Chapter 9

Specific Immunotherapy in Food Allergy — Towards a Change in the Management Paradigm

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Additional information is available at the end of the chapter

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1. Introduction

Food allergy is one of the leading causes of allergic disease and the main cause of anaphylactic reactions and mortality due to allergic problems, producing important economic problems and social restrictions for the affected patients and their families.

The increase in the prevalence and persistence of food allergy throughout the world has a significant impact not only upon patient safety but also on quality of life and healthcare expenditure. Indeed, food allergy constitutes a major public health problem.

The attitude or approach to food allergy has always been to avoid the cause and adopt measures against adverse reactions in the event of accidental intake. However, in the last few years a new management strategy has been explored: the active induction of food tolerance.

One of the most promising therapies is desensitization to specific food allergens through oral or sublingual immunotherapy, and research in this field is advancing quickly for some established allergens. In this respect, the technique has demonstrated its effectiveness, and its transfer to clinical practice is presently undergoing evaluation.

This chapter addresses the epidemiology and natural history of food allergy, the mechanisms of immune tolerance to foods, the forms of desensitization and induction of tolerance to allergens with applications to foods, and affords an update on the experience gained with the induction of tolerance to different foods, the respective protocols and guides, efficacy and safety considerations, and adverse reaction risk factors. An evaluation is also made of the current state of biological therapy utilization in conjunction with specific immunotherapy for food allergens.

Lastly, a discussion is made of the opportunities and limitations facing the clinical use of the specific immunotherapy in food allergy, and of the areas of future research.

2. Epidemiology of food allergy

Food allergy is a worldwide problem, affecting at least 1-2% of all adults and between 6-8% of the pediatric population [1–3]. The reported prevalences are conditioned by the diagnostic methods used, the patient ages considered, and also by genetic, ethnic, geographic and cultural factors. Consequently, the published data differ greatly from one country to another [4].

The diagnostic methodology used exerts a great influence. In this respect, a recent metaanalysis [5] found the self-reported incidence of allergy to cow's milk (CM), egg, peanut or crustaceans to be 12%-a figure that dropped to 3% when the diagnosis was established from double-blind, placebo-controlled food challenge(DBPCFC) or provocation testing. In the case of cow's milk, between 1.2% and 17% of those surveyed claimed to be allergic, depending on the study. In this regard, if the diagnosis was established by prick testing or the determination of specific IgE, the frequency was found to be 2-9%, versus a prevalence of 0-3% when DBPCFC was the selected diagnostic technique.

In the United States [6] it is estimated that 8% of all children will suffer food allergy, and that 40% of these patients will experience severe reactions, while 30% will be allergic to several foods – peanut, cow's milk and crustaceans being the most commonly implicated foods. In a one-year of age Australian population, the prevalence of allergic individuals as established by provocation testing (i.e., challenge-proven allergy) reached 10% [7].

The prevalence of food allergy appears to be increasing rapidly, particularly in the industrialized world [8–10] and in widely different regions such as the United Kingdom [11], the United States [12], Australia [13], Sweden [9] or China [14].

2.1. The most frequently implicated foods

The age of the studied population and the geographical setting exert a key influence upon the types of foods that cause allergy. The most common cause of food allergy in pediatric patients is cow's milk, followed by egg (and peanut in the United States). In turn, crustaceans, nuts and peanut become the most common causes of more serious allergic reactions among adults, since allergy to cow's milk and egg disappears in approximately three out of every four patients, while the opposite is observed for the rest of foods.

2.2. Cow's milk

Allergy to cow's milk is the most common type of food allergy in children, affecting 2-3% of all individuals in this age group. Approximately one-half of all cases are mediated by IgE, with the development of immediate allergic reactions which in some cases may prove systemic and serious (e.g., anaphylaxis). The rest of the cases are not mediated by IgE, and are characterized by generally less serious gastrointestinal problems-with the exception of FPIES (food protein-induced enterocolitis syndrome).

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Most patients show a favorable course, with disappearance of the allergy in up to 83% of all subjects by 5 years of age. The specific IgE levels are a good predictor of tolerance, though recent publications indicate that longer periods of time are currently needed to acquire natural tolerance, and that tolerance now develops in adolescence and not in the early schooling period as was common in the past [15,16]. Despite measures of caution, accidental intake still occurs, often on a day to day basis in the home [17], with the description of even fatal anaphylactic reactions [18].

2.3. Egg

Allergy to chicken egg (usually to egg white) is the second most common form of food allergy in pediatric patients, being observed in 1-3% of all children [19]. The underlying pathogenesis is mainly IgE-mediated. Approximately two-thirds of all patients acquire natural tolerance [13,20,21], though a recent study has evidenced the persistence of egg allergy in 42% of the patients upon reaching adolescence [22]. This change in tendency may contribute to increase the number of adults with allergy to egg. In this regard, it has been estimated that 0.2% of all adults are allergic to egg [23], so this figure is likely to increase.

2.4. Peanut

Allergy to peanut is one of the most frequent forms of food allergy in western countries, and can give rise to serious IgE-mediated reactions in response to even small intakes or exposure levels. The condition is found in up to 1.8% of all children in the United Kingdom [24] and in 1.3% of the adult population in the United States [23]. When diagnosed by provocation or challenge testing, the prevalence reaches 3% of all children in Australia [7]. The prevalence of peanut allergy appears to be increasing, and most individuals continue to suffer allergy to this food in adult life [25]. Indeed, only 20% of the affected patients overcome peanut allergy [26], and the percentage of tolerant subjects is related to the degree of sensitization [27]. Over 15% of all affected patients suffer accidental exposure on a yearly basis [28,29].

2.5. Multiple foods

Allergy to multiple foods is important, since up to 30% of all allergic children suffer allergy to more than one food [6,30] – the magnitude of the condition increasing with the degree of atopy of the patient. These patients have poorer quality of life than those with allergy to a single food [31], and are at an increased risk of suffering nutritional deficiencies [32]. Likewise, patients with allergy to multiple foods have lesser chances of acquiring natural tolerance to the implicated foods [22].

3. Current treatment of food allergy

The traditionally recommended approach to the management of food allergy consisted of strict avoidance of the causal allergen; early recognition of the allergic reaction; and the availability

of adrenalin to deal with serious reactions. However it is known that strict avoidance is very difficult to achieve, and is limited by difficulty in interpreting food labels [33] and by the existence of hidden allergens in commercial foods [34]. Accidental intake is therefore common, and can be expected to occur in up to 50% of all patients in the course of a two-year period, even in very cautious patients. Undertreatment is moreover a common problem [35].

