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Case Report Open Access

When Allergen Immunotherapy Perfectly Meets its Need: A Case Report

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Abstract

Seasonal, pollen-induced allergic rhinitis can be managed by symptomatic drug treatment, but only allergen immunotherapy (AIT) is able to work on the causes of allergy. Usually, the effectiveness of AIT is assessed by clinical criteria, though the ideal outcome is to lose the allergic sensitization to the administered allergen(s).

Here we report the case of a patient who after three years of AIT using a grass pollen extract containing *Phleum pratense*, *Dactilys glomerata*, *Anthoxanthum odoratum*, *Poa pratensis* and *Lolium perenne* but not *Cynodon dactylon*, to which the patient was also sensitized, developed a negative response to allergy tests to the administered allergens.

After 3 years of SCIT, the patient was free of both nose and lung symptoms during the grass pollen season and had negative results to the pollens included in the extract, while *C. dactylon* showed a decrease in respect to basal value but not a negative result.

The findings from this case show that AIT in optimal circumstances is able to achieve a complete tolerance to the administered allergen demonstrated by the development of negative results to the grass pollens contained in the extract used for the treatment. This confirms the recent definition of AIT as a treatment fulfilling the requirements of precision medicine.

Keywords: Allergen immunotherapy; Grass pollen; Allergic rhinitis

Introduction

As shown by aerobiological and allergological studies, grass pollen is a major cause of respiratory allergy worldwide [1-5]. Taxonomically, grasses belong to the family of Poaceae (Figure 1), the temperate Pooideae subfamily contains the most allergenic species, that include *Lolium perenne*, *Phleum pratense*, *Anthoxanthum odoratum*, *Dactylis glomerata*, *Holcus lanatus*, *Poa pratensis*, and others. However, there are further subfamilies that include species capable to induce allergic symptoms, such as Chloridoideae (*Cynodon dactylon*) and Triticeae, the latter including *Triticum aestivum* (wheat), *Secale cereale* (rye) and *Hordeum vulgare* (barley), that are involved in baker's asthma [6]. Recently, to the usual method of pollen counts in the air that produces the pollen calendars and thus provide useful indications to allergic patients on the concentration of pollen grains during spring, though it is unable to distinguish at microscopy reading the different grasses, techniques such as molecular allergy diagnostics [7] and phenology [8] were introduced. The first enables to assess the occurrence in each grass species of the various allergen molecules; some of them are species-specific and others have a high grade of structural homology and thus are cross-reactive among a number of grasses. The main grass pollen allergens are included in the group 1 and group 5 molecules. According to the Linnaean denomination, they are known as Phl p 1, Dac g 1, Ant o 1, Hol l 1, etc, and Phl p 5, Dac g 5, Ant o 5, Hol l 5, etc [9]. Instead, the cross-reacting molecules include profilins and polcalcins that due to their almost ubiquitous occurrence are knowns as "panallergens" [10]. As far as phenology is concerned, it is feasible to directly detect the pollen release for each individual grass. This allowed to observe that the various species of grasses release their pollen grains at different times during the pollen season and thus to assess their relative clinical importance [8]. Grass pollen allergy may be treated by drugs acting on allergic symptoms, such as oral or nasal topical antihistamines and topical corticosteroids, but if the treatment is aimed at working on the causes of the disease only allergen immunotherapy (AIT) can be considered, in its two forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) [11-13]. The efficacy of both SLIT and SCIT on grass pollen-induced respiratory allergy is demonstrated by meta-analysis [14]. The mechanisms of action of AIT include stimulation to produce allergen-specific IgG blocking antibodies and changes in the balance between the different T-cell phenotypes, particularly by the induction of regulatory T-cell subtypes that have been detected with both routes of administration [15]. These immunological modifications are mirrored by the development of progressive clinical tolerance to the administered allergens. On the other hand, in the natural history of allergy the levels of specific IgE, and consequently the clinical symptoms, may spontaneously decrease over time [16].

