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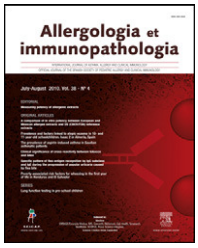

EDITORIAL

Changes in IL-10 and specific antibodies associated to successful *Dermatophagoides pteronyssinus* immunotherapy in children during the first year of treatment

Respiratory allergy is thought to be a complex of heterogeneous diseases with different phenotypes, based mainly on the nature of the inflammatory component and response to therapy. Inflammatory changes in allergy are driven by immune mechanisms, within which interleukins play an integral role. Interleukins (IL-?) are cell-signalling cytokines that are produced by a variety of cells, predominantly T cells. Over the years it became clear that the allergen-induced airway inflammation is orchestrated by activated Th2 cells. The current view is that IL-4-influenced naive T cells differentiate into Th2 cells when activated by antigen-presenting cells. These effector Th2 cells produce IL-4, IL-5 and IL-13, which mediate several regulatory and effector functions. They include allergen-specific IgE production by B cells; eosinophil development and recruitment; mucus production; and smooth muscle contraction.[1]

Various populations of regulatory T (Treg) cells have been shown to play a central role in the maintenance of peripheral homeostasis and the establishment of controlled immune responses. Their identification as key regulators of immunological processes in peripheral tolerance to allergens has opened an important era in the prevention and treatment of allergic diseases. The balance between allergen-specific Treg and Th2 cells appears to be decisive in the development of allergic and healthy immune responses against allergens. The induction of a tolerant state in peripheral T cells represents an essential step in allergen immunotherapy (SIT). Peripheral T cell tolerance is characterised mainly by the generation of allergen-specific Treg cells leading to suppressed T cell proliferation and Th2 cytokine responses against the allergen.[2]

The crucial role of IL-10 and Treg cells in the beneficial effects of immunotherapy (SIT) was first demonstrated in patients with bee venom anaphylaxis[3]; the mechanism by which SIT induces Treg cells is not completely understood, although in recent times it has become clear that the dendritic cells (DCs) play a critical role in the generation of all Treg cell subsets.[4] Well-described pathways to induce Treg cells are antigen presentation to T-cell by immature DCs or the presence of IL-10 or TGF-β in the local microenvironment. Treg cells suppress allergic responses directly and indirectly by the following mechanisms: (i) suppression of mast cells, basophils and eosinophils; (ii) suppression of effector T cells; (iii) suppression of inflammatory cell migration to tissues and tissue inflammation; (iv) suppression of mucus production; (v) suppression of inflammatory dendritic cells and induction of tolerogenic dendritic cells; and (vi) suppression of allergen-specific IgE and induction of IgG4 from B cells.[5]

Both naturally-occurring CD4+CD25+ Treg cells and **inducible** populations of allergen-specific, IL-10-secreting Treg type 1 (T_R1) cells inhibit allergen-specific effector cells in experimental models.[6]

The phenotype of natural Treg (nTreg) cells is CD4+CD25+Foxp3+IL-10−.[7] The nTreg cells induce suppressing immune responses via cell–cell interactions. The inducible (iTreg) cells induce suppressing immune responses **by secreting IL-10**. The phenotype of iTreg cells is CD4+CD25+Foxp3+IL-10+. T_R1 cells, also known as adaptive Treg cells, are defined by their ability to produce high levels of IL-10 and TGF-β.[8] On the other hand, IL-10 modulates IL-4-induced IgE production in favour of IgG4.[3,9]

Thus, IL-10 not only generates tolerance in T cells, but also regulates the allergen-specific antibody isotype formation toward a non-inflammatory direction.

In performing clinical studies on allergen-specific immunotherapy (SIT), a variety of clinical outcome parameters are utilised to evaluate the clinical efficacy. Primary outcome measures include the daily severity of symptoms as well as the daily consumption of anti-allergic concomitant medication. Secondary outcome parameters may also be evaluated as important in clinical trials on SIT. These include other surrogate markers, such as allergen-specific IgG antibodies or inflammatory parameters. In this context the production of IL-10 could be used as a marker of successful SIT.

