

Review article

Allergy to cypress pollen

Although *Cupressus sempervirens* has been spread over southern Europe since antiquity, cypress pollen allergy has not been reported until 1945 (1). In France, the very first case reports were published in 1962 (2). Since then, the prevalence of cypress pollinosis seems to demonstrate an upward trend, concomitantly with the increased use of cypress trees as ornamental plants, as wind breaks and as hedges. Hyposensitization, using improved pollen extracts, is increasingly prescribed. Besides, prevention measures begin to be implemented. Such measures include avoidance of planting new cypress trees, especially near human populations' centres, trimming of cypress hedges before the pollination season and agronomical research for hypoallergenic trees. Altogether, such new developments in cypress allergy deserve an update review.

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Cypress allergens

The genus *Cupressus* is comprised of several species that are widely spread over the East Mediterranean, central Asia, China and the western North America. The most common species around the Mediterranean basin are *Cupressus sempervirens*, *Cup. arizonica*, *Cup. macrocarpa* and *Cup. lusitanica*. A few additional species are also planted but are less common. Regarding the allergenic features of the various species, the best-studied species is *Cup. arizonica*. The pollen of this species presents six immunoglobulin (Ig)E-binding protein bands, with the 43 kDa component being predominant both in its intensity and by the frequency of recognition by human IgE antibodies (3). This band was identified as the major allergen of *Cup. arizonica* (Cup a 1). It was cloned and sequenced (4). *Cupressus arizonica* and *Cup. sempervirens* extracts show a high cross-reactivity and share a number of common epitopes (5). Nevertheless extracts of *Cup. arizonica* pollen seem to demonstrate a higher allergenic potential when compared with that of *Cup. sempervirens* and *Cup. lusitanica* (6). The differences

in IgE-binding capability among the different species may result from different sugar moieties that may intensify the IgE-mediated response and be involved in clinical symptoms of allergy (7).

Besides, there is a high cross-reactivity (75–90% homology) between Cup a 1 (major allergen of *Cup. arizonica*), Cha o 1 (major allergen of *Chamaecyparis obtusa*, the Japanese cypress) and Jun a 1 the major allergen of *Juniperus ashei*, the mountain cedar (8) (Table 1). All of them have an active pectate lyase site. Moreover, Jun a 1 possesses a high level of amino acid sequence homology with Cry j 1, the major allergen of *Cryptomeria japonica* (9) and shares the same biological activity. Recently, a new allergen from *Cup. arizonica* pollen, Cup a 3, was described (10). Cup a 3 is a thaumatin-like pathogenesis-related protein (PR-5), which shares a large homology with one of the allergens of *Juniperus*, Jun a 3 (Table 1, ref. 11).

Both proteins are expressed in different ways depending on variable ambient conditions such as climate or air pollution (10, 12). Thus, allergenicity of cypress pollen extracts may depend on where they have been collected.

Table 1. Cloned allergens from Cupressaceae grouped by biological functions (after 11)

Biological activity	Pectate lyases (kDa)	Polygalacturonases (kDa)	PR-plant proteins thaumatin (kDa)	Ca ⁺⁺ -binding polyclonal (kDa)
<i>Cupressus arizonica</i> (Arizona cypress)	Cup a 1, 37.6	Jun a 2, 55.7	Cup a 3, 23	
<i>Cupressus sempervirens</i> (Italian cypress)	Cup s 1 (96%)*, 39.8			
<i>Juniperus ashei</i> (Mountain cedar)	Jun a 1 (91%), 39.8		Jun a 3 (95%), 23.7	
<i>Juniperus oxicedrus</i> (Prickly juniper)	Jun o 1 (97%), 39.8			Jun o 4, 17.7
<i>Juniperus virginiana</i> (Eastern red cedar)	Jun v 1 (95%), 39.7		Jun v 3 (94%), 30	
<i>Cryptomeria japonica</i> (Japanese cedar)	Cry j 1 (75%), 40.6	Cry j 2 (71%), 37	Cry j 3 (81%)	
<i>Chamaecyparis obtusa</i> (Japanese cypress)	Cha o 1 (81%), 40.2	Cha o 2 (82%), 56		

*Percentage homology of different cloned allergens compared with the sequence of Cup a 1, Jun a 2 or Cup a 3.

