

Original article

Allergen immunotherapy is safe during pollen season. Results of a 10-year, real-life prospective study

L'immunothérapie allergénique est sûre pendant la saison pollinique. Résultats d'une étude prospective de 10 ans dans la vie courante

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Abstract

Objective. – Although systemic reactions (SRs) due to allergen immunotherapy (AIT) are rare, preventing them is a major concern for allergologists. Natural exposure during pollen season is a controversial risk factor, so some centers reduce AIT's maintenance dose in-season. The aim of this study was to examine whether administering the maintenance dose of subcutaneous AIT (SCIT) during pollen season, without adjustment, is safe.

Patients and methods. – Initially, a retrospective pilot study was conducted, that included thirty-four monosensitized patients treated with perennial SCIT without in-season dose adjustment during maintenance. Pollen counts were monitored with a Burkard trap, to validate the pollen season. Two SRs were registered; one during and the other out of season, showing no seasonal effect on SCIT's safety. A ten-year-long, prospective study using the same SCIT protocol, followed the pilot one. Seventy-eight monosensitized patients, allergic to Grasses or Parietaria or Olive pollen, completed this study, while 28 monosensitized mite-allergic patients served as a control group. Only standardized depot solutions were used.

Results. – A total of 2910 pollen-extracts maintenance-dose injections were administered. Four SRs (Grade 1 or 2, WAO Classification) were registered; 2/1210 during pollen season and 2/1700 off-season. One (Grade 4) reaction, out of 880 mite extract injections, was registered. The presence of SRs did not correlate with any AIT brand.

Conclusion. – In our study population pollen season does not seem to be a risk factor for SRs for monosensitized allergic patients. SRs due to pollen AIT presented with a similar frequency as with mite AIT.

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Keywords: Allergen immunotherapy; Maintenance dose; Pollen season; Anaphylaxis; Side-effect

Résumé

Objectifs. – Bien que les réactions systémiques (RS) de l'immunothérapie allergénique (ITA) soient rares, leur prévention est une préoccupation majeure des allergologues. L'exposition naturelle aux allergènes pendant la saison pollinique constitue un facteur de risque controversé, mais quelques centres diminuent la dose d'entretien de l'ITA pendant cette saison. L'objectif de cette étude était de savoir si, au cours de l'ITA par voie-sous-cutanée (ITA-SC), l'administration d'une dose d'entretien sans ajustement pendant la saison pollinique était sans risque.

Patients et méthodes. – Initialement, une étude pilote fut effectuée incluant 34 patients monosensibilisés traités par une ITA-SC perannuelle sans ajustement pendant la saison pollinique. Les pollens étaient comptés à l'aide d'un capteur de Burkard pour valider la saison pollinique.

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Deux SR furent enregistrées, l'une pendant la saison pollinique et l'autre en dehors de celle-ci, ce qui montre l'absence d'effet saisonnier sur la sécurité de l'ITA-SC. Cette étude pilote a été suivie par une étude prospective menée pendant 10 ans en utilisant le même protocole d'ITA-SC. Soixante-dix-huit patients monosensibilisés, allergiques aux pollens de graminées ou de pariétaire ou d'olivier ont terminé l'étude, tandis que 28 patients monosensibilisés aux acariens de la poussière de maison ont constitué le groupe témoin. Ils ont été utilisés, seulement des extraits allergéniques retardés (depot) standardisés.

Résultats. – Un total 2910 doses d'entretien d'extrait pollinique fut administré. Quatre SR de grade 1 ou 2 selon la classification de la World Allergic Organization (WAO) furent enregistrées : 2/1210 injections pendant la saison pollinique et 2/1700 en dehors de celle-ci. Une réaction de grade 4 sur 880 injections d'extraits d'acariens fut observée. La présence des SR n'a pas été corrélée aux marques différentes des extraits allergéniques.

Conclusion. – Dans notre population, la saison pollinique ne semble pas constituer un risque de SR chez les patients allergiques monosensibilisés. La fréquence des SR induites par l'AIT est pareille tant pour les pollens que pour les acariens.

