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Cypress pollen allergy is responsible for two distinct phenotypes of allergic rhinitis different from other pollinosis

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Key words

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Summary

Different phenotypes of allergic rhinitis have been identified based on the seasonality of the allergen involved. Within pollinosis, importance has to be paid to the responsible pollen species. Guidelines for clinical management are mostly based on studies performed in patients with grass pollen allergy. Only few data is available on tree pollen allergy and more specifically on cypress pollen allergy.

We focused on the clinical and biological features of cypress pollen allergy to determine whether it is associated with a specific phenotype of allergic rhinitis or not.

Our results suggest that cypress pollen can be responsible for two distinct phenotypes of rhinitis, both different from other pollinosis.

In the most common phenotype, cypress pollen was not responsible for bronchial hyperresponsiveness or systemic inflammation.

Close attention has to be paid to the allergen involved in allergic rhinitis. Different phenotypes leading to different pharmacological strategies may apply.

Introduction

Cypress pollen allergy is a winter pollinosis that may be caused by several *Cupressaceae* species around the Mediterranean basin, in North America and Asia (1,2). Its prevalence has increased over the last decades (1). The first cases of cypress pollinosis were described in South Africa in 1945 and in France in 1962 (3). During the following decades, cypress species have been extensively planted for ornamental purpose (1). This increased exposure (4,5) has been responsible for the increase in prevalence of sensitization and clinical manifestations of cypress pollen allergy (6-8).

Cypress pollinosis symptoms are often hard to control. Caimmi reported a 57.9% of cypress pollen allergic patients needing immunotherapy to control their symptoms (3). Most reported symptoms are rhinitis, conjunctivitis, asthma, cutaneous manifestations (1-3,9) and dry cough (1).

Several studies have highlighted the differences existing among allergic rhinitis phenotypes based on the seasonality of the al-

lergen involved (10-13). Within pollen-induced allergic rhinitis, importance has to be paid to the pollen species (14,15). Guidelines of clinical management have been built on available evidence, mostly based on grass pollen allergy studies. Only few data is available on tree pollen allergy and more specifically on cypress pollen allergy, although there is emerging evidence that clinical feature of cypress pollen allergy differs from other pollinosis. As an example, cypress pollinosis has been characterized by a lower prevalence of conjunctivitis and a higher prevalence of dry cough during pollen season than *Gramineae* pollinosis (1). In this study, we aim to focus on the clinical and biological features of cypress pollen allergy in order to determine whether cypress pollen-induced allergic rhinitis is associated with a specific phenotype of allergic rhinitis or not. This will help to rule on the clinical management of this pollinosis.