PR, pathogenesis related.

Allergens from *Cry. japonica* are carried mostly by pollen grains. However, they could also be demonstrated on minute parts of airborne particulate matter and even out of any kind of particles (13). Cypress allergens also cross-react with allergens from *Podocarpus gracilior* and *Callitris verrucosa* (14), both species, which have been put forward as surrogates for controlling cypress allergy. The ubiquitous family of calcium-binding proteins may also explain some degree of cross-reactivity. In Cupressaceae, unrelated plants, such as *Parietaria judaica*, *Lolium perenne* and *Olea europaea* (15) inhibit immunoblotting of IgE.

Cross-reactivity studies using recombinant allergens should be taken with caution because they are highly dependent on the expression vector used to get the protein. The PR-5 proteins contain in its sequence 16 cysteine residues that confer spatial peculiarities to this group of proteins. When the expression vector is *Escherichia coli*, the IgE reactivity is lower than that obtained when the vector is *Pischo pastoris*, probably due to differences in spatial conformation. Another important factor is the presence of carbohydrates in the cloned protein, which is also vector-dependent. Interestingly, cross-reactive carbohydrate determinants may be recognized by IgE in such a way that deglycosylation yields a decrease of reactivity (3, 7). This is not related only to B-cell epitopes (or to IgE reactivity). It has also been demonstrated that carbohydrates on Cry j 1 are important in T-cell responses, promoting Th2 predominance. Stimulation of cells with periodate-treated Cry j 1 gives a decrease in proliferation and a lesser production of interleukin (IL)-4 and IL-5 with no alteration in the synthesis of interferon (IFN) (16).

An oral allergy syndrome has been reported in Japanese cedar allergic patients eating some vegetables and fresh fruits (melon, apple, peach and kiwi) (17). A group of seven patients suffering from cypress pollinosis and allergy to peach has also been described (18). The responsible shared allergen was a 45 kDa allergen, which is a lipid transfer protein.

Botanical and palynological aspects

The genus *Cupressus* belongs to the Cupressaceae family of plants, and more specifically to the Cupressoideae (19).

It is native to warm temperate climates in the Northern Hemisphere, and one finds it in abundance around the Mediterranean basin, in North America and Asia (20).

The morphological characters of the pollen grains are not distinct enough to allow palynological determinations below the subfamily level. The pollen grains, which range from 20 to 30 µm in size (apart from *Cup. dupreziana*, 38 µm), are usually inaperturate (they might at times show a porus), spherical, and with rounded granules or gemmae of varying shape and size irregularly scattered on top of a thin exine. Any palynological sampling of the atmosphere will then yield results concerning the Cupressaceae as a whole (including *Cupressus*, *Juniperus*, *Thuja*, etc.) for a given area, without any further taxonomic distinction. Moreover, methods that use nonacetolysed pollen analyses cannot separate the Cupressaceae from the Taxaceae when they both occur in the same area. A good knowledge of the phenology of each species may help to assign observed pollen peaks to the genera and species occurring in the area.

The subfamily of Cupressoideae is represented by a great number of species and genera (*Cupressus*, *Juniperus*, *Thuja*, etc.) that pollinate all the year around. As for the cypress, pollination is centred in winter with variations from species to species (21). For example, pollination occurs earlier for *Cup. arizonica* – starting in October in France, Italy, Israel and California than it does for *Cup. sempervirens* – that starts in January in the same countries. The end of the pollination usually occurs in February for *Cup. arizonica* and in March, sometimes in April for *Cup. sempervirens* (Fig. 1) (22). From year-to-year, the dates of maximum pollination may differ for up to 29 days (22) and the precocity in the dates of pollination seem to run parallel to the ongoing global warming. In southern France, over a 20-year time period, the date of maximum pollination shifted from 16 March to 15 February that is to say 18 days ahead of time (22) (Fig. 2).

