Clinical Commentary Review

Immunotherapy for Food Allergy: Are We There Yet?

Yael Gernez, MD, PhD[a,b], and Anna Nowak-Węgrzyn, MD, PhD[a] *New York, NY*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: March 1, 2017. Credit may be obtained for these courses until February 28, 2018.

Copyright Statement: Copyright © 2017-2019. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Yael Gernez, MD, PhD, and Anna Nowak-Węgrzyn, MD

Learning objectives:

1. To describe current approaches to food immunotherapy under study.
2. To understand efficacy and side effects for various routes of food immunotherapy.
3. To distinguish desensitization from permanent tolerance.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: A. Nowak-Wêgrzyn has received consultancy fees from Neste and Nutricia; has received research support from National Institute of Allergy and Infectious Diseases, Food Allergy Research and Education, DBV Technologies, Nestle, Nutricia, and ThermoFisher; has received lecture fees from Nestle and ThermoFisher; has received royalties from UpToDate; and received payment for development of educational presentations from Anneberg Center at Eisenhower and Nestle. Y. Gernez declares no relevant conflicts of interest.

Current clinical research focuses on food allergen-specific immunotherapy through oral (OIT), sublingual (SLIT), or epicutaneous (EPIT) routes. Immunotherapy relies on the delivery of gradually increasing doses of specific allergens to induce desensitization (defined as temporary antigen hyporesponsiveness that depends on regular food ingestion) and, ultimately, tolerance (defined as the ability to ingest food without symptoms despite prolonged periods of avoidance or irregular intake). Although the majority of the patients treated with OIT achieve desensitization, only a minority achieves tolerance. OIT involves higher maintenance doses of food protein (300 mg-4g) compared with SLIT (2.5-7.5 mg) and EPIT (250-500 mcg). OIT efficacy is higher compared with SLIT, but OIT is associated with higher rate of systemic adverse events compared with SLIT and EPIT. OIT is also associated with a minor risk of eosinophilic esophagitis. Combined treatment of OIT and anti-IgE monoclonal antibody has improved safety but not efficacy compared with OIT alone. Early initiation of peanut OIT in peanut-allergic infants and young children may afford superior efficacy and safety. In this review, we discuss the allergen-specific strategies currently explored for the treatment of food allergy, including immunotherapy with native and heat-modified food proteins. Additional research employs strategies to improve the safety and efficacy of allergen immunotherapy through modifications of allergen structure and addition of immunomodulatory adjuvants. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:250-72)**

Key words: *Food allergy; Immunotherapy; Food immunotherapy; OIT; Oral immunotherapy; SLIT; Sublingual immunotherapy; EPIT; Epicutaneous immunotherapy*

[a]Division of Allergy and Immunology, Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, Kravis Children's Hospital, New York, NY

[b]Division of Immunology, Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

No funding was received for this work.

Conflicts of interest: A. Nowak-Węgrzyn has received consultancy fees from Neste and Nutricia; has received research support from National Institute of Allergy and Infectious Diseases, Food Allergy Research and Education, DBV Technologies, Nestle, Nutricia, and ThermoFisher; has received lecture fees from Nestle and ThermoFisher; has received royalties from UpToDate; and received payment for development of educational presentations from Anneberg Center at Eisenhower and Nestle. Y Gernez declares no relevant conflicts of interest.

Received for publication September 27, 2016; revised November 23, 2016; accepted for publication December 19, 2016.

Corresponding author: Anna Nowak-Węgrzyn, M.D., Ph.D., Division of Allergy and Immunology, Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, Kravis Children's Hospital, New York, NY. E-mail: anna.nowak-wegrzyn@mssm.edu.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaip.2016.12.004

Abbreviations used
AE- Adverse event
AR- Allergic rhinitis
DBPC- Double-blinded placebo-controlled
DBPCFC- Double-blinded placebo-controlled food challenge
EoE- Eosinophilic esophagitis
EPIT- Epicutaneous immunotherapy
FA- Food allergy
GI- Gastrointestinal
HydE- Hydrolyzed egg
OFC- Oral food challenge
OIT- Oral immunotherapy
QoL- Quality of life
SLIT- Sublingual immunotherapy
SPT- Skin prick test
SCD- Successfully consumed dose
SU- Sustained unresponsiveness
Treg- T regulatory cell
VP100- Viaskin peanut 100 μg
VP250- Viaskin peanut 250 μg

Food allergy (FA) is a global health problem affecting approximately 5% of adults and 8% of young children.[1] IgE-mediated FA is associated with risk of fatal anaphylaxis, yet there is no currently approved immunomodulatory treatment. Food avoidance and immediate treatment of anaphylactic reactions with epinephrine remain the mainstay of management.[2,3] However, accidental exposures are common and food avoidance has been shown to decrease the quality of life (QoL).[4,5] There is, therefore, an unmet need for effective therapies. In the past decade, significant advances have been made in the field of specific food immunotherapy, including oral (OIT), sublingual (SLIT), and epicutaneous immunotherapy (EPIT).[3]

Allergen immunotherapy entails a risk of an allergic reaction. Indeed, in the 1990s, a high rate of systemic reactions occurred with peanut subcutaneous immunotherapy (SCIT) in peanut-allergic adults.[6] Therefore, subsequent studies have focused on alternative routes of delivery or modification of allergic proteins to improve safety and efficacy.