3.1. Management of anaphylaxis

The main risk posed by food allergy is the induction of IgE-mediated systemic reactions. In this regard, food allergy is the leading cause of both anaphylaxis and mortality due to anaphylaxis. Between 40-100% of all deaths attributable to anaphylaxis in patients with food allergy are due to commercial foods or foods prepared outside the home [18,36,37]

Management includes teaching the patients and caregivers to quickly recognize the symptoms of anaphylaxis and promptly self-inject insulin and notify the emergency care services [38].

However, difficulties are found regarding correct use on the part of the caregivers [39], and in assuming the responsibility of care on the part of the patients [40] – particularly in the case of adolescents [41,42]. In such patients, one-fourth of all anaphylactic episodes occur outside the home. It is therefore necessary to instruct the caretakers in school on how to handle anaphylaxis, and to reinforce self-care instructions among these adolescents [43].

4. Quality of life

The need for a strict avoidance diet, the high probability of accidental exposure, and the risk of anaphylaxis in food allergies alters the life of the patients and their families, and generates anxiety and psychosocial stress, with a negative impact upon quality of life [44–46], to an extent greater than that observed with other chronic disorders of childhood [47,48].

This loss of quality of life affects even the daily relations of the patient, with an increased frequency of bullying in such children [49]. Allergic children are also at an increased risk of suffering abuse.

5. Economic costs

Food allergy implies an important economic cost [50], reaching an estimated 25 billion USD each year in the United States – the largest part of this sum (approximately 20 billion USD) being assumed by the families as direct costs, working hours lost, visits to the emergency service, etc. [51]. The generated costs are not only of a personal nature but moreover also affect the healthcare services, the food industry, the caregivers, and society as a whole [52].

http://dx.doi.org/10.5772/59105

6. Immunology of food tolerance

The gastrointestinal tract (GIT) is constantly exposed to an enormous number of exogenous antigens, including commensal bacteria and ingested proteins. In this respect, the GIT is the most relevant site of exposure to antigens in the entire body, and therefore of antigen absorption and presentation to the host.

An epithelial layer separates the allergens from the lymphocyte population, antigen-presenting cells (APCs) and other immune cells of the *lamina propria* that globally conform the so-called mucosa-associated lymphatic tissue (MALT). Within the latter, the dendritic cells (DCs) interact with the food allergens, determining the outcome of the adaptive response (immunity versus tolerance)[53]. In this respect, immune tolerance is defined as suppression of the antigen-specific cellular or humoral immune response.

Following the intake of proteins with the diet, enzyme-mediated digestion reduces their immunogenicity, probably through destruction of the conformational epitopes. However, other foods sharing common characteristics (molecular weight < 70 kDa, linear epitopes, water solubility) are resistant to both physical and chemical degradation, and thus maintain their allergenicity upon reaching the small intestine. Under normal conditions, the intact macromolecules are taken up by a transcellular transport mechanism, and the antigenic material is deposited through the basolateral surface of the epithelial cell layer; as a result, a significant amount of food allergens reach the systemic circulation following a meal.

Another antigen uptake mechanism consists of direct antigen presentation to the CD11c +dendritic cell population. The function of these cells is related to macrophage activity, and there is evidence that the CD11+macrophage population plays an important role in the T cell-mediated antigen-specific response during the development of immune tolerance to food antigens.

More recent evidence supports that impairment in regulatory T cell (Treg) induction and innate immunity might also contribute to Th2 polarization in early life. Prospective birth cohort studies have shown that IgE production in response to egg, milk, and peanut commonly occurs even in healthy infants. In non-allergic subjects, this Th2 bias appears to be transient, and IgE levels decrease, possibly through a counterbalancing induction of antigen-specific Th1 responses (i.e., IFN-γ); in contrast, these Th2 responses consolidate and strengthen in allergic children, perhaps through the induction of IL-4 signaling [54].

A full 80% of all plasmatic cells are located in the intestine. The small bowel contains cell generating pIgA (polymeric IgA)(80%), followed in order of prevalence by secretory pIgM (polymeric IgM)(15-20%) and secretory IgG (3-4%). IgA deficiency in children has been reported to be associated with an elevated frequency of food allergy. In this context, it has been postulated that IgA plays a protective role in the context of food allergy [55].

The presence of antigen-specific IgG in the intestinal lumen can exert a significant influence upon immunity to food and flora. IgG-mediated antigen uptake through FcRn in the neonatal intestine is tolerogenic, and suggests that antigen exposure through breast milk would be a

helpful preventative strategy, particularly when the mother has existing IgG antibodies to that antigen. Once allergic sensitization has been established, it is not clear whether IgG-facilitated antigen uptake through FcRn would amplify existing proallergic adaptive immune responses or promote active immune tolerance. Studies are needed to address the influence of FcRn on responses to food antigens [55].

Immunoglobulin E can be found in secreted form under the conditions of allergy and helminth infection-this being associated with an epithelial receptor for IgE. IgE-facilitated antigen uptake results in increased delivery of antigen to allergic effector cells, activates proinflammatory pathways in intestinal epithelial cells, and enhances antigen delivery to dendritic cells. IgE-facilitated antigen uptake by B cells can also have an adjuvant-like effect on the resulting adaptive immune response.

This complex interaction among physical factors, antigen characteristics and timing, together with the effects of innate immune stimulation, condition the development of oral tolerance through a common pathway directly or indirectly influenced by APCs. It recently has been shown that mucosal dendritic cells are probably the key element in determining allergic sensitization versus tolerance in naïve subjects.

Multiple tolerance mechanisms probably intervene, and may include anergy or deletion of T cells. There is evidence relating oral tolerance with the capacity of the mucosal dendritic cells to induce positive forkhead box protein [Foxp3]+Treg cells in MLNs (mesenteric lymph nodes). CD103, retinoic acid (RA), indoleamine-2,3-dioxygenase, co-stimulator molecules of the B7 family and TGF-β appear to act by allowing dendritic cells to induce such conversion. In contrast, the dendritic cells of the *lamina propria* do not express CD103, and are proinflammatory. This suggests that tolerogenic dendritic cells could inhibit site-specific signaling of the intestinal epithelium through interaction with E-cadherin (a CD103 ligand). This is probably the microenvironment provided by the mucosa to allow antigen presentation resulting in either inflammatory response or tolerance within the MLNs. Antigen-presenting cells other than conventional dendritic cells might also participate in oral tolerance induction.

Oral tolerance might be operative through multiple mechanisms in multiple tissue compartments. For example, intestinal macrophages can also efficiently induce Foxp3+Treg cells in an IL-10-, RA-and TGF-β-dependent fashion. Plasmacytoid dendritic cells, a specialized dendritic cell subset known for their ability to produce vast quantities of type I interferons, can also activate inducible Foxp3+IL-10. Integration of environmental information by dendritic cells results in specific activation and differentiation of T cell subsets, including the Foxp3+Treg cells, as the primary effectors of oral tolerance.