As with the majority of anemophilous plants, the pollen production of the Cupressaceae is abundant and differs from species to species. The differences are mainly because of the varying number of male cones per branch (23). Daily and weekly concentrations can reach record peaks in the Mediterranean regions where

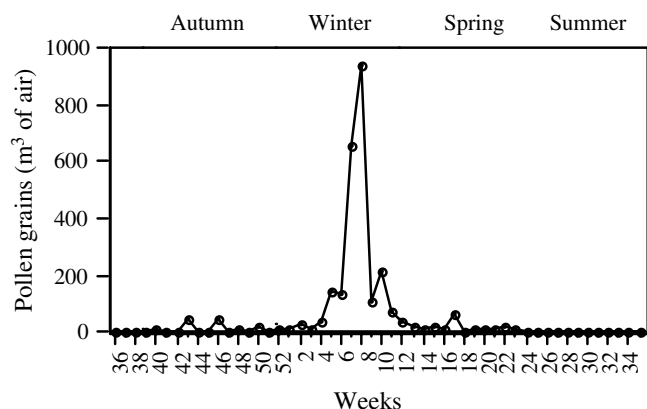


Figure 1. Mean weekly Cupressaceae pollen counts (grains/m³) measured over a 3-year time period (22).

the Cupressaceae represent up to 20–40% of the annual pollen rain (24, 25). However, pollen production may greatly vary from year-to-year depending on the meteorological conditions, which prevail during the cone development, and during the pollination time (26, 27).

In addition, since the ends of the 1970s, a progressive increase in the annual total concentrations of airborne Cupressaceae pollen was recorded in many areas of the Mediterranean (22, 28) (Fig. 3). This is mainly because of an increased plantation of these trees.

During the last decades, botanists have studied numerous cypress species and intraspecific clones in order to select those that have favourable ornamental character-

istics (fastigiated crown shape) and resistance to the canker caused by *Sereidium cardinale*. Today, their objective is also to select cypresses with a low release of pollen during the pollination period as well as of those with a low allergen concentration (29).

Epidemiology

Epidemiology of cypress allergy is poorly documented, mainly because reliable extracts have only been available only during the few last years.

Prevalence of cypress pollen allergy

Prevalence in the general population. Only three such studies have been performed so far (Table 2). The first one (30) was performed in southern France. It compared the prevalence of pollinosis to cypress and grass pollens in adults 16–65 years old living in two areas with a large difference in pollen counts. Overall, the prevalence of pollinosis was twice higher in the more exposed community, when the diagnosis was based on the questionnaire and the results of skin-prick tests. In contrast, the prevalence of asthma was similar in both communities. The percentage of pollinosis with positive skin tests only to cypress pollen extracts was equal to 2.4% in the more exposed community and 0.6% in the less exposed. The second study was also performed in southern France (31). This descriptive study assessed the prevalence of sensitization to main aeroallergens in a group of 2500