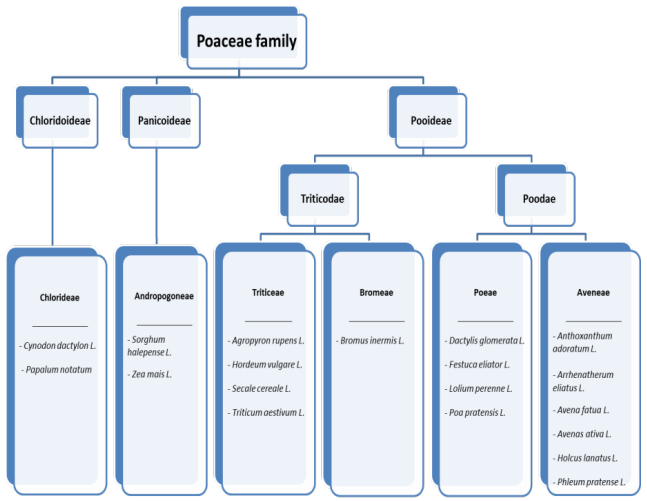

Figure 1: Taxonomy of the Poaceae family of grasses.

Case Report

Here we report the case of a patient who after three years of AIT developed a negative response to allergy tests to the specific allergens administered with the treatment. The patient was a 39 years old woman suffering from four years of persistent rhinitis and intermittent asthma caused by sensitization to grass pollen. The skin prick test (SPT) (Stallergenes, Antony, France) was positive for grass pollens, with a 3+ response to *Phleum pratense*, *Dactylis glomerata* and *Cynodon dactylon*. The values of specific IgE to such pollens, measured by CAP System (Thermo Fisher Scientific, Uppsala, Sweden) were 37.5 kU/L for *P. pratense*, 42.1 kU/L for *D. glomerata* and 32.6 kU/L for *C. dactylon*. The patient was treated with SCIT using a grass pollen extract (Phostal, Stallergenes, Antony, France) containing *P. pratense*, *D. glomerata*, *Anthoxanthum odoratum*, *Poa pratensis* and *Lolium perenne* but not *C. dactylon*. After SCIT initiation, the patient showed a significant improvement of allergic symptoms since the first year. In particular, in the first grass pollen season following the start of SCIT he had no more asthmatic symptoms, while nasal symptoms were progressively reduced during SCIT. No adverse reactions occurred during the treatment. After three years, the patients was free of both nose and lung symptoms during the grass pollen season. The absence of symptoms during the grass pollen season persisted over time. However, the patients referred for a new visit for allergy because but in the latest year she had rhinitis from mid-August to early October. SPT were performed, with a negative results for *P. pratense* and *D. glomerata* and positive (2+) for *C. dactylon*. Specific IgE values were < 0.10 kU/L for *P. pratense* and *D. glomerata* and 24.7 kU/L for *C. dactylon* (Figure 2). A positive result to SPT (3+) was found instead for ragweed pollen, thus a new immunotherapy with a ragweed extract was planned.

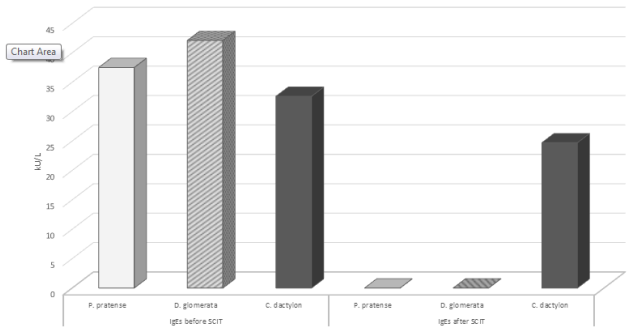

Figure 2: The measurement of specific IgE before and after SCIT shows the achievement of completely negative tests to the grasses contained in the extract used for immunotherapy.

