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Review

Oral immunotherapy for food allergy

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ABSTRACT

Food allergy is a pathological, potentially deadly cascade of immune responses to molecules or molecular fragments that are normally innocuous when encountered in foods, such as milk, egg, or peanut. As the incidence and prevalence of food allergy rise, the standard of care is poised to advance beyond food allergen avoidance coupled with injectable epinephrine treatment of allergen-induced systemic reactions. Recent studies provide evidence that oral immunotherapy may effectively redirect the atopic immune responses of food allergy patients as they ingest small but gradually increasing allergen doses over many months, eliciting safer immune responses to these antigens. Research into the molecular and cellular bases of pathological and therapeutic immune responses, and into the possibilities for their safe and effective modulation, is generating tremendous interest in basic and clinical immunology. We synthesize developments, innovations, and key challenges in our understanding of the immune mechanisms associated with atopy and oral immunotherapy for food allergy.

1. Introduction

Food allergy affects 8% of children and 5% of adults in the U.S. [1,2], and epidemiological data generally indicate an increase in its prevalence [2]. However, the current standard of care for all food allergies is minimal, consisting of food-allergen avoidance and emergency treatment of potentially fatal allergen-induced systemic reactions with injectable epinephrine; the constant risk of severe allergic reaction adversely impacts the quality of life of food-allergy patients and their families. The growing, global, unmet need for safe and effective treatment can best be met by understanding the cellular and molecular mechanisms of promising immunotherapeutic approaches under clinical investigation [3].

The mechanistic role of IgE in atopic immune responses provides a useful distinction among types of food allergy: IgE-mediated food allergy is characterized by acute, potentially life-threatening immune responses, while non-IgE-mediated food allergy is driven by slower, cell-mediated responses. This review focuses on IgE-mediated food allergy, in which food allergen epitopes bind to IgE molecules which also bind FcεRI receptors on immune effector cells, such as basophils, mast cells, and antigen-presenting dendritic cells. Epitope-specific cross-linking of the IgE-bound receptors results in degranulation of basophils and mast cells, releasing pre-formed histamine and other inflammatory molecules that generate a rapid atopic reaction [4]. Additional inflammatory mediators, such as platelet activating factor, leukotrienes and the cytokines interleukin-4 (IL-4), IL-5, and IL-13, are then produced *de novo*, augmenting the inflammatory immune response [4]. Membrane-bound IgE on B cells also forms a complex with CD23 and CD21, increasing production of soluble IgE [5] and escalating the IgE-mediated immune response. The resulting symptoms may include gastrointestinal responses (*e.g.*, pruritus, abdominal pain, nausea, vomiting), respiratory responses (*e.g.*, airway inflammation, wheezing), dermal responses (*e.g.*, pruritus, angioedema, urticaria), and systemic responses (*e.g.*, hypotension, hypothermia). An anaphylactic response involves multiple organ systems and rapidly may become life-threatening [6].

Recent clinical studies reviewed here provide evidence that oral immunotherapy (OIT) can be used safely and effectively to reduce the sensitivity of food allergy (FA) patients to food antigens (Ag). However, it is not yet clear the extent to which such patients develop desensitization (DS, defined as a lack of clinical reactivity to Ag, the maintenance of which requires regular Ag exposure), as distinct from sustained unresponsiveness (SU), in which the patient exhibits a long-term and perhaps permanent loss of reactivity to Ag that is independent of continued Ag exposure. Novel findings from our group and others are elucidating the mechanisms by which DS and SU are established through OIT.

In OIT, FA study participants ingest small but gradually increasing

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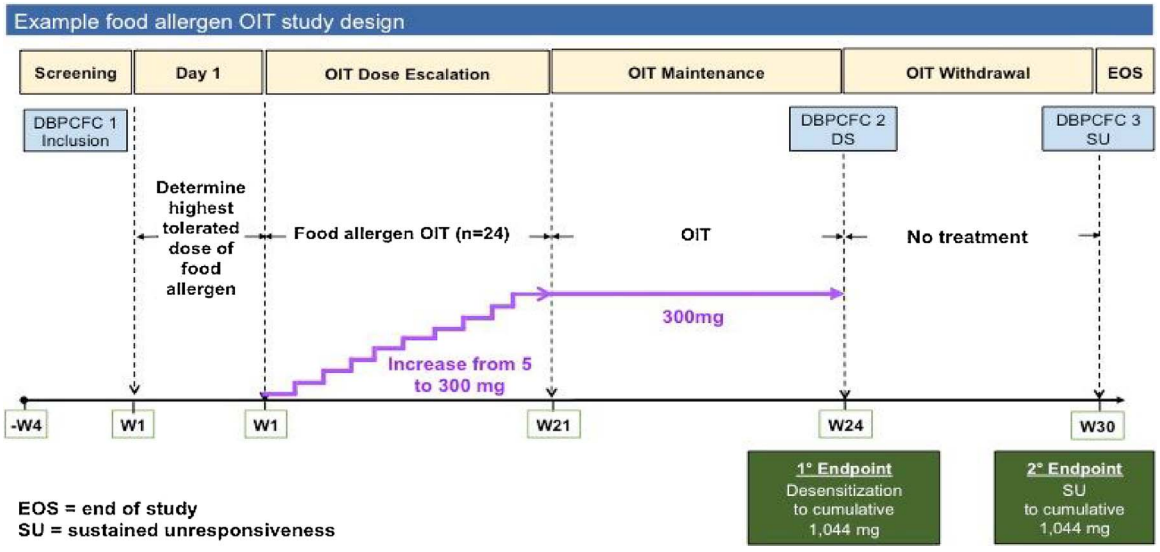