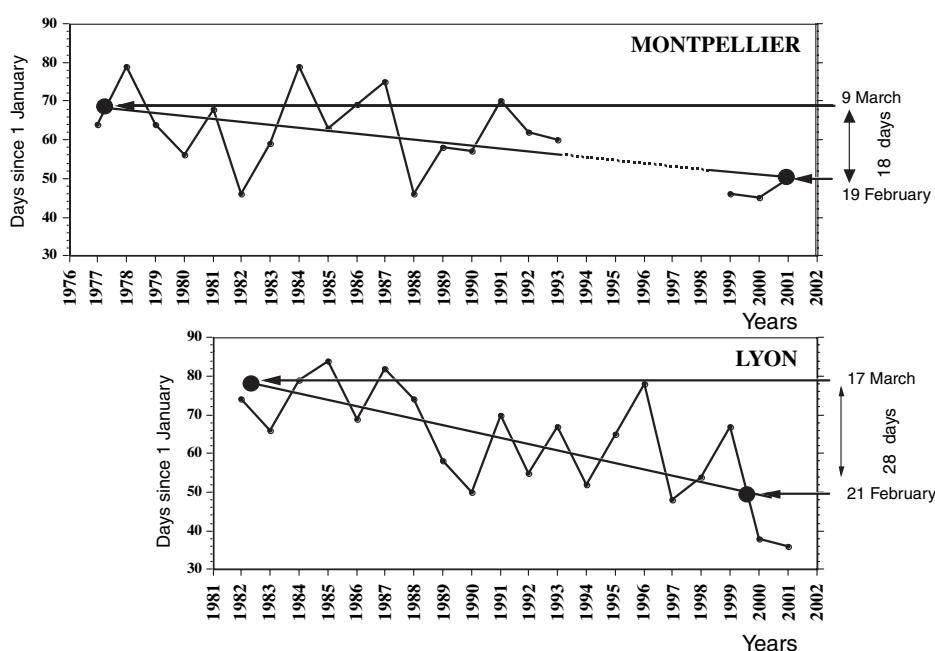


Figure 2. Trend in beginning of the cypress pollination over the 1981–2002 time period in Montpellier, France (upper panel) and Lyon, France (Lower panel) (22).

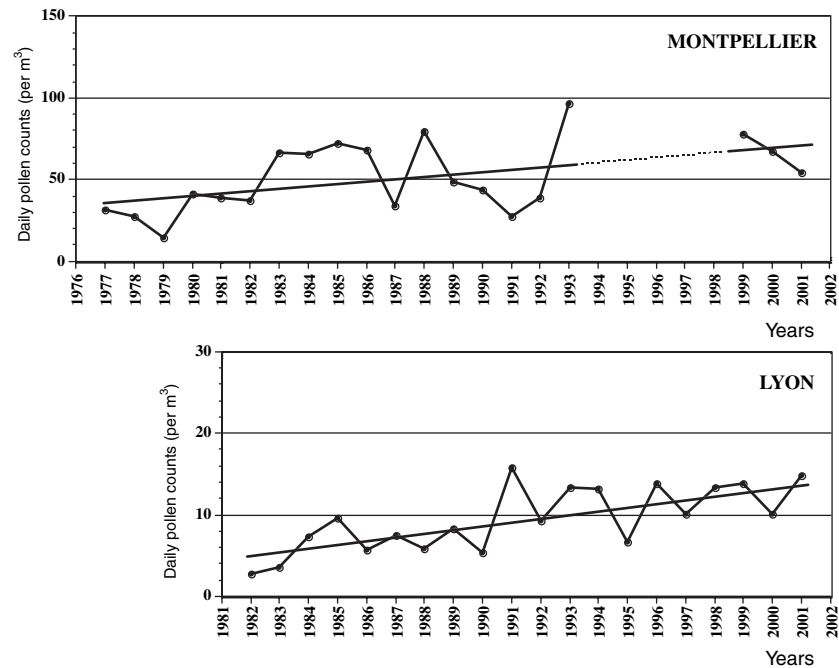


Figure 3. Trend in pollen counts over the 1981–2002 time period in Montpellier, France (upper panel) and Lyon, France (lower panel) (22).

Table 2. Summary of papers on prevalence studies of cypress allergy

Setting	Methods	Main result	Reference
General population			
4700 adults 18–65 years old (Southern France)	Questionnaire, skin-prick tests	Exposed community: 2.4% had symptoms + positive skin tests to cypress alone Less exposed community: 0.6%	30
2500 school children 9–12 years old (Southern France)	Skin-prick tests	Exposed community: 9.6% of positive skin tests to cypress pollen extracts Less exposed community: 2.7%	31
3494 subjects living in Perugia (Central Italy)	Questionnaire, skin-prick test RAST	3.6% had symptoms + positive skin tests to cypress pollen or positive RAST 4.9% had symptoms and a positive skin test or RAST	32
Outpatients clinic			
Outpatients from Central Italy	Questionnaire, skin-prick tests	Prevalence of diagnosed cypress allergy increased from 9.9% in 1991 to 24.5% in 1993 and 35.4% in 1994	33
Outpatients from Tel-Aviv, Netzer-Sireni and Shfaram	Questionnaire, skin-prick tests	24–32% of allergic patients have cypress allergy	34
3057 outpatients from 12 centres (Italy)	Questionnaire, skin-prick tests to Cupressaceae and Taxodiaceae genus	Positive skin test in 18% of the group, 9.2% in northern, 28.2% in central and 20.1% in southern Italy	36
1735 outpatients from Genoa (Italy)	Questionnaire, skin-prick tests	Only 1.04% of positive skin tests to cypress pollen Only five patients monosensitized to cypress pollen	37
1397 outpatients from Latium (Central Italy)	Questionnaire, skin-prick tests	Positive skin tests to cypress in 9.3% in 1994–96 and 30.4% in 1999	39
1146 outpatients from Roma (Italy)	Questionnaire, skin-prick tests to <i>Cupressus sempervirens</i>	Positive skin tests to cypress pollen in 7.2% of patients in 1995 and 22% in 1998	40
Outpatients visits from 1988 to 1997 (Bordighera, Italy)	Trend in sensitization rate compared with change in pollen counts	Increase in sensitization to cypress pollen while no change in pollen counts	41