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Mots clés : Immunothérapie allergénique ; Dose d'entretien ; Saison pollinique ; Anaphylaxie ; Effets secondaires

1. Introduction

Allergen immunotherapy (AIT) is a well-documented treatment for respiratory allergy, practiced for over a century. The efficacy and safety of AIT have been assessed by many well-designed studies [1,2]. Systemic reactions (SRs) due to subcutaneous AIT (SCIT) is a rare but actual side effect; it has been reported to occur in 0.5–3.2% of AIT-treated patients [3–5]. Mild reactions (urticaria or upper tract symptoms) are more common than moderate (reduction in lung function with or without other organs involvement) or severe ones (life-threatening anaphylaxis), with reported occurrences of 7.1, 2.6 and 0.4% respectively [6].

There are several risk factors for SRs due to SCIT, such as high degree of allergen sensitization, unstable or insufficiently treated asthma, the build-up phase of SCIT, dose escalation during pollinosis, current infections, cofactors (exercise, alcohol, use of beta-blockers) and the existence of concomitant diseases/conditions that consist AIT contraindications [7–9]. Identifying and minimizing them, when feasible, is the keystone for a safe SCIT at high-risk patients [10].

Exposure to high levels of pollen has also been identified as a possible risk factor for SRs, therefore 12% of practices always adjust doses during peak pollen seasons [6]. The hypothesis on this practice is that reactions to maintenance injections might relate to the priming caused by natural allergen exposure, which could enhance sensitivity to doses of previously well-tolerated allergens.

Reducing the dose of coseasonal AIT is proposed in some guidelines without specific recommendations on the quantity or the duration of dose adjustment [8,11]. Furthermore, no strong data exist to support the need for seasonal dose adjustment, while there are studies showing that allergen exposure does not affect the outcome of SCIT [3,4].

The objective of this study was to establish the potential effect of pollen exposure on SCIT-related SRs, in patients receiving a maintenance dose. SRs due to SCIT were prospectively registered in order to compare their occurrence during pollen season versus off-season. The relationship between the occurrence of SRs and a specific pollen extract was also studied.

2. Patients and methods

This study has been performed in two phases; a pilot study and a prospective one. The initial retrospective (pilot) study was performed in order to evaluate the feasibility of the assessment procedures, determine methodology and define the statistical power of a prospective study. It was performed in the Allergy Department of “Laikon” General Hospital (Athens, Greece) and was based on the review of data from January 2002 to December 2004. An approval has been obtained from the Institutional Review Board.

The same team performed the second part of the study. To this end, a Private Allergy Practice Network was created in 5 Greek cities. The prospective surveillance study covered a time span of ten years: from January 2005 to December 2014. The collection of data was generated by the routine administration of AIT following state-of-the-art protocols recommended by allergen extract manufacturers and data were handled anonymously, as in the pilot study.

2.1. Diagnosis and immunotherapy procedure

The diagnosis of allergy was made by *in vivo* (SPT) and *in vitro* (specific IgE, CAP-FEIA) testing and a clinical history of symptoms on exposure; in particular the seasonality of symptoms correlating with a specific pollen sensitization was documented.

Patients were all treated with standardized, depot solutions, absorbed onto aluminium hydroxide, calcium phosphate or L-tyrosin. Depot solutions were of six different pharmaceutical companies (Stallergènes, Allergopharma, HAL-Allergy, ALK-Abelló, Allergy Therapeutics, Lofarma Allergeni SpA). Each center continued to use the commercial products it routinely administered. Conventional up-dosing protocols, as described in package inserts, were followed. During the maintenance phase immunotherapy injections were administered every 4 weeks. The maintenance doses were the highest ones, suggested by each company.

During each visit a clinical examination and peak expiratory flow rate (PEFR) measurement preceded the immunotherapy

injection, even if no history of asthma was reported and patients remained for thirty minutes under medical surveillance. To assure uniformity of data collection, all allergists were using the same follow-up form and administered maintenance doses every four weeks, perennially. Allergic symptoms (nasal, ocular or bronchial) before the injection and possible side-effects after SCIT administration, were registered in a standardized common form, based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System [12].

