Immunological Alterations Occurring during the Induction of Oral Tolerance in Patients with Food Allergies

Urra Ardanaz JM*
Immunology Laboratory, Hospital General Universitario de Ciudad Real, Spain

Abstract

Food allergy is a potentially life-threatening condition with no approved therapies, beyond avoidance. The offending food intake develops skin, respiratory and gastrointestinal manifestations and anaphylactic reactions in the severe forms. Food allergy is established by the loss of tolerance to food proteins, and is characterized by an altered balance of regulatory T (Treg) cells and the shift to Th2 type cytokines in the intestinal lamina propria. Oral immunotherapy (OIT) is an experimental treatment in which food-allergic patients consume gradually increased doses of food to raise their threshold for allergic reaction. The ability of OIT to desensitize patients to a particular food is well-documented, although the ability to induce perpetual tolerance has not been established. At present, OIT experience with several foods offer promising results. OIT is safe producing low adverse reactions, and is effective in inducing desensitization in most subjects with food allergy. This review focuses on recent studies about modifications that OIT causes on the immune system of allergic patients, and that culminates in its desensitization of involved foods.

INTRODUCTION

The usual immune response to harmless gut antigens like milk, egg, peanut, fish and their derivatives, is the generation of local and systemic immunological tolerance known as “oral tolerance”. The induction of tolerance to harmless gut antigens represents a key step in healthy immune responses to gut antigens. Food allergy results from a failure to induce or maintain oral tolerance. In addition to the Th1 and Th2 effector T-lymphocytes subsets, there is a CD4+ CD25+ T-cell subset with immunoregulatory properties; these cells are broadly referred to as Treg cells. Treg cells are a key component in the induction and maintenance of immune tolerance to allergens [1]. In healthy humans has been shown the existence of dominant Treg subsets specific to common environmental allergens [2]. Tolerance is induced by the generation of allergen-specific regulatory T cells, which suppress the response against the harmless antigens. Accordingly, depending on the predominant cell subset in the balance between Th2 effector CD4 T cells and Treg cells, individuals may develop allergy (lymphocyte Th2 subset predominance) or does not develop any immune reaction (Treg predominance). At present are not completely known the mechanisms whereby oral tolerance is caused, but the induction and maintenance of the peripheral tolerance depends mainly of Treg cells generation.

Desensitization by repeated systemic treatment with an allergen is a recognized therapy for the atopic disease. Oral induced tolerance (OIT) in food allergy can be induced by controlled oral administration of the offending food. The initial daily dosages are very low and are gradually increased until an amount equivalent to a usually relevant daily intake is achieved [3]. The number of successful reports about OIT in food allergy has been increasing in recent years, and the great hope for a positive treatment of food allergy is now becoming a realistic goal [4]. OIT lead in patients with food allergy both, a rapid desensitization and a long-term allergen-specific immune tolerance, turning out in suppressing of allergic clinical injury in the affected tissues. Thus, OIT could provide a complete cure for a larger number of allergic patients.

DESENSITIZATION OF MAST CELLS AND BASOPHILS

The typical sequence of events in immediate hypersensitivity is as follows: firstly the sensitization process, in which specific IgE antibodies are produced by B cells in response to the
exposure to an allergen; secondly binding of the preformed IgE antibodies to FcεRI receptors on the surface of the mast cells and basophils; and finally after any re-exposition to the allergen, the activation of mast cells and basophils by cross-linking of sIgE-FcεRI complexes and degranulation of mediators. The clinical manifestations of IgE-mediated reactions are due to the actions of the released mediators.

Notably, in many allergic patients, an impact very early in OIT is a decline in the susceptibility of mast cells and basophils to degranulation. This effect is present even though all patients undergoing the desensitization protocol still remain high quantities of the specific IgE. OIT may alter the magnitude of the mediators released as previously described in bee venom allergy [5]. The release low quantities of these inflammatory mediators (below the required dose for develop allergic conditions) may affect the threshold of activation of the mast cells and basophils [6]. Recently it has been demonstrated in basophils a rapid up-regulation of histamine receptor 2 within the early stage of bee venom immunotherapy [7]. Histamine is known one of the main mediators released upon IgE receptor triggering [7], and significant changes in trafficking receptors according to their stage of activation and differentiation. It has been proven a Treg homing to lymph nodes where they act their regulatory functions [10,11].