RAST, radioallergosorbent test.

primary schoolchildren living in an industrial area heavily exposed to cypress and grass pollens, located west of Marseille. The percentage of positive test was 17.6 for mite-allergens, 13.5 for grass pollen, 11.8 for *Alternaria*, 9.6 for cypress pollen and 5.9 for cat danders. A similar

group of children living in an area of Marseille, which is less exposed to pollens, exhibited 2.7% positive skin tests to cypress pollen (unpublished data). The third one (32) was conducted in Central Italy, within the framework of the European Community Respiratory Health Survey.

The prevalence of cypress pollinosis, defined on the basis of suggestive symptoms and a positive skin test or radioallergosorbent test (RAST) to cypress extracts, was equal to 3.6%. Besides, 4.9% of the study group had an asymptomatic sensitization to cypress pollen.

Prevalence in selected groups. The prevalence of cypress allergy among patients of Central Italy increased from 9.9% in 1991 to 24.5% in 1993 and to 35.4% in 1994 (33). The authors have suggested that some of the increase in prevalence was because of either a better diagnosis, due to the use of pollen extracts of *Cup. arizonica*, or a better awareness of grass pollen (GPs) towards cypress pollinosis. Another survey performed within outpatients visiting Israeli allergy clinics concluded that cypress allergy accounted for 24–32% of all hay fever patients, depending on the geographical location (34). A multicentre Italian study (35), including 3057 pollen-sensitized patients originating from 12 Italian centres, demonstrated positive skin tests to several Cupressaceae and Taxodiaceae genus in 18% of the study group. The rate of sensitization was different in northern (9.2%), central (28.2%) and southern Italy (20.1%). Much lower rates have been documented in other reports (36). A possible explanation for this discrepancy may lie in the fact that different groups have used different pollen extracts and that the extracts were not duly standardized.

Increasing prevalence. Epidemiological data that back an increase in prevalence of cypress-pollen allergy (CPA) during the last decades are scarce (31). A descriptive study (37) based on skin-prick tests of outpatients in Marseille during 1960–91 demonstrated a dramatic increase in the percentage of patients sensitized to cypress pollen: nil in 1960 and 25% in 1991. However, such a comparison is not absolutely valid because the used pollen extracts were not the same on both occasions. In the Latium area of Italy, a retrospective survey demonstrated a large increase in sensitization to *Cup. sempervirens* pollen in a group of outpatients over a 4-year period: 7.2% were sensitive in 1995 to 22% in 1998 (38). Another study performed with 1146 outpatients living in Roma demonstrated a 9.3% prevalence of positive skin tests in 1994–96 and a 30.4% in 1999 (39). In western Liguria, Ariano et al. reviewed the trends in pollen-specific sensitization in outpatients consulting from 1988 to 1998 (40). They demonstrated a strong increase in the sensitization rate to cypress allergens, while the pollen count did not show an increase during the same time period. A similar phenomenon was observed with pollinosis caused by the closely related Japanese cedar: a low prevalence reported before 1945 but the prevalence of the disease increased dramatically between 1965 and 1984 (41). The percentage of positive RAST in 1973 was 8.7%. However, by 1984–85, the prevalence had increased to 36.7%, i.e. a fourfold increase over a 10-year time period (42).