Repeated exposures to low doses of antigen are thought to be the optimal stimulus for the development of Treg cells, which suppress immune responses through soluble or cell-bound regulatory cytokines such as IL-10 and TGF-β. Natural CD4+CD25+Treg cells develop in the thymus and express the specific transcription factor Foxp3+, which confers regulatory function to these cells to block both Th1 and Th2 responses. Inducible regulatory T cells (iTreg) are CD4+cells that can differentiate from naïve precursors, acquiring regulatory properties in the periphery after exposure to antigen. In many cases these cells acquire the expression of Foxp3,

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and they exist in at least two forms distinguished by the antiinflammatory cytokines produced: IL-10 (Tr1 cells) and TGF-β (Th3 cells). Whereas natural CD4+CD25+Treg cells are thought to primarily govern peripheral tolerance to self-antigens, Treg cells are more likely responsible for tolerance to exogenous substances, such as allergens [56].

Mechanistically, functional allergen-specific Treg cells can attenuate allergic responses through: 1.-the suppression of mast cells, basophils, and eosinophils; 2.-the suppression of inflammatory dendritic cells and induction of tolerogenic dendritic cells; 3.-the suppression of allergen-specific Th2 cells, hence contributing to T cell anergy; and 4.-the early induction of IgG4 and late reduction of IgE production. All of these mechanisms can be mediated through the secretion of IL-10 and TGF-beta, or through cell contact-dependent suppression. The Treg cells therefore appear to play an important role in tolerance following immunotherapy in food allergy [57,58].

7. Active therapy against food allergy

Between 15-20% of all patients with allergy to cow's milk and egg will remain allergic, while those who acquire tolerance will take years to become tolerant. In contrast, most patients with allergy to fish, crustaceans, peanut or nuts will remain allergic to these foods for life [59].

The health risks for such patients, the alterations in their diet, social discrimination, impaired quality of life, and the costs generated by such illnesses have led to re-evaluation of the passive management strategies with a view to establishing active treatment options – replacing the management through avoidance paradigm with an active intervention approach based on specific desensitization and tolerance of the causal food.

In this context, active intervention has been considered for years with the purpose of solving this health problem, particularly in patients with a high risk of anaphylaxis and in those who will not benefit from natural resolution of the problem. Such intervention involves nonspecific therapeutic measures and, more recently, specific treatments for each type of food.

Immunotherapy would be a plausible option in view of its demonstrated efficacy in patients with allergy to aeroallergens and stinging insect venom [60]. For this reason, the use of immunotherapy in application to food allergens has been postulated for over two decades – giving rise to a series of experiments and producing a body of knowledge over the last decade, referred particularly to the oral route, which we will try to explain in this chapter.

Considering that non-IgE mediated allergy does not appear amenable to such treatment strategies, we will only deal with IgE-mediated food allergy.

8. Immunotherapy in application to foods

The site of antigen administration and contact is important for the efficacy and safety of specific food immunotherapy. According to the administration route involved, we can distinguish

among four different types of specific food immunotherapy: subcutaneous immunotherapy (SCIT), epicutaneous immunotherapy (EPIT), sublingual immunotherapy (SLIT) and oral immunotherapy or specific oral tolerance induction (SOTI)[61].

8.1. Specific Subcutaneous Immunotherapy (SCIT)

There is extensive experience with the use of subcutaneous immunotherapy in application to aeroallergens and insect venom – more than 100 years having gone by since the technique was first developed – though very little experience has been gained to date with its use in application to food allergy. In patients with pollen-fruit syndrome [62], immunotherapy has been found to be effective against aeroallergens that share antigenicity with certain plant foods [63–65], securing desensitization to such allergens and foods. However, the utilization of specific food allergens via the subcutaneous route (e.g., peanut), produced important [66] and serious adverse reactions, with the death of one patient following error in the composition of the placebo dose containing allergen. As a result, and despite evidence of a certain degree of efficacy, these problems caused the early evaluation attempts to be suspended [67]. In effect, since then, this specific immunotherapy administration route to treating food allergy has been discontinued. However, the introduction of recombinant allergens, the elimination of epitopes for IgE with the maintenance of T cell-recognized epitopes [68], immunotherapy with peptides, DNA immunotherapy, and other advances that are currently in the preclinical investigation phase, will make it possible to resume studies with this administration route.

8.2. Specific Epicutaneous Immunotherapy (EPIT)

Specific epicutaneous immunotherapy (EPIT) is based on the capacity of the Langerhans cells of the epidermal basal layer to migrate and reach the lymph nodes, where they regulate the cells implicated in allergic inflammation [69,70]. A pilot study in patients with allergy to cow's milk [71] demonstrated a modest increase in the amount of milk tolerated, with only local symptoms, none of which proved serious. A recent phase IIa double-blind, placebo-controlled (DBPC) efficacy study in patients with allergy to peanut (ARACHILD) [72] was able to secure a more than 10-fold increase versus baseline in the tolerated levels after 18 months of treatment in 67% of the patients. The study has currently been extended to 36 months, with good safety results. Other studies involving this same administration route for the induction of peanut desensitization are currently also in course.

8.3. Specific Sublingual Immunotherapy (SLIT)

Specific sublingual immunotherapy (SLIT), which makes use of the capacity of the Langerhans cells of the oral mucosa to suppress allergic cell response [69,73,74], has been successfully applied against aeroallergens in rhinitis and asthma [75,76]. In the same way as SCIT, the technique has afforded improvement in patients with plant allergy exhibiting cross-allergenicity with certain pollens. In this regard, SLIT has been used against the latter [77] and against latex – avoiding the increase in foods to which reactions occurred [78].

http://dx.doi.org/10.5772/59105

Use has been made of SLIT with specific food allergens such as kiwi [79]. One case report documented persistent tolerance after 5 years [80]. DBPC studies have been made with hazelnut [81], with the maintenance of protection over the long term [82], and with peach [83], in which tolerance could be increased 3-to 9-fold. At present, an observational study is underway to evaluate the efficacy and safety of SLIT with Pru p3 extract in pediatric patients. A pilot study with cow's milk [84] was able to increase the tolerated amount of milk three-fold in a group of 8 children. A placebo-controlled SLIT study with peanut [85] in turn secured a 10-fold increase in the amount of peanut that could be ingested without symptoms after 44 weeks of therapy in the active treatment group. A more recent placebo-controlled SLIT study with peanut [86] found 70% of the patients to be able to ingest 5 g of peanut or increase the tolerated amount up to 10-fold versus the amounts tolerated at baseline, after 44 weeks of treatment.