Discussion

Specific allergen immunotherapy (AIT) is the only disease-modifying treatment for AR, based on its ability to alter the Th2-influenced immune response, while pharmacotherapy acts only on symptoms [17,18]. The capacity of AIT to improve the symptoms of respiratory allergy and to decrease the consumption of drugs is clearly demonstrated by meta-analyses that included a large number of randomised, double-blind, placebo controlled trials [19]. Such outcome is founded on the modification of the immunological response to the administered allergen. In the early 1990s, the definition of the Th1–Th2 paradigm paved the way to a deeper understanding of mechanisms of action of AIT, as well described in complete reviews [20,21]. The first observations, obtained by both *in vitro* and *in vivo* models concluded that SCIT turned the allergen-specific responses from the Th2 allergic phenotype to a tolerogenic Th1 phenotype. Based on the fact that alterations in circulating T cells do not mirror local response in target organs, a redirection induced by SCIT in respiratory mucosa was suggested. In fact, in SCIT-treated patients the T cells expressing IFN-γ mRNA were increased in the nasal mucosa after pollen challenge. Also in nasal biopsies and in nasal fluid of SCIT-treated patients the increase of IFN-γ and the concomitant decrease of IL-5 and IL-9 during the pollen season was apparent. The discovery of regulatory T cells (Treg) further expanded the knowledge, highlighting that their increased activity (immunosuppression) was the main or mechanism explaining the clinical efficacy of SCIT. The suppressor activity of Treg is mediated by regulatory cytokines including IL-10, TGF-β and IL-35. In particular, during pollen exposure CD4+CD25+ Treg cells from grass-sensitive patients were shown to be weakened in suppressing IL-13 and IL-5 production compared to healthy controls. These AIT-induced changes in immunological response to allergens have an important outcome in the prolonged effect of immunotherapy over time once the treatment is discontinued [22].

The drawback of SCIT has always been the risk of systemic reactions that rarely may also be life-threatening [23]. However, recent studies showed that, if SCIT is performed following strict safety rules, the risk of systemic reactions is very low [24]. Indeed, the new option of administering the allergen extracts by the sublingual route was mainly introduced in the 1980s for safety reasons [11]. The good safety profile of SLIT, the common side effects being local reactions in the mouth, while systemic reactions are very rare [25], allows the administration

of the treatment at home and makes SLIT less time-consuming than SCIT. Notwithstanding, when patients receive complete information on the characteristic of SCIT and SLIT before starting the treatment, the rate of patients who choose SCIT is comparable to that of patients choosing SLIT [26].

The findings from this case show that SCIT in optimal circumstances is able to achieve a complete tolerance to the administered allergen demonstrated by the development of negative results to the grass pollens contained in the extract used for the treatment. Instead, specific IgE to the pollen not included in the extract, i.e. *C. dactylon*, showed a decrease in respect to basal value, that is likely to be related to the natural history of allergy, while maintaining the positive response to SPT.

Natural history is claimed to be able to achieve similar results. In 2003, studies addressing the effects of aging on both sensitization to Japanese cedar pollen (JCP) and development of JC pollinosis, as assessed by serum IgE titers to JCP and clinical examination were conducted in Japan. In a vertical-sectional study, the serum IgE titer to JCP was significantly influenced by the amounts of pollen in the air. An increase in age by 6 years did not reduce serum IgE to JCP in subjects aged up to 40 years, while in subjects with JC pollinosis aged over 40 with a moderate-high IgE titer, spontaneous remission of JC pollinosis was observed in 16.1% over a period of 6 years [27]. However, the literature on spontaneous remission of pollen allergy is quite scarce. In particular, no study suggesting a selective development of negative allergy tests for some pollens but not for others are available, while thus occurred in our patient due to the lack in the extract of the pollen to which the patient was also sensitized.

Conclusion

This case report offers data confirming the recent definition of AIT as a treatment fulfilling the requirements of precision medicine [28], which is an innovative approach to medical diagnosis and treatment that is likely to be extensively applied in the next years [29].

Conflicts of Interest

Conflict of interest is a scientific consultant for Stallergenes Italy. E.B., E.M. D.P. and M.M. declare that they have no competing interests related to the content.

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