2.2. Pilot study

For the pilot study the records of 27 monosensitized pollen-allergic adults (14 men, 13 women; 37.8 ± 10.6 years old), with a history of seasonal rhinitis and/or asthma, were reviewed. Patients received perennial SCIT with pollen extracts from *Olea europaea* (olive) or *Graminaceae* mix (grass) or *Parietaria* spp (wall-pellitory). Grass mix was considered a mono-allergen extract. Olive, grasses and wall-pellitory are the main sources of allergenic pollen in Greece and the pollen season for these plants generally lasts from spring to summer [13,14].

The maintenance dose of SCIT (as suggested by each pharmaceutical company) had been achieved before the first pollen season, to avoid a priming effect of the natural pollen exposure, and was kept throughout the study, without any adjustment. A 10% step-down for the next visit was allowed in the case of anaphylaxis, followed by step-up to the formerly well-tolerated maintenance dose two visits after the reaction (or after the pollen season was over).

The levels of the atmospheric concentration of pollen were registered in parallel with the study, in order to allow the investigators to determine which SCIT injections had been administered during the respective pollen seasons. Daily pollen counts were performed with a Burkard, 7-day volumetric trap (Burkard Manufacturing Co, Rickmansworth, UK). The counts, calculated and expressed in number of pollen grains per m^3 of sampled air, were presented as 7-day moving averages [13].

Only injections during the maintenance phase of AIT were registered. Updosing consists a risk factor for adverse reactions, so including SRs that occurred during the updosing phase (always expected to occur more frequently) would have affected the results [3]. Moreover, it is the Institution's practice to avoid updosing during pollen season, so local and SRs due to updosing can be expected to happen with a higher frequency outside the pollen season. Focusing only on maintenance phase offers a more clear view on the effect of the pollen season on SCIT adverse reactions' frequency and severity.

A total of 1175 SCIT shots were administered, among which 477 were performed during the pollen season. Minor variations of pollen periods were noticed between the different years of the study. The pilot study encountered two SRs, both due to grass pollen extracts of the same manufacturer. The first was a grade 1 reaction in a male patient who presented generalized urticaria fifteen minutes after the shot, during the grass-pollen season in April 2003 (Fig. 1). The second was a grade 2 reaction with urticaria and an asthma attack in another male patient, which occurred outside the season in February 2004.

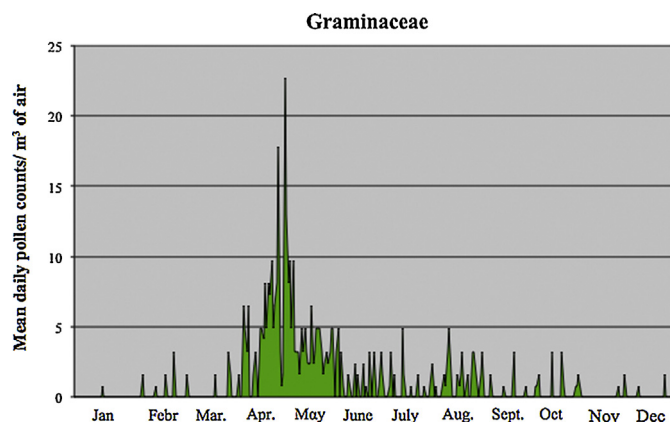


Fig. 1. Pollen report of Graminaceae, in Athens, Greece, during 2003. Counts are expressed as pollen number/ m^3 , in 24 hours.

As a conclusion 0.20% (1/477) of the injections administered during the pollen season and 0.14% (1/698) of those administered out-of-season caused a SR. No effect of the pollen season on the frequency of SRs could be documented.

2.3. Prospective study: patients and allergen extracts

The study group of the prospective study included monosensitized patients, with a history of seasonal rhinitis with/without asthma. Monosensitization to pollen, detected with SPT and conformed with sIgE (>0.35 kUA/L) and symptoms directly connected to the relevant pollination was the prerequisite for the consideration of our patients as monoallergic and their inclusion in the study. Our monoallergic patients were treated with single pollen extracts. Study's inclusion and exclusion criteria are described in Table 1.