8.4. Specific Oral Immunotherapy / Specific Oral Tolerance Induction (SOTI)

Specific oral tolerance induction (SOTI) is currently the most widely evaluated approach, having exhibited effectiveness over the short and long term, though with limitations in relation to its safety profile. Tolerance is taken to represent non-reactivity to the allergen even after a period of time without contact with the allergen. In this regard, desensitization constitutes a prior step, but does not guarantee lasting tolerance. SOTI is able to achieve desensitization in a large percentage of patients – this being enough to avoid reactions secondary to accidental ingestion and incorporation of the food to the diet. Such desensitization is possibly the most important objective of the technique, since the number of patients that are able to achieve permanent tolerance is considerably smaller. As a result, it has been proposed that SOTI should actually be referred to as specific oral desensitization induction.

A prospective comparison of SOTI versus SLIT [87] has confirmed greater efficacy if SLIT is followed by a SOTI phase involving high maintenance doses. The retrospective comparison of SLIT and SOTI in application to peanut allergy [88] has shown greater efficacy with the latter technique, though with more adverse effects. In this respect, it seems that SLIT is comparatively safer but less effective than SOTI in application to foods.

Since SOTI is the most widely investigated type of specific immunotherapy in food allergy, we will address the technique a little more in depth.

8.4.1. Mechanism of immune tolerance in SOTI

SOTI acts at intestinal dendritic cell level [89,56], lowering the specific IgE levels and increasing the specific IgG4 titers, with an increase in IL-10, IL-5, IFN-γ, TNF-α and Foxp3 cells. Studies involving T cell microarrays have shown inhibition oriented towards apoptosis at genetic level [90]. The technique also reduces basophil IgE receptor production [91].

8.4.2. Regimens and phases in SOTI

The technique aims to induce desensitization and subsequent tolerance by administering small amounts of allergens that cause no clinical manifestations or only mild manifestations. The

amounts are gradually increased over time until the ingested allergen level reached is considered to protect against adverse reactions and secure tolerance after ingestion of the food over the following months.

Three phases can be distinguished during this process. On the first day an initial rush-type **rapid desensitization phase** is established, followed by an **escalation or up-dosing phase** involving daily administration of the tolerated dose in the home of the patient, with controlled periodic up-dosing (usually on a weekly basis) until the maintenance or desensitization dose is reached. This represents the start of the **maintenance phase**, in which the maximum dose reached is ingested either daily or on alternating days over the subsequent months in order to maintain desensitization and protection against accidental exposure, and to secure full tolerance in at least some of the patients. This in turn must be confirmed through provocation testing after an exclusion period or treatment cessation period of one or more months.

The different management protocols use these phases in different ways as regards the doses and times. Some protocols prolong the initial rush phase to reach maintenance dosing within about 5 days [92–94], avoiding the weekly up-dosing phase which usually covers 2-4 months. This practice typically implies more adverse effects. In contrast, the initial protocols used by Patriarca et al. did not use the rush phase and prolonged the escalation phase for more months, with increments in the home of the patient introduced on a daily basis or every few days in the form of very small amounts, until the full desensitization dose was reached [95]. The mentioned group continues to maintain this protocol in modified form [96,97]. There is also some experience with the use of a SLIT desensitization phase followed by SOTI [87] – this being an option in those patients who fail to tolerate the initial rush phase. In other studies the rush phase is prolonged to two days and the up-dosing or dose escalation phase to 16 weeks [98,99]. The authors use a one-day rush phase and a 10-week dose escalation phase.

The most recent protocols typically contemplate all three phases, and follow-up evaluation after the last phase, which is essential in order to confirm tolerance.

8.4.3. Experiences and clinical trials with SOTI

8.4.3.1. Peanut

In a non-controlled SOTI study, 28 children between 1-16 years of age with peanut allergy were randomized 2:1 to active treatment or placebo. Three patients in the active treatment group abandoned the study due to adverse effects, while the rest reached the 4000 mg dose, and after 12 months were able to tolerate 5000 mg (20 peanuts), versus 280 mg in the control group ($p<0.001$). Significant reductions were observed in the size of the prick test and in the specific IgE and Th2 cytokine levels – with a significant increase in specific IgG4 titers and Treg cell count [100].

In another study, 29 patients completed the protocol and were able to consume 3.9 g of peanut protein, with a significant decrease in the size of the prick test and in basophil activation after 6 months of maintenance dosing. Specific IgE was seen to decrease, with a significant increase in specific IgG4 between months 12-18 of this treatment phase, together with elevations in the

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levels of IL-10, IL-5, IFN-γ, TNF-α and Foxp3 T cells, with demonstration of inhibition oriented towards apoptosis at genetic level [90].

In another non-controlled study, 23 patients with anaphylaxis due to peanut allergy diagnosed by DBPCFC received SOTI in the form of a rush protocol during 7 days until a dose of 0.5 g was reached. After 8 weeks of daily intake and a two-week avoidance phase, DBPCFC was repeated, with tolerance of only 0.15 g of peanut. Twenty-two patients continued with the maintenance phase, and after an average of 7 months, 13 of them (60%) reached the protective dose, with a final tolerance of 0.25-4 g of peanut (initial tolerance being 0.02-1 g). Three of the 22 patients suspended intake during this phase. A significant increase was recorded in specific IgG4, with a decrease in Th2 cytokine levels [101].

8.4.3.2. Cow's Milk (CM)

A total of 22 children with allergy to cow's milk were randomized 2:1 to SOTI with 500 mg of CM protein (15 ml CM) daily during four months, or to placebo. At final challenge testing, the active treatment group tolerated 5140 mg, versus 40 mg in the control group. The IgE levels did not vary, though the IgG4 levels increased significantly in the SOTI group [102].

Another study selected 97 children with DBPCFC-diagnosed allergy to CM with serious reactions and very high anti-CM IgE titers. Sixty patients reacted to very low doses. The subjects were randomized 1:1 to SOTI or an exclusion diet. After one year of treatment, 36% of the patients in the SOTI group were fully tolerant (> 150 ml), 54% were able to consume limited amounts of milk (5-150 ml), and 10% were unable to complete the protocol because of persistent respiratory or digestive problems. None of the control subjects passed the final DBPCFC test. [103]

A case series has described CM desensitization as a result of a rush-type SOTI protocol in four patients, with long-term desensitization being achieved in all cases [93].

A multicenter study involving 60 pediatric patients with a mean age of two years (range 24-36 months) randomized the subjects 1:1 to an exclusion diet or SOTI (2-day rush phase followed by a 16-week escalation phase until reaching a maintenance dose of 200 ml of CM). After one year, 90% of the patients in the SOTI group were fully tolerant, versus 23% of the patients in the exclusion diet group [98].