Risk factors for cypress pollen allergy

The influence of the immediate environment is obviously of major importance (30). Data related to Japanese cedar pollen suggest that early life exposure is a determinant for sensitization, especially severe sensitization to this pollen (43). However, the increase in sensitization in human populations does not closely parallel the trend in pollination (40), suggesting the intervention of additional factors besides the airborne load. The relevance of particulate air pollution to increased allergy was put forward by Ishizaki et al. in 1987 (44). More recently, such a correlation between exposure to heavy traffic and risk of sensitization to grass pollen and hay fever has been presented (45).

Some personal characteristics may also be involved in pollen allergy. Using a case-control design including 102 patients with CPA and 38 patients with grass-pollen allergy (GPA), a higher proportion of females, and a higher mean age at onset of symptoms has been shown in the former group (46). In addition, in another case series it was found that patients monosensitized to cypress pollen had a lower total IgE level than polysensitized patients (47). The Italian multicentre study (35) demonstrated that 14.7% of the Cupressaceae-sensitized patients were monosensitized, their average age being higher than in polysensitized patients (43.3 vs 35.9). Similarly, patients monosensitized to *Cry. japonica* featured a higher age at onset of allergic symptoms, a lower prevalence of a family history of atopic diseases, a high percentage of patients born out of the studied geographical area (i.e. not previously exposed to those pollen) and a lower total IgE level (48). These observations clearly show that at least some of the cypress (or mountain cedar)-sensitive patients behave like allergic rather than like atopic patients. In such patients, the specific sensitization seems to result from a heavy and long-lasting exposure to cypress pollen, in the absence of a family or personal history of atopic diseases. Thus, the allergic disease has a later onset, a long latency period and does not include biological signs suggestive of atopy. This scheme is quite comparable with the one described in the field of occupational allergy in relation to low-molecular weight agents. Such peculiar behaviour could be linked to the low-molecular weight carbohydrate nature of Cupressaceae allergens (7).

Clinical aspects

Clinical symptoms

The clinical features of CPA have been compared with GPA, in a large case series (46, Table 3). The former was characterized by a lower prevalence of conjunctivitis and a higher prevalence of dry cough during the pollen season. However, conjunctivitis was considered as the most impairing symptom by 72% of the cypress pollen allergic patients, when compared with 26% of patients

Table 3. Clinical responses to cypress (CPA) and grass (GPA) pollen by allergic patients

	CPA (n = 110)	GPA (n = 42)
Rhinitis (%)	96.2	100
Conjunctivitis (%)	86.7	100
Dry cough (%)	16.5	0
Asthma (%)	38	38.4

allergic to grass pollen. In Bousquet's study, the percentage of monosensitized patients with CPA who suffer from conjunctivitis reached a value of 88.5%, whereas it was only 76.0% in a group of polysensitized patients and 73.7% among a group of patients with other allergies (47). The Italian multicentre study (35) concluded that the main allergic symptom were rhinitis (49%), conjunctivitis (32%), asthma (18%) and dermatitis (3%).

Juniperus and Japanese cedar species can induce similar symptoms. Noteworthy, *Thuya*, another member of the Cupressaceae family, has also been involved in a few cases of winter pollinosis (49).

Diagnostic procedures

- Skin-prick tests remain the main tool for diagnosing CPA. Extracts of *Cup. sempervirens* pollen were first commercially available, but proved less effective than in-house extracts of *Cup. arizonica* (50, 51), which were subsequently commercialized. Later on, extracts of *J. ashei* (52) and of a mixture of *Cup. sempervirens* and *Cup. arizonica* (53) have also been commercialized.
- Measurements of specific IgE provide different results according to the allergen extract source and the method used. Using RAST tests, Mari et al. (50) obtained better results for specific IgE using *J. ashei* than those obtained by *Cup. sempervirens* extracts. In

any case, some *in vitro* systems could be successfully used as a complementary tool in cypress allergy diagnosis.

