Group 2, which comprised 10 patients, correlated with *S kali* and *Bassia scoparia* flowering together (R=0.86), and was characterized by 2 medium-intensity symptom peaks: the first one between late July and early August, and a second one in late August. The mean global VAS was 4.66 (1.97). All 10 patients had allergic rhinitis, which was associated with conjunctivitis in 80% and asthma in 30%. In this group, 90% of the patients recognized Sal k 1, 10% Sal k 5, 10% Sal k 6, and 20% Sal k 7; none recognized Sal k 4. A patient who recognized Sal k 6 was negative for Sal k 1.

Group 3, which comprised 27 patients, was characterized by very intense symptoms throughout spring and summer in Spain. All patients' symptoms were correlated (R=0.74) with sensitization to *Amaranthus muricatus*, *S kali*, and *B scoparia*. The mean global VAS was 5.43 (1.83). All patients in this group had allergic rhinitis, which was associated with conjunctivitis in 59% and asthma in 56%. In this group, 89% of patients recognized Sal k 1, 11% Sal k 4, 11% Sal k 5, 7% Sal k 6, and 7% Sal k 7.

For all groups, only 33% of the patients who recognized Sal k 5 (Ole e 1–like) also recognized Ole e 1. Asthma was well controlled in all cases. No other prevalent sensitization was observed in patients with asthma in this case.

Figures showing the scores recorded, the analysis for each group, and all *S kali* allergens studied can be consulted in the online supplement (Tables 1 and 2).

No significant differences were observed between the 3 groups in the clinical presentation of allergy to Sal k 1 (P=.168),

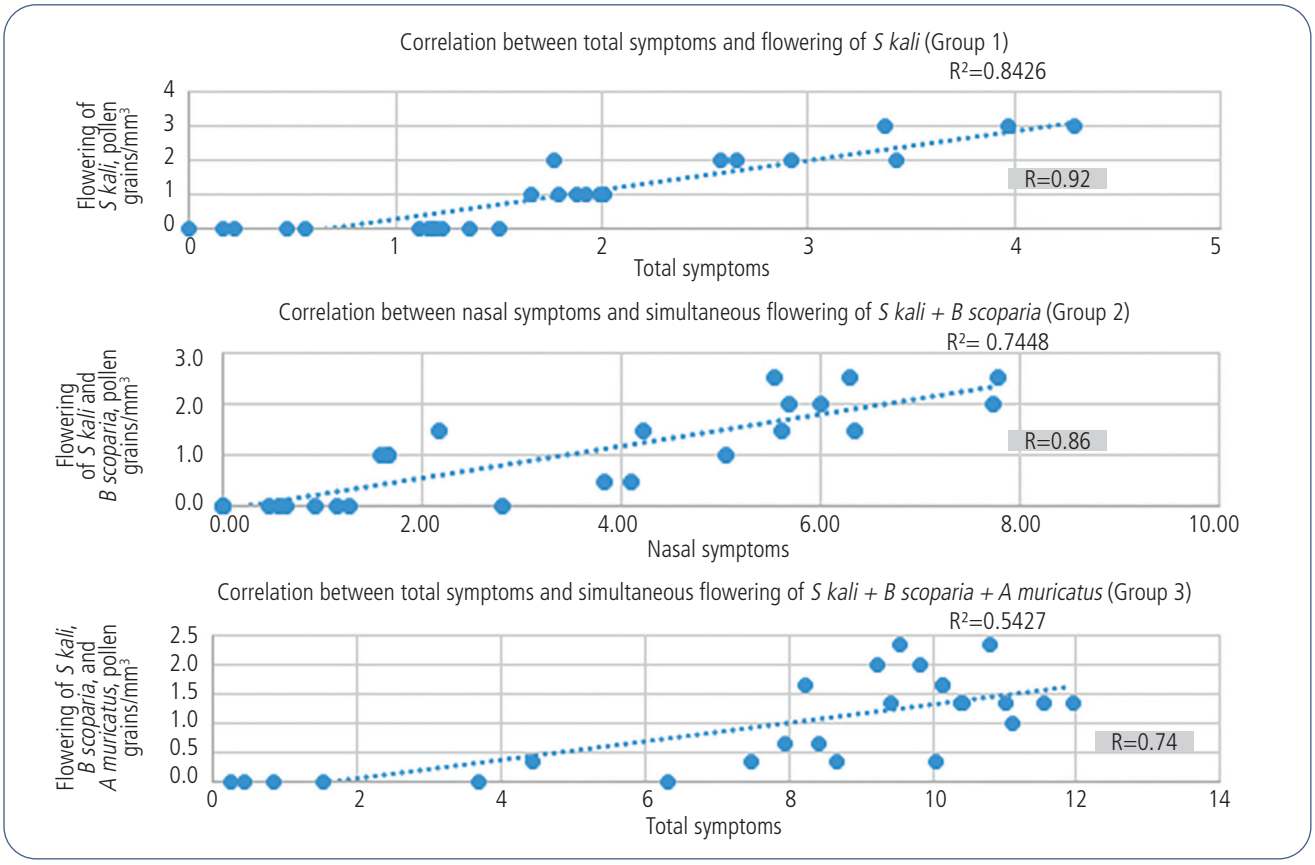

Figure. Correlation between symptoms and flowering of the 3 groups. Symptom severity was scored using the Total Symptom Severity 4 questionnaire.

Sal k 4 (*P*=.592), Sal k 5 (*P*=.474), Sal k 6 (*P*=.662), or Sal k 7 (*P*=.643). Similarly, no significant differences in VAS symptom values were observed. Sal k 1 and Sal k 5 were predominant in group 1, as were Sal k 1 and Sal k 6 in group 3. However, the absence of relevant allergens, such as the panallergens Sal k 4 and Sal k 7, in some of the groups could be of interest for further studies. Besides, other unknown allergens could be responsible for these discrepancies, because different patterns of bands of around 40 kDa were visible in the immunoblotting assay (Online supplement, figure 3). This 40-kDa molecular mass is the one reported for Sal k 1 and Sal k 6.

In contrast, significant differences were observed in the values of *S kali* sIgE (*P*<.05), with lower values in group 1 (6.25 [3.72] kU/L) than in groups 2 (38.10 [1.56] kU/L) and 3 (29.53 [16.42] kU/L), implying that the total *S kali* extract IgE levels correlate with the intensity of symptoms. The lack of significant differences between allergen components could imply the existence of other, unknown allergens that could be responsible for these differences in clinical presentation.

To our knowledge, this is the first study to analyze the relationship between the molecular profile of patients sensitized to Amaranthaceae, allergic symptoms, and the seasonality of *S kali* pollen.

Our results reveal different sensitization profiles that may help to include other relevant allergens in the diagnosis and treatment of Amaranthaceae allergy. However, further studies are needed to confirm these findings.

In conclusion, *S kali* pollen is more complex than other pollens we have analyzed in the past owing to the presence of different species and the large number of isoforms of certain allergens. Significant differences are observed with the complete extract of *S kali* but not with the remaining allergens studied. Therefore, other, unknown allergens could be responsible for differences in clinical presentation.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ana Agulló García
Servicio de Alergia
Hospital Clínico Universitario Lozano Blesa
Avda. San Juan Bosco, 15
50009 Zaragoza, Spain
E-mail: aagullog@gmail.com