Another study randomized 30 patients diagnosed with CM allergy by DBPCFC to SOTI or placebo (soya milk), with an 18-week up-dosing phase and no prior rush period. Thirteen patients were maintained in the SOTI group, of which 10 reached the final dose of 200 ml (77%). None of the control subjects passed the DBPCFC test [104].

Thirteen patients with CM allergy were subjected to SOTI with no initial rush phase and with an 18-week escalation period until a dose of 200 ml of CM was reached. The three controls received soya milk. Tolerance was achieved in 8 of the patients in the SOTI group (7 cases of full tolerance and one partial tolerance), while the controls maintained DBPCFC positivity [105].

In another study, 28 children between 6-14 years of age with CM allergy (36% of an anaphylactic type) were recruited after oral provocation testing and randomized in a double-blind, placebo-controlled SOTI study. Sixteen out of 18 patients in the active treatment group and 8 out of 10 in the placebo series completed the study. After one year of SOTI, 81% of the children consumed 200 ml of CM or equivalent products. After confirming the absence of tolerance among the controls, the latter were enrolled in a similar protocol and were seen to tolerate 200 ml of CM after 6 months. After 3.5 years, tolerance was maintained in 79% [106].

Lastly, in another study, 60 children aged between 13 months and 6.5 years were randomized to SOTI or an exclusion diet. After 6 months, 89% of the patients in the active treatment group tolerated 200 ml of CM, versus 60% of the controls ($p<0.025$). A decrease in the size of the prick test was recorded in the active treatment group, while the size was seen to increase among the controls [107].

8.4.3.3. Egg

A total of 55 patients with egg allergy were included in a randomized, double-blind, placebo-controlled trial. Forty patients received SOTI. Of these, 55% passed a 5 g oral egg white powder provocation test after 10 months, versus none of the individuals in the control group. In turn, 75% of the subjects in the active treatment group passed a 10 g oral provocation test after 22 months. Desensitization was associated to a decrease in specific IgE, an increase in IgG4 after 10 months, a reduction in basophil activation, and a decrease in the size of the prick test after 22 months [108].

Eighty-four patients with egg allergy that tolerated up to 1 g of raw egg white were randomized to SOTI or an avoidance diet. After 6 months, 69% of the patients in the active treatment group and 51% of the controls passed a oral provocation test, and the mean size prick test size and specific IgE titers decreased significantly in the active treatment group. Furthermore, the patients subjected to SOTI who failed to pass the provocation test had comparatively greater tolerance and lesser severity of symptoms [107].

Of 19 patients between 4-14 years of age who started SOTI for egg allergy, 16 achieved full tolerance (85%), being able to consume a 10 g dose of powdered pasteurized egg (equivalent to one egg). In addition, a decrease was recorded in the population of effector-memory CD4+T cells, with an increase in a subclass of CD4+T cells with a hypo-proliferative and non-reactive phenotype [109]. These authors also recorded an increase in Treg cell count in those individuals who reached tolerance [110].

In a study comprising 72 patients between 5-15 years of age, the presence of egg allergy was confirmed by open oral challenge testing. Forty subjects were randomized to SOTI with powdered pasteurized egg – tolerance being achieved in 92.5% of them, and in 21.8% of the controls [111].

Another study involving 8 patients documented desensitization in 6 subjects (75%) [112].

In a retrospective review of 43 children with egg allergy, 30 were found to be willing to participate in a SOTI study with egg, involving maintenance of the maximum tolerated dose

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two or three times a week. The 13 patients who declined to participate conformed the control group. Nine of the 30 children in the active treatment group reached tolerance of one egg after one year of SOTI – a figure that was seen to increase to 17 out of 30 subjects after two years of treatment. In comparison, none of the controls achieved tolerance. Of the 14 desensitized patients that could be followed-up on, 11 reached full tolerance [113].

A randomized and controlled study recorded partial tolerance (10-40 ml of raw hen's egg emulsion) in 90% of the patients (n=9) subjected to SOTI with egg during 6 months, versus none of the controls [114].

8.4.3.4. Metaanalyses

A metaanalysis of SOTI with cow's milk included 5 randomized controlled trials (RCTs) and 5 observational studies that met the inclusion criteria. The RCTs comprised 218 patients and showed that oral immunotherapy versus an elimination diet increased the probability of acquiring full tolerance to cow's milk [relative risk: 10.0 (95%CI: 4.1-24.2)]. The adverse effects of immunotherapy included frequent local symptoms (16% of the doses), mild laryngeal spasm [relative risk: 12.9 (1.7-98.6)], mild asthma [rate ratio: 3.8 (95%CI: 2.9-5.0)] and reactions requiring oral corticosteroids [relative risk: 11.3 (95%CI: 2.7-46.5)] or intramuscular adrenalin [relative risk: 5.8 (95%CI: 1.6-21.9)]. The findings of the observational studies were consistent with those of the RCTs. The metaanalysis concluded that larger RCTs are needed [115].

Another metaanalysis of SOTI with cow's milk selected 16 publications, of which 5 were clinical trials. The studies were generally small and presented methodological inconsistencies, with low quality evidence. Each study used a different SOTI protocol. A total of 196 pediatric patients were studied (106 subjected to SOTI and 90 controls). Sixty-two percent of the patients in the SOTI group and 8% of the controls reached tolerance of about 200 ml of cow's milk [relative risk 6.61 (95%CI: 3.51-12.44)]. In addition, another 25% of the subjects in the SOTI group achieved partial tolerance (10-184 ml), versus none of the controls [relative risk 9.34 (95%CI: 2.72-32.09)]. None of the studies evaluated the patients some time after immunotherapy suspension. Adverse reactions were common, affecting 92% of the patients, though most were mild and of a local nature. One out of every 11 patients receiving SOTI required intramuscular adrenalin. The studies conducted to date have involved small numbers of patients, and the quality of the evidence is generally low. The current data show that SOTI can lead to desensitization in the majority of individuals with cow's milk allergy, though the development of long-term tolerance has not been established. A major drawback of such therapy is the frequency of adverse effects, although most are mild and self-limited. The use of parenteral epinephrine is not infrequent [116].

Regarding SOTI for allergy to cow's milk, achieving desensitization or even tolerance to cow's milk does not imply desensitization to milk from other mammalian species to which the patient may be sensitized [117,118] – a circumstance observed in 25% of the cases in one study [119]. Consequently, the exclusion of milk and milk products from other species must be maintained if exposure testing does not confirm the existence of tolerance to such foods.

8.4.3.5. Other foods

Individual SOTI studies have yielded positive results in reference to other foods such as tomato [94], celery [120], apple [121] or wheat [122,123].