Fig. 1. Example food allergen OIT study design.

doses of specific food Ag over the course of several months, with the goal of progressively retraining their immune responses to establish DS and possibly SU to the Ag (Fig. 1) [7]. Because other FA diagnostic tools, such as measurements of blood levels of Ag-specific IgE and skin-prick tests, are known to generate false positives that could confound research results [8,9], an initial, definitive FA diagnosis is made using a double-blind, placebo-controlled, oral food challenge (DBPCFC) with one or more target Ag. On the first day of OIT, the participant ingests increasing doses of the target Ag under clinical care to determine the highest tolerated dose. After this initial-day dose escalation, the highest tolerated dose is used to begin a dose-escalation phase, in which the dose is increased in a visit to the clinic every 1–2 weeks until the designated maintenance dose is tolerated. Then, during the maintenance phase which ranges from months to years, the participant daily ingests the maintenance dose of the FA. A desensitization DBPCFC is administered in the clinic at the end of the maintenance phase, to assess the efficacy of the treatment protocol. If a statistically significant increase in the tolerated dose to a level that is protective against accidental Ag exposure is found, the OIT is deemed successful. DS, or a reduction in adverse immune response that is maintained through regular Ag exposure, is often achieved through OIT, along with lower risk of anaphylaxis and increased quality of life for FA participants and their families.

To test for SU, an Ag avoidance phase of weeks to months may be added after the termination of OIT, ending with a followup DBPCFC. If the target dose is tolerated after the avoidance phase, the participant has achieved SU to that dose, a reduced immune response to Ag that persists even without continued, regular Ag exposure. Since a DBPCFC is not prospective, the duration and variance of SU are unknown. The mechanisms underlying SU, its potential durability and defeat, and its comparison to healthy tolerance are promising research areas that could be of tremendous benefit to our understanding of healthy, atopic, and therapy-induced immune states.

The field of FA OIT is very active and growing. This review focuses on recent, peer-reviewed studies, prioritizing phase II trials with a placebo arm, clearly defined dosing, and those that required a screening DBPCFC (sDBPCFC) to avoid confounding due to false positive FA diagnoses. We also prioritize studies with associated, long-term followup to assess SU, and associated mechanistic studies. We highlight recent advances in the safety, efficacy, and mechanistic understanding of OIT.

2. Immune mechanisms

The immunological mechanisms of: (1) the establishment and maintenance of a healthy state of immune tolerance to food antigens; (2) food allergy; and (3) desensitization established through OIT are drawing increasing research interest. The evolution of this research is addressed in several recent reviews [10–16]; key features are outlined here. While we focus on food allergy research in humans, we also cite relevant hypotheses based on research in closely related atopic diseases, and in mouse models.

2.1. Tolerance

The variety of cells forming the healthy intestinal epithelium present a selective barrier to food antigens in the intestinal lumen (Fig. 2). Segmented, filamentous bacteria (SFB) and secreted, dimeric IgA promote homeostasis at the luminal surface [17]. SFB may induce IL-17- and IL-22-producing $CD4^+$ T helper cells (Th17) in the lamina propria [18]. In Peyer's patches, Th17 may convert to T follicular helper cells (Tfh) and contribute to IL-21-mediated B-cell homing and secretion of IgA [19].

Food Ag are taken up by absorptive enterocytes [15], and are also sampled directly from the lumen by $CD103^+$ dendritic cells (DC), which can extend a process through the transcellular pore of a microfold (M) cell in a Peyer's patch [20], or through a tight junction between epithelial cells [21]. CX_3CR1^+ macrophages also sample luminal food Ag, and can transfer Ag directly to DC [22,23].

Ag-bearing DC then migrate to a draining lymph node and present antigen to naïve CD4+ T cells, producing TGFβ and retinoic acid to promote the induction of Ag-specific, $FoxP3^+$ regulatory T cells (T_{reg}) [22,24–26]. T_{reg} then express gut-homing markers such as α4β7 and return to the lamina propria [27], where they produce IL-10 and TGFβ, potentially inhibiting mast cell degranulation [28] and sustaining tolerance [10,29]. CX_3CR1^+ macrophages also produce IL-10, contributing to the induction of T_{reg} in the lamina propria [30,31].

2.2. Atopy

Cellular and molecular mechanisms underlying T helper 2 cell-mediated atopic response to food antigens are outlined in Fig. 3. It is possible that exposure to food allergens through a compromised epithelial barrier in the skin may lead to allergic sensitization [32]; atopic dermatitis is the first step of the atopic march to food allergy [33,34]. In