As in the pilot study, patients received a SCIT schedule with perennial administration of extracts containing olive, grasses or wall-pellitory pollen. Ninety-two patients were recruited into the study, providing informed consent; there were 14 dropouts, for reasons described in Table 1. No patient dropped out due to a SCIT-related SR. Seventy-eight monoallergic pollen-allergic patients (40 males; 38 females; 34.4 ± 12 years old,) completed

Table 1
Inclusion, exclusion and drop-outs criteria of the prospective study.

Inclusion criteria	
Adults	
Allergic rhinitis and/or asthma	
Allergy only to pollen, or only to mites, for more than 2 years	
Use of extracts containing only an allergen. Graminaceae mix and mites mix (Dermatophagoides pteronyssinus 50% - D. farinae 50%), were considered uniform	
Exclusion criteria	
Use of AIT in the past (any route)	
Allergen sensitization to other than the treated pollen, or to animal dander, molds or latex	
Use of extract mixtures	
Drop-outs	
Incomplete compliance of a patient (big delays to the appointments requiring a decrease of the next dose)	
Failure to complete AIT for a minimum of 3 years	

Table 2
Mean daily in-season pollen counts (grains/m³) and pollen seasons' months.

Pollen	Highest	Lowest	Pollen season
ATHENS			
Graminaceae	23	< 5	April–August
Urticaceae	45	≤ 5	April–July, October
Oleaceae	45	5	May
IRAKLEION			
Graminaceae	15	< 2	March–May
Urticaceae	93	≤ 10	March–June
Oleaceae	275	≤ 5	April–May

the study; 33 grass-allergic, 33 allergic to wall-pellitory and 12 allergic to olive.

In order to achieve uniformity, all centres used a common “visit form”. The date, AIT dose, injected arm, clinical examination (pulses, blood pressure and PEFR), as well as any noticed side effects, were registered. It was the same monitoring form that had been used in the pilot study. Local aerobiological reports and former data on pollen season were used to set the frame of pollen season for each centre.

Thirty-one patients receiving mite-SCIT served as a control group, of whom 28 (10 males; 18 females) that completed the study. They were patients with perennial allergic rhinitis with/without asthma. Including a control group allowed the investigators to register the incidence of SRs due to a perennial allergen, not affected by fluctuations in pollen exposure.

Rescue therapy (oral antihistamines, nasal corticosteroids, asthma inhalers) was prescribed, and allowed as needed when allergic symptoms occurred during season. However patients were asked not to use antihistamines hours before AIT's visit, in order to avoid the effect of pre-treatment to probable side effects. Data on pollen counts for our area, during the prospective study, are reported in Table 2.

3. Results

Study group: 2910 maintenance injections were administered; 1210 during the pollen season and 1700 out-of-season. Since the purpose of the study was to examine the effect of allergen exposure on the SRs rate during the SCIT maintenance phase, no data on the build-up phase are included.

Four SRs were registered in four patients with an overall rate of SRs 1.3/1000 injections. Two of these SRs were registered during the pollen season (0.16% of the in-season injections), while two occurred out-of-season (0.11% of the out-of-season injections) (Table 3).

As far as extracts are regarded grass pollen extracts were responsible for three of the four SRs; one occurring during the grass pollen season. The responsible grass pollen extracts were from three different manufacturers, so SRs were not related to a specific brand. The single SR due to *Parietaria* pollen extract was registered during the *Parietaria* pollen season, while no reaction was noticed related to the *Parietaria* pollen extracts outside the season. No reaction was registered due to olive pollen extracts. The commented SRs that occurred due to the administration of pollen extracts were all of grade 1 or 2 (WAO 2010 classification) [12].

Table 3
Patients that presented SRs (WAO, 2010 classification).