8.4.3.6. Multiple foods

A field of great interest refers to the study of simultaneous allergy to multiple foods (up to 5), since one-third of all patients with food allergy are allergic to two or more different foods. In this respect, a trial has been carried out in 40 patients [124], of which 15 were allergic only to peanut, while 25 were allergic to more foods. The patients received up to 4 g of each food during the maintenance phase, and tolerance was seen to increase 10-fold versus the initial DBPCFC dose. The same authors have conducted a study of desensitization to multiple foods with omalizumab therapy, which allowed a shortening of the dose escalation phase [125].

8.4.3.7. Global metaanalyses

A metaanalysis of 33 case reports and 21 trials (18 RCTs and 3 controlled clinical trials) revealed a substantially lesser risk of allergic food reactions in those individuals subjected to SOTI [relative risk 0.21 (95%CI: 0.12-0.38)]. The immunological data showed a significant decrease in prick test size and an increase in the specific IgG4 titers. The risk of local reactions was seen to increase (in the form of mild oropharyngeal and gastrointestinal manifestations)[relative risk 1.47 (95%CI: 1.11-1.95)], though no significant increase in systemic reactions was observed [relative risk 1.08 (95%CI: 0.97-1.19)]. The authors concluded that there is strong evidence that oral immunotherapy is able to induce immune changes and promote desensitization to different foods. However, oral immunotherapy should not be used outside the defined experimental conditions [126].

9. Safety

The side effects associated to SOTI are generally mild or moderate, with a predominance of oropharyngeal manifestations that are easy to deal with [100–102,127,128]. However, more serious reactions have also been reported, such as generalized urticaria / angioedema, wheezing and dyspnea, laryngeal edema, intense abdominal pain and recurrent vomiting. This latter adverse effect is the most limiting problem, preventing the continuation of SOTI in 10-15% of the patients [129].

There have been reports of eosinophilic esophagitis during the maintenance phase in patients who did not have this problem before SOTI [130]. Although large series report a low incidence (2%), in our experience the problem may be more frequent (10% in a small series of patients). In this respect, the suspicion of eosinophilic esophagitis should be reinforced in cases with classic symptoms of retroesternal pain, dysphagia, or less specific like recurrent cough or digestive discomfort.

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In a study of SOTI with peanut [100], most patients suffered some symptoms. During the first day of the up-dosing phase, two subjects abandoned the study, another two made use of adrenalin, and 47% developed symptoms requiring antihistamines. Symptoms were observed in 1.2% of the 407 doses during the escalation phase. Despite this observation, however, 16 of the 19 patients subjected to SOTI were able to tolerate 4000 mg with only minimal adverse effects. Likewise, in SOTI with cow's milk, 45% of the doses produced symptoms, versus 11% in the placebo group – most manifestations being mild and of an oropharyngeal nature [102]. During the first year of SOTI with egg, 25% of the 11,860 active treatment doses were associated with symptoms, versus 4% of the 4018 placebo doses [127].

The frequency of adverse reactions is 10 times greater if the patient is moreover asthmatic [17].

9.1. Triggering factors

Viral infections, menstruation and physical exercise have been associated with reductions in the tolerance threshold among patients who are already receiving SOTI maintenance doses [131]. The development of other acute disease conditions may also require temporary SOTI dose adjustment [101]. In a long-term SOTI follow-up study, 22% of the patients with allergy to cow's milk who had previously completed SOTI and had passed provocation testing with the food reported limitations in milk intake due to symptoms often associated with physical exercise (25%) and disease processes (6%) [132].

Rush-type SOTI protocols designed to shorten the interval required to reach maintenance therapy have been associated to an increase in the incidence of undesired symptoms and adrenalin use [103,101, 133, 134].

9.2. Prevention

It is advisable to avoid physical exercise in the hours before and after administration of the dose, and to temporarily reduce the amount ingested by 50% in the case of viral disease or respiratory symptoms. It is also advisable to administer the dose with other foods in order to avoid gastrointestinal adverse effects.

Antihistamines have been used as premedication, and a study has used antileukotrienes to control the gastrointestinal manifestations [135].

Thus, SOTI appears to be effective in securing desensitization, but it is not without risks. Different metaanalyses indicate that the existing body of information is still insufficient to guarantee the efficacy of the technique, and concern is still expressed about the safety of SOTI. In this respect, further studies are recommended before considering transfer of the technique from the experimental setting to clinical practice [115,116,126,136–138].

10. Long-term outcome

Does desensitization to a food imply long-term tolerance or only temporary tolerance?

Although a considerable number of years have gone by since the first inductions of oral tolerance to food were performed, few controlled studies have examined what happens after several years of SOTI. Such information is crucial in order to define the frequency with which full tolerance is achieved, as well as to identify the underlying patient-related factors involved, and characterize the different desensitization options.

A communication published in 2005 [139] reported the loss of tolerance in two patients after a two-month exclusion period following tolerance of the allergen maintenance dose during several months (cow's milk allergy with 27 weeks of tolerance of the 100 ml dose in one case, and egg allergy with 39 weeks of tolerance of half an egg in the other). In turn, a third patient who took 52 weeks in reaching the maximum dose again developed symptoms after four weeks of exclusion. In these individuals the specific IgE titers did not exceed class IV. The authors postulated that tolerance is dependent upon a series of variables such as the baseline tolerance level, the duration of SOTI, the elimination diet involved, and the course of the illness at individual level. Patients with a low probability of natural remission of their allergy may require long-term maintenance therapy. There is little information on the interval between the doses in the maintenance phase needed in order to preserve the acquired tolerance, though for safety reasons, daily intake should be recommended.

A study published in 2007 [140] reported the follow-up data corresponding to four patients who had undergone desensitization to cow's milk three years earlier. Three of them were found to have no detectable levels of specific IgE against casein, and presented no symptoms during intake – though no exclusion period followed by reintroduction of the allergen had been applied to ensure definitive tolerance.

The first long-term follow-up study on patients with cow's milk allergy [141] revealed that 86% of the individuals reached desensitization (18 out of 21 patients), and tolerance persisted in 14 out of 20 individuals (70%) upon evaluation an average of four years and 8 months after the start of desensitization [142]. In addition, none of the patients needed to use adrenalin.

Since no control groups were established, these studies could not rule out the possibility that tolerance in some of these individuals may have been attributable to natural mechanisms, and were unable to establish whether tolerance persisted after the cessation of daily allergen intake.

In another study [143], 15 patients with successful induction of desensitization to cow's milk were subjected to oral provocation after 13 to 75 weeks with doses of 16 g. This dose was tolerated by 6 of the patients, though here again there was no prior exclusion period. During the follow-up period, adverse reactions were recorded that required adrenalin injection on 6 occasions (0.2% of the doses).

