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G. Ciprandi

Clinical bystander effect exerted by allergen immunotherapy: a hypothesis

IRCCS-Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

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Allergen immunotherapy; poly-allergy; bystander effect

Summary
Allergen Immunotherapy (AIT) is able to restore a physiological Th1 response and Tregs function. This effect is allergen-specific, even though it has been reported that it may also be non-specific, such as also extended to allergens not used in AIT. This immunological phenomenon may also be of clinical nature. This case report shows that a poly-allergic patient, successfully treated with Parietaria extract, also achieved a clinical tolerance towards other causal allergens, such as mites and cat. Of course, this was an anecdote, but it is reasonable to prospect the hypothesis that a bystander clinical effect may be observed during AIT in poly-allergic patients.

Corresponding Author
Giorgio Ciprandi
Viale Benedetto XV 6,
16132 Genova, Italy
Phone: +39 010 3533 18 20
Fax: +39 010 353 86 64
E-mail: gio.cip@libero.it

Allergy is characterized by a dysregulation of immune response sustained by a functional defect of T regulatory cells (Tregs), that induces a Th2 polarization and consequently a reduced production of Th1-dependent cytokines, namely IFN-g. In fact, it has been reported *in vitro* that allergic subjects have a diminished allergen-specific production of IFN-g, whereas non-specific stimuli, such as PHA, induce normal IFN-g production (1). Allergen immunotherapy (AIT) is the only cure of allergic disorders as it is able of: i) controlling allergic symptoms and inflammation, ii) modifying their natural course, and as iii) its effects last long time after discontinuation (2). Immunologic mechanisms of action include physiologic restoration of Tregs function, abolition of Th2 polarization, and increased production of IFN-g, such as a skewed Th1-response (the so called immune-deviation) (3,4). These immunologic effects are surprisingly fast. In this regard, it has been reported that sublingual immunotherapy (SLIT) significantly affected allergen-specific IFN-g production just after 3 months from starting (5). Very interestingly, it was also demonstrated that an *in vitro* bystander effect on IFN-g production, induced by AIT, could also occur (6). A group of allergic patients, sensitized to both pollens and mites, were treated with AIT only to pollens. AIT provided a significant increase of both pollen-induced as well as mites-induced IFN-g production. Therefore, this study provided evidence that though the defective IFN-g production is typically allergen-specific in allergic patients, the AIT effect on increased IFN-g synthesis may also be non-specific. This fact is not particularly surprising, as it is well known that antigen booster promoted by vaccinations generates both antigen-dependent and antigen-independent memory B cell response (7-9). Therefore, AIT is able of modulating immune response both via allergen-specific pathway and through non-specific effects (6). This phenomenon probably depends on a polyclonal activation of Th1 cells (6).

On the other hand, it is quite common to observe in the clinical practice that poly-allergic patients treated with AIT may develop a wide clinical immune tolerance also toward allergens not used in AIT. However, there is no formal demonstration of this issue. Therefore, a case representative of this issue is described here.

This case report was carried out in accordance with the ethical standards established in the *Declaration of Helsinki*, and a written informed consent was obtained at the first visit.

S.C. is a young man 18 years old suffering from allergic rhinitis and asthma since early childhood. He is poly-allergic to several allergens and symptoms occurrence is perennial, but with exacerbations during spring and fall. The exposure to dust often caused severe symptoms as well as cat exposure. In fact, he was not able to frequent the home of his best friend, as two cats lived there. Every time he moved to his home, severe breathlessness, wheezing, cough, sneezing, rhinorrhea, lacrimation, ocular itching, and swelling of eyelids sudden occurred.

He was treated with medications, including inhaled corticosteroids, antihistamines and antileukotrienes for long time, but allergic symptoms were not optimally controlled. Therefore, AIT was considered as new treatment option. Before AIT prescription, serum allergen-specific IgE were assayed: Der p 1 44 kU_A/L; Der p 2 35 kU_A/L; Par j 2 31 kU_A/L; Fel d 1 7.4 kU_A/L; Bet v 1 4.1 kU_A/L; Can f 1 3.4 kU_A/L; Ole e 1 2.5 kU_A/L. Despite poly-sensitization and perennial symptoms, it was decided to prescribe SLIT for Parietaria, as there was a periodicity of symptom exacerbations typically during Parietaria pollen peak.

He assumed a pre-co-seasonal SLIT course started in November 2013 and completed on March 2014. AIT was well tolerated. The symptom perception and medication use were assessed by visual analogue scale (VAS), comparing before- and after-AIT periods (10). Symptom VAS diminished from 8.1 to 3.5; drug VAS diminished from 6.2 to 0.4 (actually he did not assume any medication); and the VAS of perceived AIT effectiveness was 8.9. Very interestingly, he tolerated house dust, and overall he could move to the home of his best friend without relevant complaints.

This clinical case underlines the possibility of a clinical bystander effect induced by AIT. Indeed, Parietaria SLIT was able not only of improving pollen-dependent symptoms, but also of inducing an immunological tolerance, clinically relevant, also to other sensitizing allergens, such as mites and overall cat. Of course, this is an anecdotal report, thus there is the need of performing rigorous studies addressing this issue. In fact, even though this hypothesis of bystander effect of immunotherapy is interesting, it has been not formally demonstrated until now.

Anyway, the hypothesis that AIT might also exert non-specific mechanisms of action seems convincing. In fact, high allergen concentration may induce an immunological tolerance towards the used extract, responsible for the clinical improvement, as well known. In addition, AIT could provide non-specific effects that might explain these *in vitro*, such as increased IFN-g production, and in vivo, such as extended allergen tolerance, positive effects. However, one single patient's reported clinical benefit alone is not sufficient for formally supporting this hypothesis. If it is quite common to observe in the clinical practice that poly-allergic patients treated with AIT may develop a wide clinical immune tolerance also toward allergens not used in AIT, anyway, this impression requires at least a systematic observation of many cases for moving from impression to perception, and many experimental designs for moving from perception to formally demonstrated evidence.

In conclusion, it seems possible to hypothesize at present that a clinical bystander effect may be exerted by allergen immunotherapy.

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