Material and methods

The study was conducted in Marseille, Southern France. This was a monocentric prospective study that aimed to enrol adults from 18 to 65 years with a diagnosis of allergic rhinitis to cypress pollen. The diagnosis was confirmed by positive skin prick test to at least one pollen from the *Cupressaceae* family.
Patients could be sensitized to other allergens, even perennial ones, but had to be clinically free from symptoms related to these allergens. Patients with diagnosed asthma were excluded from the study as well as patients that underwent allergenic immunotherapy during the past 5 years. Pregnant women, patients treated with beta-blockers, suffering of a clinically unstable disease during the past three month or a respiratory infection during the month preceding enrolment were not eligible to the study.
According to local legislation, all patients signed an informed consent form approved by an ethics committee (Comité de protection des personnes Sud Méditerranée I, project reference 2011-A00211-40). The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946 and the international guidelines of Good Clinical Practice.
Thirty-six patients were enrolled into this protocol consisting in 2 visits. One visit outside the pollinisation and one during symptoms period. 32 patients attended both visits.
Outside the pollen season, patient profile of allergens sentitization was assessed using standardized skin prick tests with a battery of allergenic extracts consisting of *Juniperus ashei*, Mix of *Cupressaceae* (*Cupressus arizonica* and *sempervirens*), Grass, *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat, dog, cockroach, *Parietaria*, *Olea* and Platane tree.
The skin reaction was recorded 20 minutes after the test by evaluating the skin response in comparison to the wheal induced by the histamine positive control test. A wheal diameter of at least half of the histamine wheal diameter was considered a positive reaction.
During and outside the allergic season, patients filled a symptom questionnaire, the Mini Rhinoconjunctivis Quality of Life Questionnaire (RQLQ) (16). It consists in 5 questions referring to allergic rhinitis symptoms and overall control. Each question consists in a 5 values scale. The total score range from 5 (uncontrolled rhinitis) to 25 (absence of symptoms).
Patients also reported personal and familial history of atopy, they underwent pulmonary function test and standardized methacholine challenge to assess bronchial hyperreactivity. Levels of IL10, IFNɣ, IL12p70, IL5, IL4, IL2, IL17a, IL1β, TNFα and CXCL8 were measured in serum sample with Cytometric Bead Array™ Flex Sets (CBA, Becton Dickinson, Le Pont de Claix, France) following the manufacturer's instructions. Briefly, specific antibody-coated beads detected target cytokines or chemokines, the signature of each type of bead being unique phycoerythrin-fluorescence intensity. Experiments were performed with a FACS Canto II flow cytometer using the FacsDIVA software (Becton Dickinson, Le Pont de Claix, France). Results are expressed as concentration (fg/ml).
Statistical analysis was performed using Graphpad Prism software. Depending on the data analysed we used different statistical tests. Patients' characteristics of coughing and non-coughing subgroups were compared by the Student test, excepted for percentages that were compared with the chi square test. The Wilcoxon test was used to compare data measured during and outside pollen season in the same patients (methacholine challenge results, symptom scores and blood cytokines levels). In all tests, we used a two-tailed hypothesis and a significance level of 0.5.

Results

As reported in **Table I**, the most frequent symptom in our cypress pollen induced allergic rhinitis population was rhinorrhea (94% of patients). Dry cough was present in 31% of patients. Mean age at onset of symptoms was 27 (± 17) years. Disease duration was 13.6 ± 9 years.

Table I *- Frequency of reported symptoms during the allergic season.*

rhinorrhea	94%
ocular itching	79%
sneezing	76%
nasal itching	44%
throat itching	44%
watery eyes	38%
nasal obstruction	33%
dry cough	31%

Table II *- Patients characteristics.*

	All patients	**Coughing patients**	**Non coughing patients**	**p-value**
men	42%	36%	44%	0.67
age	40 ± 17	42 ± 19	39 ± 17	0.69
age at symptoms onset	27 ± 17	28.8 ± 18	26.5 ± 17	0.73
disease duration	13.6 ± 9	13 ± 6.5	13.9 ± 10	0.83
symptom score during pollen season	17.7 ± 3.4	17.3 ± 3.9	17.8 ± 3.2	0.68
symptom score outside pollen season	24.1 ± 1.8	24.3 ± 1.5	24.1 ± 2	0.71
atopic disease history in mother	22% (allergic rhinitis) 5.6% (asthma) 5.6% (eczema)	18% (allergic rhinitis) 9% (asthma) 9% (eczema)	27% (allergic rhinitis) 4.5% (asthma) 4.5% (eczema)	0.66 0.5 0.5
atopic disease history in father	19.4% (allergic rhinitis) 2.8% (asthma)	9% (allergic rhinitis)	27% (allergic rhinitis) 4.5% (asthma)	0.27 0.49
atopic disease history in both parents	2.8% (allergic rhinitis in both parents)	0%	4.5%	0.49
atopic disease history in siblings	33% (allergic rhinitis) 14% (asthma)	20% (allergic rhinitis)	52% (allergic rhinitis) 16% (asthma)	0.09 0.21
number of positive skin prick tests	4.3 + /- 2,1	3.3 ± 2.3	4.7 ± 1.9	0.12
monosensitization to cypress pollen	22%	36%	16%	0.18
sensitization to cypress	100%	100%	100%	1
Juniperus ashei	89%	64%	100%	0.006
Cupressaseae mix (*arizonica and sempervirens*)	97%	91%	100%	0.3
both	86%	54%	100%	0.001
grass	47%	27%	56%	0.16
house dust mite	31%	36%	28%	0.70
Dermatophagoides pteronissinus	28%	36%	24%	0.45
Dermatophagoides farinae	19%	0%	28%	0.08
both	17%	0%	24%	0.15
cat	42%	27%	48%	0.29
dog	31%	27%	32%	1
cockroach	0%	0%	0%	NA
Parietaria	14%	18%	12%	0.63
Olea	44%	27%	52%	0.28
Platane tree	14%	9%	16%	1