In a much larger patient sample [144], 66 subjects were diagnosed with allergy to cow's milk by DBPCFC (including 44 anaphylactic cases). Initial tolerance was achieved in 64 patients (97%) – complete in 51 (> 150 ml) and partial in 13 (5-150 ml) – and was seen to persist after one year of follow-up, with significant reduction of the specific IgE titers and of the size of the prick test. As in the above studies, tolerance was not evaluated after an exclusion period.

In another study [145], following SOTI with egg or milk during a mean period of 21 months, tolerance as demonstrated by DBPCFC was recorded in 36% of the patients two months after

http://dx.doi.org/10.5772/59105

suspending SOTI. Surprisingly, tolerance in the control group reached 35%, indicating a lack of efficacy of SOTI in achieving tolerance. In another non-controlled study, 7 patients received SOTI with egg [146], and four of them passed DBPCFC testing after 24 months. In turn, two of these four individuals passed a second DBPCFC test three months after suspending SOTI.

The commented relatively low yet promising success rates in inducing tolerance were improved upon in a follow-up study [112] involving a SOTI dosing regimen in which the maintenance dosage was increased stepwise until the levels of specific IgE against egg were < 2 kU/l. At this point DBPCFC was performed, and those patients who passed the test again underwent DBPCFC one month after suspending SOTI. The 6 patients that passed the first test also passed the second test.

Another study [87] first administered sublingual immunotherapy (SLIT) with milk, followed by patient randomization to either continuation with SLIT or conversion to SOTI with two different maintenance doses during 80 weeks. Six weeks after the end of immunotherapy, one of the 10 patients in the SLIT group (maintenance dose 7 mg/day) was found to be tolerant, versus three of the 10 patients administered 1000 mg of milk as maintenance in SOTI, and 5 of the 10 patients administered 2000 mg of milk as maintenance in SOTI. Although this was a non-controlled study with few patients, the results obtained support the idea that higher doses and longer durations of immunotherapy can afford a sustained lack of allergic responses after the end of therapy, or tolerance of the allergen.

A placebo-controlled study of SOTI with egg [127], involving 40 children in the active treatment group and 15 in the placebo group, recorded desensitization in 75% of the patients after 22 months, with a 28% tolerance rate after 24 months as established by DBPCFC performed two months after the end of SOTI. None of the controls passed the provocation test after 10 months, though they were not again subjected to oral challenge after 22 or 24 months – except one subject with specific IgE levels of < 2 kU/l, who failed to pass the test. After 30 to 36 months of follow-up, those patients who had acquired tolerance were seen to retain tolerance. This study suggests that approximately one-quarter of all children with egg allergy achieve tolerance after two years of SOTI – though the absence of provocation testing after two years in the control group may complicate interpretation of the data – particularly in view of the high degree of spontaneous tolerance registered among the controls [147].

In another study, after SOTI and 5 years of maintenance therapy with 4000 mg of peanut, 50% of the patients passed oral provocation testing and were able to incorporate peanut to their diet without restrictions [148].

11. Biological therapies associated to SOTI

In the course of the induction of oral tolerance to foods, patients may experience serious adverse effects (e.g., anaphylaxis) or problems of lesser magnitude but which preclude desensitization in 10-20% of the cases. This raises doubts not only about the safety of such techniques but also as regards their efficacy in application to patients with antecedents of food-

induced anaphylactic reactions, which are precisely the individuals that could benefit most from desensitization or even tolerance.

For these reasons, different authors have recommended the use of a protective "umbrella" during the initial phases, in which IgE-mediated allergic reactions are most frequent, with a view to avoiding at least the most serious incidents.

11.1. Omalizumab

The availability of a humanized anti-IgE monoclonal antibody marked as omalizumab (Xolair®, Genentech / Novartis) has allowed its use to prevent adverse effects – particularly anaphylaxis – in those patients who because of their degree of sensitization or seriousness of previous adverse reactions are at particularly high risk. In addition to improving patient safety, such preventive treatment would result in improved efficacy, since it would allow us to reach doses sufficient to ensure complete desensitization and possible subsequent tolerance [149].

On the other hand, under this type of protection against anaphylaxis, we could shorten the escalation or up-dosing period and even reach doses higher than those previously used.

Omalizumab is a recombinant anti-IgE monoclonal antibody (anti-IgE mAb) with a molecular weight of 150 kDa; 95% of the antibody is derived from human kappa IgG1, to which certain murine complementary determinant regions are coupled. These in turn bind selectively and with high affinity to the CHε3 domain of the Fc of IgE, preventing binding of this domain to the high-affinity IgE receptors ($Fc_{\varepsilon}RI$) of mast cells and basophils – thus inhibiting the release of mediators by these cells through Fab binding to the antigen. Binding to the low-affinity receptors ($Fc_{\varepsilon}RII$) of dendritic cells, T cells, eosinophils and other cells related to allergic inflammation is also inhibited.

The absence of binding to these receptors also down-regulates the expression of IgE receptors ($Fc_{\varepsilon}RI$) on the part of mast cells and basophils, which is dependent upon the levels of IgE. On the other hand, the antigen-presenting cells (APCs), i.e., dendritic cells, also reduce their activity [150], and the formation of Th2 lymphocytes is consequently not stimulated. The basophils also experience a change in activity, paradoxically increasing their sensitivity to the allergen, but maintaining lowered activity in the presence of a specific IgE / total IgE ratio of < 4% [151,152].

The circulating anti-IgE/IgE complexes do not activate complement, and by keeping the antigen-binding fraction free, are able to capture antigens from the bloodstream – preventing them from reaching the specific IgE already bound to the cells.

One week after the start of treatment with anti-IgE mAb, basophil FcεRI expression is strongly suppressed, while mast cell FcεRI expression is suppressed after 10 weeks [153]. This rapid basophil suppression, together with the clinical improvement, reflects the importance of these cells [154,155].

After the first hour of treatment with omalizumab, the free IgE titers in blood decrease linearly with respect to the dose, a maximum effect being observed within 6 days, when more than 96% of the IgE levels are cleared from plasma – though total IgE increases because the half-life

http://dx.doi.org/10.5772/59105

of the IgE-Anti-IgE complex is longer than that of IgE. The half-life of omalizumab is about 3-4 weeks [156].

11.2. Administration regimen and dose

The dose is established according to the instructions of the manufacturer in relation to the total IgE titers and patient body weight. In this regard, the minimum dose is 0.016 IU/kg/IgE (IU/ml)/4 weeks, in fractionated subcutaneous doses if needed [157].