Treg cells perform their role in different ways. First, activation of allergen-specific Th2 cells is inhibited by Treg cells, thereby minimizing the production of IL-4, IL-5, IL-13 and IL-9, which are essential cytokines during the effector phase in allergic reactions [12]. Second, decreased the allergen-stimulated T-cell proliferation, and finally inhibit eosinophil, mast cell and basophils activity [12].

Treg cells use multiple suppressive mechanisms such as the release of the immunomodulatory cytokines IL-10 and TGF-β, and the surface expression of the inhibitory ligands cytotxic T lymphocyte antigen 4 (CTLA-4) and the programmed death 1 (PD-1) [2]. Peripheral tolerance is initiated by the cytokines IL-10 and TGF-β, which are increasingly secreted by the allergen-specific Treg cells during the course of OIT [13]. The induction of clinical tolerance by OIT originates a change in the frequency of cytokine-producing T cells. There was a marked loss of IL-4-producing T-cells (Th2) and an increase in the number of IL-10-producing antigen-specific T-cells [14].

Certain circumstances and particular microenvironments encourage the generation of Treg cells, though this mechanism is not well understood. A role for DCs (antigen presenting cells) in the induction of different subsets of Treg cells in specific microenvironments has been supported in several studies. Peripheral conversion of T lymphocytes to Treg cells occurs primarily in gut-associated lymphoid tissue after oral exposure to antigen and in a lymphopenic environment [15]. The oral intake of doses of allergens seems to be a prerequisite for the differentiation and proliferation of regulatory cells. Low doses favor the induction of Treg, whereas higher doses favor the induction of energy or deletion of specific immune cells. These mechanisms are not exclusive [16]. The application orally of controlled doses of antigen promotes the induction of Treg cells which play an important role in generating the antigen desensitization.

**CHANGE IN THE IMMUNOGLOBULIN ISOTYPE UPON OIT**

Specific oral desensitization induces a transient increase in serum specific IgE followed by a gradual decrease usually visible after 3-6 months of protocol [17]. The suppressive cytokine IL-10, produced by Treg cells, also affects the immunoglobulin synthesis through strong suppression of allergen-specific IgE, while it increases an IgG4 isotype production. Measurements of the immunoglobulin subtype levels during oral desensitization showed a specific increases in the range of 10-100 fold in the concentrations of IgG and particularly of IgG4 [18]. Allergen specific IgG4 in serum shows a relatively early and rapid increase and continues to increase during the whole duration of the desensitization protocol [19]. These IgG4 immunoglobulin isotype does not have ability to bind to receptors on surface of the effector cells such as the mast cells and basophils. Their specific affinity for the antigen competes with IgE located on the cell surface for binding to the allergen [20]. IgG4 is a blocking antibody that prevents the activation and degranulation of effector cells by competing with allergen binding to the IgE on the FcεRI receptors of mast cells and basophils.

**CONCLUSION**

In conclusion, as shown in Table (1), OIT induces the desensitization to food allergens by a variety of mechanisms, in which the Treg cells play a pivotal role directly inhibiting the effector cells, regulating Th2 lymphocytes and inducing isotype switching from IgE to IgG4. In many allergic patients these

<table>
<thead>
<tr>
<th>CD4 T Lymphocytes</th>
<th>Sensitization</th>
<th>OIT desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th2</td>
<td>Treg</td>
<td></td>
</tr>
<tr>
<td>Cytokines released</td>
<td>IL-4, IL-5, IL-13</td>
<td>IL-10, TGFβ</td>
</tr>
<tr>
<td>Mast cell release mediators</td>
<td>IgE induced</td>
<td>Histamine type2 receptor inhibition</td>
</tr>
<tr>
<td>Immunoglobulin isotype</td>
<td>IgE</td>
<td>IgG4</td>
</tr>
</tbody>
</table>

Table 1: Cellular and humoral changes induced by OIT in the desensitization to food allergen.

email: jmarra@sescam.jccm.es
mechanisms altogether will develop tolerance to the offender food, thus improving their quality of life.

REFERENCES