Coughing patients had less personal and familiar history of atopy and were more likely to be monosensitized to cypress than non coughing patients: 36% and 16% of monosensitized patients in the coughing and non-coughing patients groups respectively. Nevertheless, these differences did not reach the statistical significance. Patients were considered to be monosensitized to cypress pollen if they had a positive SPT to one or both of the *Juniperus ashei* and *Cupressaceae* mix (*Cupressus arizonica and sempervirens*). The patients' profile of sensitization to other tested allergens is shown in **Table II**: we found no statistical difference between coughing and non-coughing patients profiles, excepted for cypress pollens species sensitiza-

***Figure 1** - Change in methacholine response during pollinisation.*

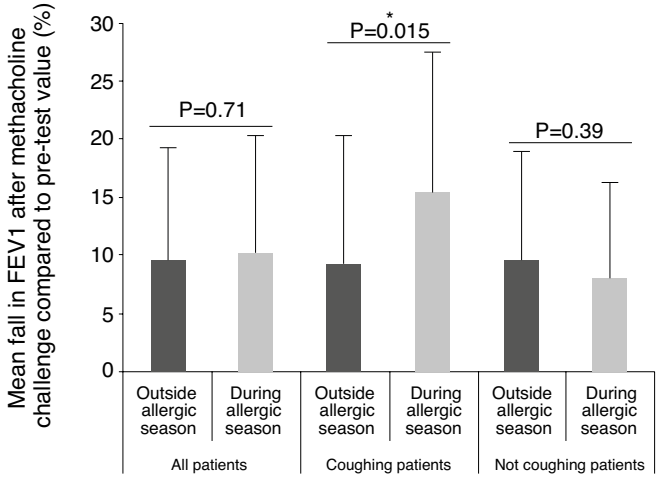
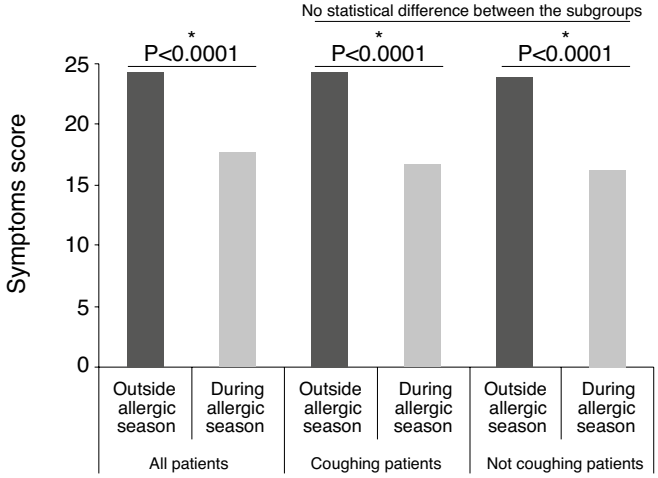


***Figure 2** - Change in symptoms score during pollinisation.*



tion. Non-coughing patients are more likely to be sensitized to *Juniperus ashei* in addition to other cypress pollen species than non coughing patients.

All patients had significantly more symptoms during season, as assessed by a decrease of 7 points in the mini rhinoconjunctivitis quality of life questionnaire score in all groups. There was no difference in symptoms score during or outside the pollen season based upon the coughing status (**Figure 2**). The mean RQLQ score was 17.7 ± 3.4 during pollen season and 24.1 ± 1.8 outside the pollen season.

