Adjuvant Therapies in Food Immunotherapy

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KEYWORDS

• Food allergy • Adjuvants • Probiotics • Bacterial adjuvants • Omalizumab • Interferon gamma

KEY POINTS

- Although oral immunotherapy (OIT) for food allergy is effective at inducing desensitization, it seems to have a limited ability to induce tolerance and is associated with high rates of adverse reactions.
- Use of an adjuvant with food immunotherapy may reduce adverse reactions and/or enhance tolerance induction (also referred to as sustained unresponsiveness).
- Adjuvants like anti–immunoglobulin E monoclonal antibody and interferon-gamma improve tolerability of OIT by reducing adverse reactions, whereas immune response modifiers such as probiotic bacteria or bacterial components may enhance OIT-induced sustained unresponsiveness.

INTRODUCTION

Currently, food allergy management relies on allergen avoidance and emergency treatment of allergic reactions. Although most reactions are managed effectively, fatalities can rarely occur, with an estimated incidence of approximately 3 per million person-years for children aged 0 to 19 years.[1] The constant vigilance required to maintain food allergen avoidance and the potential for life-threatening reactions result in a reduced quality of life.[2] Finding a curative treatment is imperative to improve quality of life and prevent food allergy–related deaths.

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Allergen immunotherapy has been successfully applied to treat allergic rhinitis, asthma, and venom anaphylaxis. However, an attempt to use subcutaneous immunotherapy for treatment of peanut allergy in the 1990s resulted in high rates of systemic reactions and the approach was abandoned.[3] Subsequently, alternative routes of delivery, such as oral or sublingual immunotherapy (See Christopher P. Parrish and colleagues' article, "Interventional Therapies for the Treatment of Food Allergy," in this issue.), use of modified allergens (See Melissa L. Robinson and Bruce J. Lanser's article, "The Role of Baked Egg and Milk in the Diets of Allergic Children," in this issue.), and cotreatment with adjuvants to reduce adverse reactions or improve efficacy have been investigated with varying results. This article discusses the use of adjuvants to improve the safety and/or effectiveness of food immunotherapy.

IDENTIFYING AN OPTIMAL OUTCOME: DESENSITIZATION VERSUS SUSTAINED UNRESPONSIVENESS

Potential food allergy treatments can offer 2 possible outcomes: desensitization or tolerance. Desensitization is defined as an increase in the threshold for reaction and requires continued regular allergen exposure.[4] This clinical unresponsiveness is temporary and lasts only while allergen ingestion is maintained. Tolerance is the state of prolonged immune unresponsiveness that persists after withdrawal of the allergen for a period of several weeks or months. There is currently no consensus on the duration of secondary allergen elimination required to accurately identify tolerance. Consequently, the term *sustained unresponsiveness* (SU) has been introduced to describe the state of unresponsiveness after a period of secondary avoidance following food immunotherapy[5] and is the preferred term when describing food immunotherapy trial outcomes.

There is a lack of consensus regarding the ultimate goal of immunotherapy. Desensitization offers the individual protection against accidental ingestion to limited amounts of food allergen, however, they remain allergic to the food allergen; hence, reactions can and do occur, including to previously tolerated doses. In the case of oral immunotherapy (OIT), approximately 65%-75% of desensitized individuals reported frequent and often severe allergic reactions to previously tolerated doses.[6,7] Furthermore, approximately 50% of desensitized individuals were unable to continue regular allergen intake because of adverse reactions.[7] Another limitation of desensitization as a treatment outcome is that protection can be lost over time.[7] It is, therefore, uncertain whether desensitization offers an improvement for individuals with food allergy compared with allergen avoidance. Achieving tolerance or SU would seem to be the preferred treatment outcome following food immunotherapy, as this would theoretically allow consumption of unrestricted amounts of the allergenic food ad libitum without a reaction.

LIMITATIONS OF ORAL IMMUNOTHERAPY AS A POTENTIAL TREATMENT OF FOOD ALLERGY

Cumulative evidence confirms that OIT is effective at inducing desensitization in most peanut, egg, and milk allergic patients[8,9]; however, SU is only achieved in about a third of patients following peanut, egg, or milk OIT.[8] Furthermore, OIT-induced SU seems to be short-lived, with 50% of subjects who achieved SU at 3 months after peanut OIT losing SU by 6 months after treatment.[10,11] Suppression of the allergen-specific immunologic response similarly seems to be transient.[12]

Adverse events with OIT are frequent. Reactions requiring adrenaline occur more frequently than with dietary avoidance.[9] Up to 20% of participants fail to reach the