Summary of the 2008 National Institute of Allergy and Infectious Diseases–US Food and Drug Administration Workshop on Food Allergy Clinical Trial Design

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This article summarizes the proceedings of a 2008 Workshop on Food Allergy Clinical Trials Design co-organized by the National Institute of Allergy and Infectious Diseases and the US Food and Drug Administration. The use of food allergens both as therapy and for oral food challenges is associated with a risk of anaphylaxis. Investigators are strongly encouraged to address regulatory considerations by discussing proposed studies with the US Food and Drug Administration. Food allergen administration through the oral or sublingual routes might be less risky than through the subcutaneous route, but this hypothesis has not been proved, and subjects with food allergy might still be at high risk of allergic reactions to such allergen administration. Two distinct mechanisms might lead to beneficial clinical outcomes: desensitization (reversible when food allergen therapy is stopped) and tolerance (persistent benefit even after allergen therapy is stopped). There are important clinical distinctions between desensitization and tolerance. The efficacy of a therapy for food allergy can be evaluated by assessing changes in the dose response to double-blind, placebo-controlled oral food challenges before and after therapy and also by assessing changes in the number of allergic episodes during a longitudinal natural history/exposure study; both approaches have strengths and limitations. (J Allergy Clin Immunol 2009;124:671-78.)

Key words: *Food allergy, clinical trials, clinical trial design, oral food challenge, precautions, prevention, treatment, tolerance, desensitization*

This article is the first in a 2-part series dealing with clinical trial design: considerations and potential challenges. This first article summarizes the recent National Institute of Allergy and Infectious Diseases (NIAID)–US Food and Drug Administration (FDA) Workshop on Food Allergy Clinical Trial Design. The second article will summarize policies and procedures that apply to NIAID-funded clinical trials and provide guidance to investigators on how to navigate this complex process.

Abbreviations used

AIC:	Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate
CMC:	Chemistry, manufacturing, and controls
DBPC:	Double-blind placebo-controlled
FDA:	US Food and Drug Administration
IND:	Investigational new drug
NIAID:	National Institute of Allergy and Infectious Diseases
NIH:	National Institutes of Health
SPT:	Skin prick test

Food allergy is emerging as a major public health problem that affects 3% to 4% of adults and 6% to 8% of children in the United States and has been increasing in prevalence over the past several decades.[1] In 2007, 3 million children younger than 18 years were reported to have had a food allergy reaction in the previous 12 months, and from 1997 to 2007, the prevalence of reported food allergy increased 18% in this group of children.[2] Food allergy is associated with severe reactions and is the most common cause of emergency department visits for anaphylaxis.[3] Even though subjects with food allergy attempt to avoid known allergens, reactions from unintentional exposure are relatively common. In a 2-year period, approximately 50% of subjects with food allergy will have an unintentional exposure that leads to an allergic reaction.[4] Allergies to peanuts and tree nuts, the most common causes of life-threatening allergic reactions, persist throughout life in the majority of individuals. There are no current treatments other than food allergen avoidance and symptomatic treatment of adverse reactions. Recently, several clinical trials to prevent and treat food allergy have been supported by funding from the NIAID. These trials have often used allergenic foods as the therapeutic intervention and oral food challenges to measure desensitization, tolerance, or both as an end point.

On March 13-14, 2006, in response to a requirement of the Food Allergen and Consumer Protection Act of 2004 (Public Law 108-282), a National Institutes of Health (NIH) Expert Panel on Food Allergy Research (http://www3.niaid.nih.gov/topics/foodallergy/research/reportfoodallergy.htm) was convened. The panel recommended that the NIH and the FDA meet to identify challenges to the design and conduct of clinical trials for the prevention and treatment of food allergy. In response to this recommendation, the NIAID and the FDA co-organized a workshop, held on June 16, 2008, to discuss food allergy clinical trial design. The goals of this workshop were to examine the design of clinical trials for the prevention and treatment of food allergy, as well as the various factors that should be considered when designing such trials. For the purpose of this workshop summary, food allergy is defined as

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an immune-mediated adverse reaction to food, thus representing a subset of all adverse reactions to food.[5] This working definition excludes subjects who are sensitized to foods but are clinically asymptomatic. Although this broad definition includes reactions mediated by any immune mechanism, the reactions of greatest concern are those mediated by IgE antibodies because such reactions are associated with a risk of anaphylaxis, which can be life-threatening. The issues discussed at this workshop largely focused on food allergy mediated by IgE antibodies to food allergens.

RECENT ADVANCES IN FOOD ALLERGY RESEARCH

Research into the immunologic mechanisms that bring about the natural tolerance to food and how these mechanisms are perturbed in subjects with food allergy has significantly increased our understanding of these processes. Because most individuals are naturally tolerant to food, there has been substantial interest in treating food allergies by inducing tolerance. Clinical tolerance induction in human subjects has been defined operationally as inducing unresponsiveness to an antigen that persists for a long time after the therapy has been discontinued. Subcutaneous allergen immunotherapy to treat aeroallergen-induced rhinitis or insect venom–induced systemic allergic reactions results in amelioration of allergen-induced symptoms that lasts for years. However, the immune mechanisms that underlie tolerance induction are not fully understood. Moreover, it is not known whether tolerance induced by immunotherapy and "natural" tolerance to foods that lasts a lifetime share a common mechanism.