In this review, we discuss allergen-specific strategies currently explored for the treatment of FA, including immunotherapy with native and modified food proteins. Figure 1 summarizes diverse therapies undergoing active investigation.[7-15]

OUTCOMES OF FOOD IMMUNOTHERAPY: DESENSITIZATION VERSUS TOLERANCE

Food immunotherapy entails the delivery of gradually increasing doses of allergens with the objective of inducing desensitization, and ultimately, tolerance (Figure 2). Desensitization is a state of temporary antigen hyporesponsiveness that develops relatively early during immunotherapy. Desensitization depends on regular food exposure; when dosing is interrupted (eg, due to illness or nonadherence), the protective effect of desensitization is lost. The exact mechanism underlying desensitization is not well understood, but there is an increase in allergen-specific IgG_4 antibodies, observed as early as 8 weeks after starting OIT, followed by decreases in specific IgE.[16-19] Basophil activation is suppressed by IgG antibodies, and this inhibition can be blocked by antibodies against FcγRII.[20] Peanut OIT induces hyporesponsiveness in basophils consistent with pathway-specific anergy previously described *in vitro*, suggesting that effector cell anergy could contribute to clinical desensitization.[21]

In the rapid high-dose milk OIT combined with 8 weeks of omalizumab pretreatment, within a week of starting OIT, the $CD4^+$ T-cell response to milk was nearly eliminated, suggesting anergy or deletion of milk-specific $CD4^+$ T cells, with no detectable increase in T regulatory cells (Tregs).[19]

Permanent tolerance is defined as the ability to ingest food without symptoms despite prolonged periods of avoidance or irregular intake. Potential mechanisms underlying oral tolerance are presented in Figure 3.

Because there is no agreement on the exact period of food avoidance after treatment, defining tolerance, the studies report on sustained unresponsiveness (SU) as a surrogate for permanent oral tolerance.[10,11,17,22-33]

MECHANISMS OF OIT

An overview of the immune changes associated with OIT is presented in Figure 4.

Effector cells

In the early stage of OIT, a decrease in nonspecific reactivity of basophils and mast cells is observed.[10,25,28,33-37] The decrease in basophil and mast cell reactivity could be secondary to a decreased surface expression of high-affinity IgE receptors[38] or generation of IgG blocking antibodies.[20]

Humoral changes

OIT is associated with reduced serum levels of food-sIgE and increased levels of food-$sIgG_4$ and -IgA.[10,25,28,33-37,39,40] Peanut OIT is associated with an increased frequency of peripheral blood peanut-binding B cells expressing mutated and isotype-switched antibodies.[41]

T lymphocytes

Increased Tregs have been observed from 9 to 32 months after starting OIT,[42] but the exact changes in induced T-effector cells remain unknown. Successful OIT caused an expansion of allergen-specific $CD4^+$ T cells and shift toward an anergic Th2 phenotype, largely absent in pretreatment allergic subjects and healthy controls.[43] Similarly, within 1 week of starting a high-dose rapid milk OIT after 8 weeks of omalizumab pretreatment, the $CD4^+$ T-cell response to milk was greatly reduced, indicating anergy or deletion of milk-specific $CD4^+$ T cells.[19]

OIT TO NATIVE FOOD PROTEINS

OIT utilizes the pathways underlying oral tolerance that is the physiologic response to ingested food proteins. Although there is considerable variability among the published trials, most OIT protocols include 3 phases: (i) an initial dose escalation day (up to 8 doses in 1 day), followed by (ii) a gradual build-up every 2 weeks until a target dose is reached (usually within 6-12 months), and (iii) maintenance dose (months-years) (Figure 2). Although many trials established desensitization as the primary outcome, fewer have evaluated permanent tolerance, referred to as SU.[10,11,17,22-33] Table I summarizes selected clinical trials of peanut, milk, egg, and wheat OIT.

Download English Version:

https://daneshyari.com/en/article/5647360

Download Persian Version:

https://daneshyari.com/article/5647360

Daneshyari.com