- Basotest[®], a newly available *in vitro* test for the detection of allergen-specific IgE based on the level of cellular activation, proved more sensitive (91.2%) than CAP system (76.0%) for the diagnosis of CPA (54). However, it is not available for daily practice.
- Measurement of total IgE has very low diagnostic value, especially when testing monosensitized cypress-pollen allergic patients whose results are usually within the normal range (47).
- Nasal challenge test, using standardized pollen extracts, has been performed in studies evaluating diagnostic procedures (54) or results of immunotherapy regimens (55–57). However, it is not used in routine evaluation of cypress pollen allergic patients.

Treatment

Preventive treatments

- At the community level, the following procedures can be recommended (58): eliminate all diseased trees because they produce two- to threefold more pollens than the healthy ones; trim hedges during autumn in order to remove the male cones that had been initiated during the late-summer; avoid planting cypress trees close to human dwellings (in some areas of southern France, when the building licence is given, the owner is advised not to plant cypress trees). At mid-range, select and commercialize low- or nonallergenic trees for planting in population centres. The question of how much would such an elimination programme change the airborne pollen load needs further investigation.

Table 4. Papers on double-blind, placebo-controlled specific hyposensitization trials of cypress, Japanese cedar and mountain cedar pollen allergic patients

Author	Number of patients included	Allergenic extract used	Route of administration	Duration of treatment (months)	Main results
Ariano et al. (55)	A: 10, P: 10	Unstandardized (PNU) <i>Cupressus arizonica</i> or placebo	Sublingual	12	Lower symptom and medication scores Lower allergen-specific nasal reactivity
Charpin et al. (56)	A: 22, P: 18	Standardized <i>Juniperus ashei</i> or placebo	Subcutaneous	16	Lower rhinitis and conjunctivitis scores
Vervloet et al. (57)	A: 37, P: 39	Standardized <i>Juniperus ashei</i> or placebo	Sublingual	16	Lower medication scores
Miller et al. (59)	A: 17, P: 17	Unstandardized (PNU) <i>Juniperus ashei</i> or placebo	Subcutaneous	3	No statistically significant difference
Pence et al. (60)	A: 20, P: 20	Unstandardized (PNU) <i>Juniperus ashei</i> or placebo	Subcutaneous	3	Lower daily symptom score
Fling et al. (61)	A: 12, P: 12	Unstandardized (PNU) <i>Juniperus ashei</i> or placebo	Subcutaneous	3	Decrease of the late cutaneous response. Increase in IgG and IgG4
Parker et al. (62)	A: 26, P: 25	Unstandardized (w/v) <i>Juniperus ashei</i> or placebo	Subcutaneous	6	Suppression of the late-cutaneous response. Comparable efficacy in mono- and polysensitized patients
Ariano et al. (63)	A: 10, P: 10	Mix, unstandardized Cupressaceae and Taxodiaceae pollens	Subcutaneous	12	Clinical improvement, decrease in drug consumption and nasal-specific reactivity
Ito et al. (64)	A: 16, P: 16	Unstandardized Japanese cedar or placebo	Subcutaneous	4	Decrease in the symptom medication score
Demoly et al. (65)	A: 30, P: 30	Conjugated decapeptide from the Fcε4 domain of the IgE	Intramuscular	4	No statistically significant difference

A, active; P, placebo; PNU, protein nitrogen unit; IgE, immunoglobulin E.

- At the patient level, specific immunotherapy has been tested using different pollen extracts and different routes (Table 4) (55–57, 59–65). Specific immunotherapy seems to provide variable results. However, the latest trials, using standardized extracts, have led to significant improvements, using both the subcutaneous and the sublingual routes. Thus, the effects of specific immunotherapy should be further exploited.

Curative treatment with medications

Although cypress pollinosis is known to be more severe than other types of pollinosis, no study has so far substantiated a specific statement. Noteworthy, a clinical trial using second generation antihistamines pointed out that 28% of the included patients have withdrawn because of the lack of efficacy (66).

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Conclusion

Although knowledge about cypress allergens and allergy has increased over the last 20 years, there are still large gaps in our knowledge that need to be better understood in order to insure a better diagnosis of such a type of allergy and recommend a proper management for such patients. Besides, cypress pollen allergy has some peculiar epidemiological features whose study could bring new insights in the understanding of the immune response.

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