It is estimated that 9 weeks are needed to reach the maximum effect, reduction of IgE and a decrease in the expression of its receptors. A clinical trial involving asthmatic patients found the clinical response to manifest after 16 weeks of therapy in most patients (158], though a study in children and adolescents found the maximum effect to manifest after four weeks of treatment (159,160]. Differences in criterion and patient population may account for this discrepancy. Most studies establish a minimum treatment period of 8 weeks prior to the start of induction therapy. The posterior coverage period varies, but corresponds at least to the interval required to reach the maximum maintenance dose. Treatment cessation has been abrupt, and the protective activity is known to cease completely within about three half-lives (some 9-12 weeks). Stepwise cessation over time and/or dose could result in a prolongation of the protective action without incurring in major costs increments.

11.3. Clinical applications

Soon after the marketing of omalizumab, the use of these anti-IgE antibodies in food allergy was considered [161]. Data evidencing its benefit referred to food tolerance were obtained in patients who received the drug for asthma control, and who were seen to be able to consume a larger amount of foods to which they were known to be allergic. Indeed, the patients were able to start consuming some foods which they were previously unable to consume even in very small amounts.

The usefulness of omalizumab in avoiding IgE-mediated allergic reactions other than allergic asthma, such as for example food allergy, has been evidenced in different studies [162,163]. The drug has been shown to be effective in raising the oral provocation sensitivity threshold among patients with peanut allergy, when used in monotherapy [155,164,165].

The protective activity of omalizumab has been confirmed in immunotherapy for allergic rhinitis [166,167] and asthma [168]. Its utilization in rush immunotherapy [169], involving an increased frequency of systemic adverse reactions, afforded increased protection, including protection against anaphylaxis, when administered during the 9 weeks prior to immunotherapy and then for 12 months concomitant to immunotherapy. In this respect, omalizumab was seen to be superior to the use of antihistamines as premedication. Likewise, increased efficacy of immunotherapy has been documented in patients receiving anti-IgE mAb.

11.4. Clinical trials with omalizumab and SOTI

The above considerations have led to the use of omalizumab pretreatment in food tolerance induction protocols [170]. To date, only non-controlled double-blind pilot studies involving

few patients are available, though several randomized, double-blind, placebo-controlled trials are currently underway.

The first published study to report a possible role for omalizumab administered together with oral immunotherapy in allergic patients [171] assessed the usefulness of the drug in inducing tolerance to cow's milk in the context of a phase I pilot trial involving a small patient sample. Evaluation of the immunological changes revealed the inhibition of cutaneous mast cells and peripheral blood basophils in a non-specific allergen manner during therapy with omalizumab, and in an antigen-specific manner after completing the milk desensitization protocol [172].

Thirteen patients with peanut allergy confirmed by DBPCFC participated in a pilot trial involving pretreatment with omalizumab during 12 weeks, after which the drug was continued in combination with the immunotherapy up-dosing phase for another 8 weeks [173]. This made it possible to increase the initial peanut dose without major side effects, and to shorten the weekly up-dosing phase. With the dose of the first day (992 mg of peanut flour, equivalent to about 2 peanuts), the patients could be protected against anaphylactic reactions caused by accidental ingestion of the allergen. Within 8 weeks, the maintenance dose of 4000 mg was reached in 12 out of 13 patients, with tolerance after 30-32 weeks of 8000 mg as evidenced by DBPCFC – this dose being 160-400 times greater than the dose causing symptoms at first DBPCFC testing. Fifty-four percent of the patients (7 out of 13 individuals) suffered no adverse reactions during the first rush phase, while the rest experienced grade 1 effects requiring antihistamine use in only two patients. During the weekly up-dosing phase, 49 adverse effects were documented, of which 97% corresponded to grade 1 and none to grade 3. During maintenance therapy, without the administration of omalizumab, a total of 17 adverse effects were recorded, two of which corresponded to grade 3. Those patients that experienced adverse effects after suspending omalizumab had higher specific IgE titers both at the end and at the start, as well as a larger prick test size. The prolongation of omalizumab in patients of this kind was thus proposed.

Another non-controlled phase I study used omalizumab during 16 weeks, including 8 weeks as pretreatment, in the induction of tolerance to different foods in combination with oral immunotherapy [174]. This management strategy allowed rapid desensitization using higher starting doses than those used in another trial carried out by the same authors [175], involving up to 5 foods at once, and with no grade 2 (moderate) or grade 3 (severe) symptoms during the up-dosing phase. Adrenalin proved necessary in only one case, during the maintenance phase (representing 0.01% of the administered maintenance doses).

11.5. Side effects of omalizumab

These antibodies have been reported to cause side effects [156,157] – the most important being local inflammatory reactions. Anaphylaxis has been reported in 0.2% of the patients. It has been suggested that such treatment should be administered in an appropriate healthcare setting, with an adequate period of observation after administration (2 hours on the first occasion and half an hour with the subsequent doses), with the availability of preloaded

http://dx.doi.org/10.5772/59105

adrenalin [176,177]. A recent study has observed no increased risk of tumors associated to long-term treatment [178]. In contrast, the risk of parasitic infestations appears to increase; treatment in high-prevalence areas therefore should be restricted.

Another very important aspect to be taken into account is the cost-effectiveness ratio, with a view to ascertaining whether the treatment is acceptable from the healthcare and insurance perspectives. No such data referred to the specific therapeutic indication of food allergy have yet been obtained, however.

Further clinical data are currently needed, involving double-blind, placebo-controlled trials, as well as cost-effectiveness analyses, in order to establish the recommendations for use in concrete patient groups as treatment in combination with SOTI, such as for example:

- Patients at particularly high risk due to increased sensitivity (usually associated to increased clinical reactivity) and/or who have suffered serious reactions to the food allergen
- Patients unable to reach levels considered necessary to ensure desensitization
- Protocols involving a rush phase and rapid up-dosing
- Patients undergoing desensitization to several foods at the same time

11.6. Interferon-γ and SOTI

Few data are available on the usefulness of interferon-γ in combination with SOTI, though the preliminary results are encouraging [179].

12. Conclusion

Immunoglobulin E-mediated food allergy in high risk patients or in individuals with a poor prognosis in terms of tolerance may benefit from new immunotherapeutic techniques such as SOTI. The advantages of SOTI are a great decrease in the risk of serious allergic reactions in patients with particularly severe food allergy, and the possibility of introducing such foods in the patient diet – with the resulting improvement in quality of life. Further studies are needed to better characterize those patients most amenable to effective SOTI, establish the required duration of therapy, define the immunological markers for assessing the course of treatment, the role of associated biological therapies and draft safe and effective consensus-based protocols and guides, before transferring desensitization to the general clinical practice setting.

There is evidence that this new approach is changing the management paradigm in food allergy, and in our opinion, like other authors [180], possibly it´s time for the practice of SOTI in medical centers with medical staff trained and under secure supervision of his risks.

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