In the majority of patients (69%) who have cypress pollen induced allergic rhinitis without dry cough, there was no change in the methacholine challenge results during and outside the pollen season. In non-coughing patients, FEV1 decrease was equal to 8.0% and 9.6% outside and during the pollen season, respectively.

An increase in methacholine challenge response does exist in the coughing patients group as compared with the non-coughing patients group (**Figure 1**). In coughing patients the mean decrease in FEV1 after methacholine challenge was 9.3% outside the pollen season and 13.9% during pollen season. However, in both groups, none of the patients having a negative methacholine challenge outside the pollen season reached the threshold of positivity during pollinisation.

Blood cytokines concentrations were stable outside and during the allergic season in the "all patients" analysis (**Figure 3**) and in both cough-related subgroups.

Discussion

Several limitations may apply to our findings. Firstly, only a small number of participants were experiencing cough during pollen season (31% corresponding to 11 patients). Secondly, as demonstrated by Polosa and colleagues, adenosine 5' monophosphate challenge may be a better way to assess bronchial hyperresponsiveness in these patients (17). This may underestimate the actual bronchial hyperresponsivness in this subgroup.

Nonetheless, our study succeeded in identifying two distinct phenotypes of cypress pollinosis. These phenotypes can be clinically discriminated by the presence or absence of dry cough during pollinisation.

Basically, the most frequent phenotype of cypress pollen induced allergic rhinitis does not include dry cough as a symptom (69% of patients). A subset of patients (31%) experience dry cough. This difference may lead to distinct therapeutic managements.

Severity of the disease

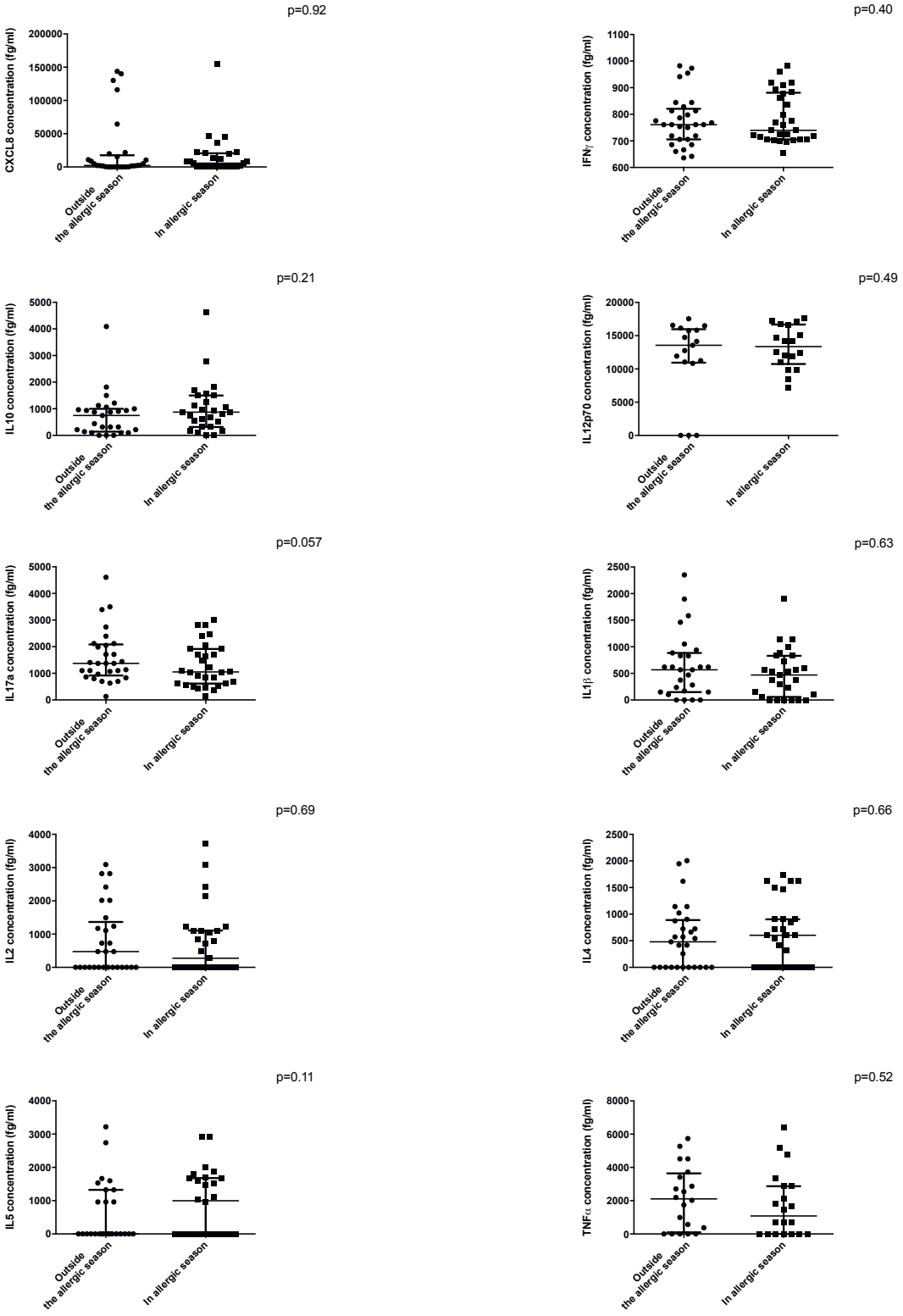
In our study, we failed to identify a difference in the disease severity between subgroups. The symptom score was similar in both groups, thus cough is not a marker a severity of the disease.