	Age, sex	Allergy	Allergen	SR grade	Month of SR	Season
1	28, M	AR + AS	G	1	Sep 2009	No
2	29, F	AR	P	2	Jul 2010	Yes
3	25, F	AR	G	1	Apr 2010	Yes
4	25, F	AR	G	2	Oct 2010	No
CG	29, F	AR	M	4	Mar 2014	–

AR: allergic rhinitis; AS: asthma; CG: Control Group. G: grasses; P: *Parietaria*; M: mites.

3.1. Control group

An amount of 880 SCIT maintenance shots were administered during the study and only one (0.11% of the administered doses) SR occurred. However, this SR was a grade 4 reaction with cutaneous symptoms accompanied by marked hypotension, without loss of consciousness. A subsequent dose adjustment, with 10% reduction of the maintenance dose, was well tolerated in the next visit, while up dosing was also well-tolerated two months after the SR (2 visits later).

In our prospective study, the frequency of SRs during the pollen season resulted to be similar to that outside the pollen season and also similar to that of the control group treated with a house dust mite extract. However, as for severity: there was no severe SR in the pollen-SCIT study group, while there was a severe one in the mite-SCIT control group.

4. Discussion

Although a SCIT schedule with no in-season dose-adjustments for pollen extracts was used in this study, an increased rate or severity of SRs due to in-season SCIT administration was not observed. The overall rate of SRs was similar to other studies; it was 0.13% per injection (for pollen extracts, but also for overall injections), with a reported rate in literature of 0.06–0.3% per injection [12,15–20].

One of the strong points of our study was the inclusion of exclusively single-allergen-AIT-treated patients (monoallergic), which allowed us to specifically study the effect of SCIT with a certain pollen extract on the SRs rate. Polysensitive patients are mostly treated with single allergens [21], but safe results cannot be extrapolated by including them in such a study. The inclusion of various pollen allergens in a vaccine may have an add-on effect, if they relate to the same pollen season. On the other hand in a mix of extracts each diluted allergen is less probable to cause a SR, due to its lower concentration.

The downside of such a design is the restricted number of patients, which might under-power the study of rare variables such as SRs. Also, one might argue that using extracts from one manufacturer might have improved the uniformity of our study. However, the reported results here are closer to the real-life situation and by using the same standardized registration form and strict criteria for the selection of our participants, we tried to reduce as much as possible the variability in our study.

It is difficult to directly compare the grading of our SRs to other studies, since most of them have used former severity

classifications. However, if we consider our grade 1 and 2 as “mild SRs” (that make for 87.5% of all SRs in our study), this figure appears to be similar to that reported in literature, with 67.6–74.5% of all SRs being of mild severity [6]. In the USA, near fatal reactions have been reported to occur with a rate of 5.4 events/million injections (0.0054/1000 injections) [22]. Fatal reactions are extremely rare, according to the AAAAI-ACAAI SCIT surveillance study, reporting 7 fatalities that occurred in the United States of America, between 2001 and 2012 [6,15,23,24].

Contrary to our findings, the administration of AIT during the peak of the pollen season has been cited as one of the most important contributing factors in AIT-induced near-fatal reactions, followed by dosing mistakes and AIT administration in patients with uncontrolled asthma [22]. The AAAAI-ACAAI SCIT surveillance study found that practices that always reduce doses during peak pollen seasons are more likely to report only mild, or no SRs and less likely to report any moderate or severe SRs, than practices that often, sometimes, or never reduce doses [6]. Also, 30% of the practices that never reduced doses in maintenance vials, experienced severe SRs, whereas such reactions were experienced by 12% of the practices that sometimes, often, or always reduced doses [23].

The safety of coseasonal SCIT has been assessed by two large American prospective studies, in the 1990s [3,4]. Season was proved not to be a risk factor for pollen extracts. Although major drawbacks exist in the study performed in Atlanta, USA, since it included patients with multisensitivities (including molds and mites), different maintenance doses, various administration maintenance intervals and a randomly selected control group, a strong point of that study is the large number of patients (4578) and injections (346,251) [3]. Authors reported SRs with a visit rate of 1/1831, during the maintenance dose [3]. The other study was a prospective one that involved 513,368 injections; authors didn't note any increase in SRs during grass and ragweed seasons among patients receiving grass or ragweed immunotherapy [4].

