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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.

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 utilises, 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 corrélé 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.

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