Bronchial hyperresponsiveness

Many studies highlight an increase in bronchial hyperresponsiveness during pollinisation in patients suffering from pollen induced allergic rhinitis. The large majority of these studies are addressing grass pollen allergy (15,18-20) and evidence of this finding is lacking in cypress pollen allergy.

Allergic rhinitis and asthma are airways diseases that often occur concomitantly. Epidemiological evidence from studies conducted in industrialized countries show that 60 to 98.9% of asthmatics patients have concomitant rhinitis and that 20 to 40% of rhinitics patients show clinical evidence of asthma (12,21-24).

Figure 3 *- Cytokines serum concentration during and outside the pollen season in all patients.*



This concomitant manifestation of symptoms in both upper and lower airways supports the concept of "united airways disease" (25). Because the association between asthma and rhinitis is observed in non-atopic subjects (24), the relationship cannot be explained by common risk factors, and it has been suggested that rhinitis might itself be a risk factor for asthma (26).
Both diseases are inflammatory, so biomarkers can overlap suggesting a common pathogenesis. The united airways disease theory relies on the idea that upper and lower inflammatory manifestations influence each other, and that therapeutic management of one or the other disease can help controlling symptoms at another bronchial level (27). Indeed, comorbid allergic rhinitis has been identified as a marker for more difficult to control asthma, and may worsen asthma outcomes (27). The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative recognizes the interactions between these two entities and supports a global therapeutic and diagnostic management described in evidence-based guidelines (28).
Triggers of allergic rhinitis may play a role in the concomitant existence or onset of symptoms in the lower airways.
Firstly, it may depend on the seasonality of the sensitization. An interesting finding supporting this point comes from the work of Ricconi and colleagues in 2002. They highlighted the fact that perennial allergy is associated with greater bronchial hyperresponsiveness than seasonal allergy (10). This was confirmed in 2014 by Ciprandi and colleagues, stating that patients showing bronchial hyperresponsiveness had significantly more frequent mite allergy (11). In the same way, Linneberg and coworkers reported asthma in 25% of patients with allergic rhinitis who were pollen-sensitive and in 50% of those patients who were mite-sensitive or animal-sensitive (12). Ciprandi demonstrated that bronchial hyperresponsiveness was present in 50% of seasonal allergic rhinitis patients and in 70% of patients experiencing perennial symptoms (13).
Secondly, in pollen induced rhinitis, lower airways impairment may depend on the pollen species. Di Lorenzo and colleagues brought out that bronchial hyperresponsiveness incidence among allergic rhinitis patients during pollen season and off season depend on the kind of pollen responsible for the allergy (14). In this study conducted on 49 patients with Parietaria, Gramineae and Olea pollen induced rhinitis, the authors conclude that Parietaria pollen allergy is more important than Gramineae or Olea pollen allergy as a risk of developing nonspecific bronchial hyperresponsiveness, measured as response to inhaled methacholine. Indeed, 16 patients showed bronchial hyperresponsiveness during pollen season (100% were parietaria sensitized) and 8 patients off pollen season (7/8 were parietaria sensitized). In grass pollen induced rhinitis, Kurt has demonstrated that 50% of patients experience bronchial hyperresponsiveness during the pollen season (15).