The same pollen and mites allergens that were included in our study, have also been used in an Italian study that took place in a geographical area similar to ours [24]. Authors reported a similar rate of SRs per injection to the pollen of grass (0.08%), *Parietaria* (0.08%) or olive (0.09%), with a statistically non-significant trend of more SRs to mites (0.13%) [25]. A surprising outcome of that study was that SRs due to pollen allergens occurred mainly outside the pollen season [25].

SRs only to grass pollen extracts had been registered in our pilot study. The majority of SRs in our prospective study were also due to grass pollen extracts, confirming that in our country performing SCIT to grass might need more caution, although the number of SRs was so low that it consists no real alert. In an Italian study, on the safety of SCIT for respiratory allergy, it was shown that ragweed (8.1%) and grass extracts (4.2%) were associated with a significantly higher rate of SRs [26]. In the same study, the occurrence of SRs with *Parietaria* pollen extracts was much lower (0.7%), which is in agreement with our data [26].

In our study, mites had a low rate of SRs, similar to that due to *Parietaria* pollen and lower than the overall SRs rate

due to pollen. This is in contrast to the results of a Spanish study showing that mite SCIT during the maintenance phase, is more likely to cause SRs than pollen SCIT [20]. The fact that conclusions from different studies, regarding which allergen is more likely to cause SRs, are contradictory, may be explained by the use of different SCIT solutions, some non-standardized, resulting in different allergen concentrations.

In a surveillance study that collected data from all regions of the United States, Canada and Puerto Rico, about 12% of practices had reported adjustment of the SCIT dose when administered coseasonally [6]. To our knowledge, no similar data from other parts of the world exist. Recently the same team of investigators reported that although half of the study-included practices adjust doses (most of them do the adjustment “sometimes”), the number of registered SRs occurring during pollen seasons (referring to grass, ragweed or tree pollen) was three times more than the ones out-of-season [26]. They reported that, during pollen season, reducing doses for patients with previous SRs or with highly positive SPT results, is a commonly followed strategy [27].

Scarce data on the percentage of dose-reduction exist. Italian references mention an up to 50% dose decrease for depot solutions [26,28]. If an allergist might decide to decrease the dose of an allergen in-season, no specific guidelines exist regarding the quantity of reduction and its duration. A significant decrease (e.g. reducing the dose to half the suggested dose), for the complete duration of the pollen season with subsequent up-dosing during the next out-of-season visits, might cause a decrease of AIT's effectiveness due to prolonged low-dosing.

We would like to underline that it might be difficult to compare our data to those from US studies because of differences in several parameters. To only name some: first, we perform SCIT with depot solutions while in the US aqueous solutions are used. Secondly, there exist genetical differences between both populations and thirdly average natural exposure and exposure during the peak of our pollen season differs from US, with some pollination also outside the pollen season. For example, during pollen season, the Gramineae daily count in our area shows highest concentration of 23 pollen/m³, while in USA counts are higher, with peaks exceeding 500 pollen/m³ [14,29–31].

Although no study in our area has determined the threshold levels of aeroallergen concentration that cause pollinosis and allergic asthma, a clear correlation of symptoms with the pollination period as described in Table 2, has been clinically determined. Cut-off levels, setting the frame of pollen season in Greece are > 5 pollen grains/m³ for Gramineae and > 20 grains/m³ for Urticaceae and Oleaceae [29,31].

5. Conclusions

It appears that conserving the pollen extract maintenance dose during the pollen season, in countries with similar pollination to Greece, might not pose any specific risk for untoward reactions due to SCIT. Our conclusions can be applied to AIT with standardized grass, *Parietaria* and olive pollen depot extracts, since those were the ones we have studied, in areas with similar counts of pollen. Further multicenter trials including a higher number

of patients would be ideal to confirm our data and extend them to global levels.

Disclosure of interest

The authors declare that they have no competing interest.

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