

Oral immunotherapy for the treatment of food allergy

Ee Lyn Su

Mimi LK Tang

Abstract

In the absence of a curative treatment, patients with food allergy continue to live with the risk of accidental exposure to food allergens and the possibility of severe allergic reactions. Over the last 5 years, research in the area of immunotherapy for food allergy has intensified. Although this novel therapeutic option has not reached routine clinical practice, results from immunotherapy studies have yielded encouraging results. In this review article, we will discuss the immunological mechanisms involved in tolerance induction and the clinical efficacy and safety of oral and sublingual immunotherapy for food allergy.

Keywords desensitization; food allergy; oral immunotherapy; oral tolerance; peanut allergy; sublingual immunotherapy

Introduction

Over the last decade, there has been a growing body of evidence pointing towards an increasing prevalence of food allergy and anaphylaxis in westernized countries. In the United Kingdom, hospital admissions for food allergy and anaphylaxis increased by 500% and 700% respectively between 1990 and 2004. Similar trends have been observed in Australia.

Early studies suggested rapid resolution of cow's milk and egg allergy by school age, however more recent data indicates that children may not outgrow these food allergies until well into their teenage years. Rates of resolution for egg and cow's milk allergy were 68% by 16 years and 64% by 12 years respectively. Only 20% of children outgrow their peanut allergy by early school age.

Currently, there is no curative treatment for food allergy, and management involves strict avoidance of the food allergen, education regarding the recognition and emergency management of allergic reactions, and the provision of a self-injectable

adrenaline device for those who have had a previous anaphylactic reaction or have risk factors for anaphylaxis. This strategy is not optimal as the risk of allergic reactions from accidental ingestion is 58% within 5 years and 75% within 10 years, and even small amounts of food allergen can cause a serious reaction. Given the daily discipline required for food avoidance and constant anxiety surrounding the possibility of serious allergic reactions, it is understandable that for many, the psychosocial impact of living with a food allergy is significant.

Despite significant advances in the diagnosis and understanding of allergic responses at the molecular level, an effective curative treatment for food allergy remains elusive. Efforts to understand the immune mechanisms that determine acquisition or loss of oral tolerance have intensified and a breakthrough in this area of research will pave the way for development of preventative and therapeutic strategies. Recently, studies have focused on immunotherapy as a novel treatment for food allergy.

Immunological mechanisms of tolerance

Food allergy is thought to be the consequence of breakdown in or failure to achieve oral tolerance. 'Oral tolerance' has been defined as the suppression of cellular and humoral immune responses to an antigen following prior administration of the antigen by the oral route. The gut associated mucosal immune system closely regulates the balance between induction of tolerance to dietary proteins and commensal organisms, and active immunity to pathogenic organisms.

T regulatory (Treg) cells play a central role in the induction and maintenance of oral tolerance (Figure 1). There is growing evidence that in food allergy, there is a failure of Treg activity, allowing induction of Th2 responses that in turn propagate the allergic response.

Several Treg subsets have been identified including naturally occurring (thymus derived) and peripherally induced CD4⁺CD25⁺ forkhead box (FoxP3)⁺ Tregs, transforming growth factor (TGF)- β -producing Th3 cells and interleukin-10 secreting type 1 regulatory T (Tr1) cells. Tregs mediate their suppressive effects through cell-cell contact and/or secretion of the anti-inflammatory cytokines TGF- β and IL-10. The Treg cytokine TGF- β is an inhibitor of lymphocyte proliferation, Th1 and Th2 differentiation, and together with IL-10, switches antibody production to the non-inflammatory isotypes IgA and IgG4, respectively.

Allergen specific immunotherapy for aeroallergen or insect sting allergy is effective for the induction of tolerance to the specific allergen(s) concerned. Such treatment has been shown to induce allergen-specific CD4⁺CD25⁺ Tregs and to result in reduced allergen-specific IgE, elevated allergen-specific IgG4, and corresponding reduction of Th2 and increase in Th1 cytokine production. More recently, allergen-specific immunotherapy has been investigated as a promising treatment for food allergy with the aim of restoring tolerance.

Allergen specific immunotherapy for food allergy

Two therapeutic outcomes can be achieved after a period of immunotherapy – *tolerance* describes the long lasting ability to ingest a particular food allergen despite cessation of regular immunotherapy treatment and is considered to involve reprogramming of the immune response to allergen; whereas

Ee Lyn Su MBBS is a Allergy and Immunology Fellow in the Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia. Conflict of interest: none.

Mimi LK Tang MBBS PhD FRACP FRCPA is Director of the Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia; Group Leader, Allergy and Immune Disorders, Murdoch Childrens Research Institute (MCRI), Melbourne, Australia; and Associate Professor, Department of Paediatrics, University of Melbourne, Victoria, Australia. Conflicts of interest: MT is a member of Medical Advisory Boards for Nestle Nutrition Institute, Wyeth, and Pfizer.