In our study, the majority of patients (69% i.e. non-coughing patients) showed no change in their methacholine challenge results during and outside the cypress pollen season. Thus, there is no allergen induced bronchial hyperresponsiveness in these patients. A significant increase in methacholine challenge response does exist in the coughing patients group as compared with the non-coughing patients group. Therefore, none of the patients having a negative methacholine challenge outside the pollen season reached the threshold of positivity during the season (decrease of at least 20% in FEV1). This may assess an increase of bronchial reactivity in patients coughing during cypress pollinisation, but cough cannot be considered a marker of bronchial hyperresponsiveness in cypress pollen induced allergy.
A limitation of our study is the lack of FeNO dosage. This is indeed considered an important parameter for the early characterisation of bronchial hyperresponsiveness, and this could have been complementary to methacholine challenge (29-33).

Systemic inflammation

Blood cytokines dosages failed to demonstrate a systemic inflammation as all concentrations are stable outside and during the allergic season.
In grass pollen induced allergic rhinitis, several inflammatory biomarkers have been identified to increase during pollen season and to correlate to bronchial hyperresponsiveness. IL5, IL18 blood levels, blood and sputum count of eosinophils have been shown to increase during pollen season and to parallel bronchial hyperresponsiveness (14,15,18-20).
Given these observations, the stability of proinflammatory cytokines during and outside the pollen season in our study are consistent with the absence of cypress pollen induced bronchial hyperresponsiveness in the majority of patients.
As mentioned previously, the small number of coughing patients does not allow us to extrapolate this result to this specific subgroup and a systemic inflammation may exist in coughing patients.
Nonetheless, in the majority of cypress pollen allergic patients, the absence of systemic inflammation is in favour of an ear-nose-throat local inflammatory reaction.

Implication for diagnosis and therapeutic management

Two distinct phenotypes of cypress pollen induced allergic rhinitis have been identified in our study. Both phenotypes differentiate from other pollinosis by their late onset.
The "coughing phenotype", which is the less common, has similarities with other pollinosis, as it may be characterized by an increase in bronchial hyperresponsiveness.
Nonetheless, these patients have less personal and familiar history of atopy and are more likely to be monosensitized to cypress

pollen than non coughing patients. This differentiates this first phenotype of cypress pollen induced allergic rhinitis from other pollinosis. In these patients, treatment of both nose and bronchi may improve disease control.

The most frequent phenotype, the "non-coughing" phenotype, also differs from other pollinosis and contradicts the united airway disease theory. Cypress pollen is in most of the cases responsible for a local reaction that does not affect lower airways. In those patients, a local treatment of symptoms should be preferred.

Conclusion

Overall, we would like to stress the importance to pay close attention to the allergen involved in allergic rhinitis. Depending on the allergen involved, different phenotypes leading to a different pharmacological strategy may apply, and more surprisingly one allergen may be responsible for different phenotypes. As mentioned, due to a modest number of patients enrolled, this study remains a preliminary work, and further investigations are required to strengthen these findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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