In clinical trials, SIT has been shown to increase the production of IL-10 by antigen presenting cells (APCs), including

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B cells, monocytes, and macrophages.[10,11] This phenomena was not always be observed in house dust mite (HDM) specific immunotherapy. Some studies found that the percentage of IL-10+ T cells significantly decreased at three months of HDM-SIT in asthmatic children and at 12 months of SIT the proportion of IL-10-secreting T cells was high in only two from 16 patients.[12] In contrast, after SIT for one year, other studies have found a positive significant correlation between increased levels of Tr1 cells and improvements in nasal symptoms,[13] which was also correlated with the levels of allergen-specific Tr1 cells, IgG4, and allergen-induced IL-10 synthesis.

In the current issue of Allergologia et Immunopathologia, Martín-Muñoz et al. detail a prospective multi-centre study carried out in Spain.[14] This study sought early predictors of SIT effectiveness with *Dermatophagoides pteronyssinus* in children with asthma and/or rhinitis, combines primary outcomes including pulmonary function, skin test evaluation, symptom score and visual analogue scale with secondary outcomes: determination of specific Ig G4 and IgE to Der p1, Der p2 and Der p10 and quantification of IL-10. Over one year, thirty-eight children were treated with a standardised *D. pteronyssinus* extract and the different variables were studied at the beginning, at the moment of the maintenance phase, and after one year of maintenance monthly doses.

The study shows a good correlation among the improvement evaluated by symptoms score of the patient perceived severity and the *D. pteronyssinus* IgG4 evolution. However, this parameter had a low sensitivity and specificity as an early predictor of successful SIT. At the same time they found an initial rise in the levels of IL-10 that preceded the favourable changes in clinical evolution, skin test and the IgG4 responses. This increase was not sustained and the IL-10 levels at the end of one year were below the initial ones. The authors suggest that ''the early IL-10 response with an increase in specific IgG4 levels and an associated beginning of the decline in Der p1 and Der p2 IgE levels in the first year of treatment could be efficacy predictors of the allergen specific immunotherapy''. With respect to the non sustained increase in IL-10, they state that Treg cells have shown to have a short life span probably in relation with regulatory features of the immune system. It should be stressed that similar findings, a transient increase in antigen specific Treg cells IL-10 dependent, have been described in other studies.[15,16]

This is a valuable study although it has some limitations:

In the assessment of clinical efficacy they do not provide data of medication consumption, although the study was probably more directed at establishing a good predictor of efficacy than to prove it, as the authors consider the efficacy of SIT to have already been demonstrated.

As the authors stated, the number of patients is relatively small. In their study the increase in IL-10 is maximal after one month of treatment while in others[16] it last three months. It is known that the differential T-cell activation and regulatory patterns induced by SIT depend on the severity of the underlying allergic sensitisation. The increment in natural and acquired Treg cells develops earlier and reaches higher levels in less severe subjects.[17] Although it could be presumed that the majority of patients were mild cases, a large number of subjects would be desirable to stratify them by grade of severity in order to achieve more complete information. In addition, a normal control group to compare with is missing.

From a more theoretical approach, it has been shown that vitamin D3 leads to an increase of IL-10 production by human T cells.[18] Combination of SIT with administration of compounds that inhibit DCs maturation, such as the biologically active form of vitamin D3 (1α,25-dihydroxyvitamin D3), might be novel immunotherapeutic strategies to improve SIT. In a mouse model of allergen immunotherapy, co-administration of 1α,25-dihydroxyvitamin D3 effectively suppressed AHR to methacholine and potentiated the reduction of serum allergen-specific IgE levels and BAL eosinophilia.[19] A recent study performed in 54 children who were treated with HDM SIT and a supplementation of vitamin D3 of 1000 IU/week in a single dose, showed a protective effect of the vitamin with respect to the induction of T regulatory lymphocytes impaired by prednisone administration.[20] These observations open a new discussion about the possible effect of naturally produced Vit D3 on the IL-10 synthesis and the observed clinical improvement. It could be interesting to state when the blood is taken. Is it taken in or out of summer? How reproducible are the assays, in terms of levels of vitamin, for a given individual? Does seasonality affect the result?

Maybe these and other questions will be answered in the very near future, meanwhile it seems wise to conclude with the words of the authors ''early IL-10 response ... could be an efficacy predictor of SIT ... Further studies are necessary to confirm our results''.

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