The development of food allergy in neonates is likely to arise from a combination of genetics, exposure to foods, changes in gut permeability, and exposure to microbial products. This exposure can occur as a consequence of direct ingestion of the food, as well as ingestion of breast milk from mothers who have consumed the food, and inhalation or skin contact with dust containing allergen.[6,7] Neonatal sensitization through ingestion alone does not explain the development of food allergy because the natural consequence of exposure to new foods is tolerance. Additional factors, such as decreased gastrointestinal barrier function, mucosal barrier function, or both; overexpression of T_H2-biasing cytokines, such as IL-4, IL-5, IL-13, and, in some models, thymic stromal lymphopoietin; and defective regulatory T-cell responses are probably needed to bias the host response toward sensitization rather than tolerance. The intrinsic properties of the food allergens, such as resistance to digestive enzymes or immunologic cross-reactivity with aeroallergens, as well as the presence of immunostimulatory factors in the food, contribute to whether food allergens can directly induce allergic immune responses. For example, the major glycoprotein allergen from peanuts, Ara h 1, is a ligand for the pattern-recognition receptor dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin and acts as a T_H2 adjuvant *in vitro*.[8] This T_H2 adjuvant activity is dependent on the Ara h 1 glycan adduct, which might also serve to target the entire Ara h 1 glycoprotein to dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin–expressing dendritic cells. The intrinsic protease activity of foods such as papaya and the presence of chitin in foods such as shellfish might also contribute to allergic sensitization through their immunostimulatory properties.

In contrast, early exposure to foods might prevent the development of food allergy under some conditions. One ongoing longitudinal clinical trial currently supported by the NIAID compares the incidence of peanut allergy at 5 years of age in groups of infants who avoid peanuts in their diet for more than 4 years versus infants who regularly consume peanut-containing foods. The rationale for this study is based on the observation that Israeli children, who frequently consume a popular peanut snack beginning before age 1 year, have a 10-fold lower prevalence of peanut allergy compared with children in the United States and United Kingdom.[9,10]

Allergen-specific immunotherapy could be a successful treatment for food allergy, although to date, its effectiveness has been largely demonstrated for allergic diseases caused by aeroallergens and insect venoms.[11,12] Successful immunotherapy to aeroallergens and insect venoms appears to work in 2 ways. There is a short-term improvement in symptoms (lasting up to several months) that might be related to the level of allergen-specific IgG antibody, although increased levels of regulatory T-cell products, such as IL-10 and TGF-β, have also been observed. Long-term improvement (lasting >1 year and probably at least 2 or 3 years) is considered to be true tolerance and has not generally been correlated with the levels of allergen-specific IgG antibody.[13] More recent studies have reported that long-term improvements were paralleled by significant changes in the levels of some subsets of allergen-specific IgG4 and IgA antibodies.[14] It should be noted that the short-term effects are as clinically beneficial as the long-term effects. It is generally believed that long-term successful allergen immunotherapy arises as a consequence of inducing tolerance through several possible mechanisms. These include induction of anergy in allergen-specific effector or memory T cells, deletion of allergen-specific T cells from the repertoire, and activation of regulatory cells T capable of inducing "bystander" tolerance through their suppression of effector T cells. These beneficial adaptive immune responses depend on the processing and presentation of food allergens by mucosal dendritic cells that in turn "instruct" T effector, memory, or regulatory responses that lead to tolerance instead of allergy.

The success of immunotherapy to aeroallergens and insect venom depends on the dose and frequency of allergen administration, as well as the route of administration. In almost all clinical trials performed to date, at least 2 years of continuous immunotherapy was necessary to induce long-term symptom control that has often been interpreted as tolerance. The possibility that establishing tolerance might not require years of immunotherapy comes from a pilot study with an allergen chemically conjugated to immunostimulatory oligonucleotide sequences of unmethylated DNA (Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate [AIC]) to treat allergic rhinitis. A placebo-controlled study tested the effect of 6 injections of AIC before the beginning of the ragweed season.[15] AIC induced a reduction in symptoms during the 2001 season, as well as during the 2002 season, indicating that tolerance was achieved. It should be noted that in subsequent studies this compound has been less effective.[16]

Developing a safe and effective immunotherapy for food allergens has proved to be more challenging than for aeroallergens and insect venoms. Subcutaneous immunotherapy with food allergens is not feasible because of an unacceptably high rate of systemic allergic reactions,[17] especially with subcutaneous rush immunotherapy.[18] Several additional treatments for food allergy are currently being tested or are in development. Some of these novel approaches include using alternative routes of administering an immunotherapeutic (oral, sublingual, or rectal), using modified allergens and allergen peptides, coadministering allergen and anti-IgE, and reprogramming of dendritic cells to enhance regulatory T-cell responses.