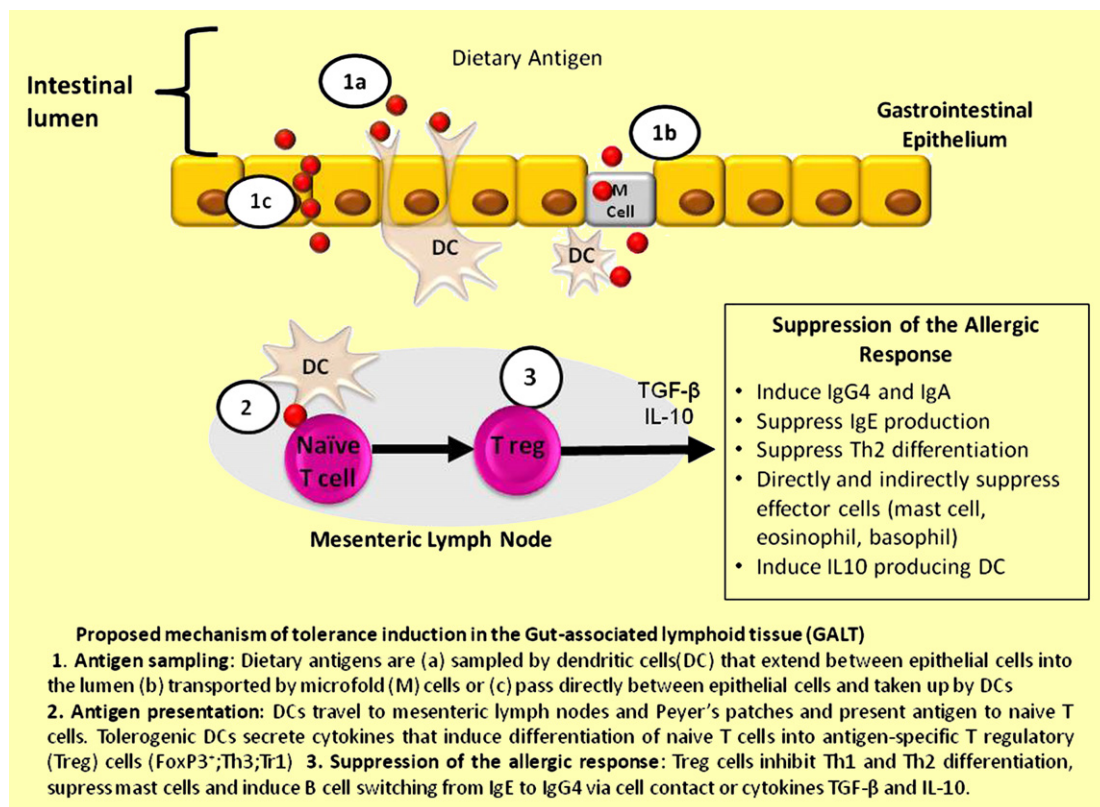


Figure 1

desensitization describes the short term ability to ingest higher doses of allergen without reaction, without altering the underlying allergic response to the food allergen. Desensitization is only maintained with ongoing regular administration of the immunotherapy or food, and is lost when the immunotherapy or food is discontinued.

Subcutaneous immunotherapy (SCIT)

Pioneering studies of SCIT for the treatment of food allergy showed that SCIT was effective in inducing desensitization. Nevertheless, a high rate of serious adverse events was observed and hence this approach has been abandoned.

Investigation of peptide immunotherapy as an approach to improve the safety of SCIT for food allergy is ongoing. In the pursuit of novel candidates for peanut immunotherapy, Prickett et al have recently identified peptide sequences of the major peanut allergen, Ara h 2, that are recognized by CD4⁺ T cells but are too short to cause cross linking of IgE on mast cells. Compared to immunotherapy using whole peanut, peptide immunotherapy is proposed to have the advantage of stimulating CD4⁺ T cell responses necessary for induction of tolerance, whilst avoiding IgE mediated allergic reactions. Development of recombinant engineered food allergens for subcutaneous immunotherapy is also being pursued and results from preclinical trials are promising.

Sublingual immunotherapy (SLIT)

Sublingual immunotherapy (SLIT) has also been evaluated for the treatment of food allergy. In SLIT, an allergen preparation is delivered to the sublingual region and must be held there for 2–5 min before swallowing or expelling. SLIT has been shown to be

effective for the treatment of aeroallergen allergy and fewer allergic adverse reactions have been observed with SLIT as compared to SCIT suggesting that this approach may be safer than SCIT for the treatment of food allergy. The first report of SLIT in a subject with kiwi allergy suggested tolerance induction although this was not specifically assessed. Subsequently, three randomized controlled trials of SLIT (hazelnut, peach and peanut) have been reported. All three RCT have demonstrated partial or complete desensitization. Immunological changes were also observed, including decreased allergen-specific IgE, increased allergen-specific IgG4 and reduction in Th2 cytokines, suggesting the potential ability for tolerance induction. A non-significant increase in CD4⁺CD25⁺FoxP3⁺ Tregs was also reported in one study. The ongoing peanut SLIT study will formally assess for tolerance and results should be available in a few years.

Oral Immunotherapy (OIT)

Given the high rates of systemic reaction during SCIT, OIT has been explored as a means for inducing tolerance to food allergens. Indeed, OIT is considered a logical approach to inducing tolerance to food allergens given the primary role of the intestinal mucosal immune system. Although a standardized protocol has yet to be developed, most studies have administered a powdered allergen (mixed with a food vehicle), once daily, in three phases: rush, buildup and maintenance (Figure 2). In the following section, we discuss the various OIT studies that have assessed for the study outcome of desensitization and those that have assessed for acquisition of tolerance separately. Table 1 provides a summary of the main OIT studies.

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