

Workshop summary

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* ■■■■;■■■:■■■-■■■.)

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

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

to NIAID-funded clinical trials and provide guidance to investigators on how to navigate this complex process.

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

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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 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.

Food allergy is often first observed in young children, although many of these children will eventually outgrow cow's milk and egg allergy. Earlier population-based studies suggest that milk allergy resolves at a young age, with most children outgrowing their allergy by age 3 years,^{19,20} and that egg allergy resolves in 66% of children by age 5 years and in 75% of children by age 7 years.^{21,22} More recent studies with different inclusion criteria found that the resolution of IgE-mediated cow's milk allergy²³ and egg allergy²⁴ is slower than shown in earlier studies. By comparison with milk and egg allergy, resolution of peanut allergy is much slower. Thus only about 20% of children will outgrow their peanut allergy, and less than 10% of children will ever outgrow their tree nut allergy.^{25,26} Study designs that aim to evaluate the effectiveness of immunotherapy against milk and egg allergies must contend with the natural rate of resolution of these allergies in the enrolled participants during the course of the treatment. Thus inclusion of a placebo arm, as well as enrollment of participants with similar age distributions in both the treatment and placebo arms, are essential components of optimal study designs.

NIAID-FDA WORKSHOP ON FOOD ALLERGY CLINICAL TRIAL DESIGN

In response to the recommendations of the 2006 NIH Expert Panel on Food Allergy Research, a workshop on the design of food allergy clinical trials was co-organized by the NIAID and FDA in 2008 (see [Appendix 1](#) for a list of participants). The workshop participants discussed 2 types of clinical trials in food allergy, namely prevention trials and treatment trials. Prevention trials intervene in young children at risk of food allergy before they become allergic to food, whereas treatment trials treat children, adults, or both who already have a clinical food allergy. A summary of this workshop is presented below.

One successful approach to the treatment of human allergic disorders has been to use specific allergens for immunotherapy. For example, subcutaneous immunotherapy has been used successfully to block severe allergic reactions to stinging insect venom, such as honeybee and yellow jacket venoms, and to reduce rhinitis symptoms resulting from exposure to inhalant allergens, such as ragweed and house dust mite allergens. However, in pilot studies more than 10 years ago, it was observed that the subcutaneous injection of food allergens is associated with an unacceptably high rate of adverse reactions.²⁷ Recent data indicate that mucosal routes of inhalant allergen administration, particularly the sublingual route, are clinically efficacious and associated with a very low rate of systemic allergic reactions.²⁸ These European studies of sublingual immunotherapy have, to date, not been reproduced in the United States. One recent US study demonstrates the efficacy not of sublingual but of oral immunotherapy with milk.²⁹ Based on these results, several studies have taken this experimental approach to food allergen immunotherapy, anticipating that it will be possible to more safely administer food allergens through the mucosal rather than the subcutaneous route.

In comparison with studies that use mucosal immunotherapy to inhalant allergens, there are special considerations that potentially affect clinical trials that will use mucosal immunotherapy with food. Food allergy predominantly affects children, and the

safety of mucosal immunotherapy with food allergen is unknown. Thus there is a need for caution and rigorous attention to the safety aspects of clinical trials that propose such therapy. Lastly, there are special regulatory considerations associated with clinical trials of food allergen immunotherapy based on the possibility that foods given orally can be obtained from any grocery store and might be used by patients and their families who do not understand the risks associated with exposure to food allergens.

FOOD ALLERGY CLINICAL TRIALS RESEARCH IN YOUNG CHILDREN

Clinical trials of food allergy therapies might involve young children, who have a generally higher prevalence of food allergy than older children. Thus clinical trials that initially enroll adult participants to identify potential safety issues related to food allergen immunotherapy will ultimately need to enroll children to assess safety and efficacy in this special population. Food allergy in young children might represent a disorder that is distinct from food allergy in older children, adults, or both. Published data suggest that therapy with allergens might be more effective in younger children than in older children and adults,³⁰ which is consistent with the concept that allergy in children might differ clinically and immunologically from allergy in adults. Moreover, the workshop participants noted that it is not currently known whether therapeutic approaches that are ineffective in adults with food allergy might still be efficacious in children with food allergy.

PREVENTION TRIALS

The workshop participants discussed only one type of prevention trial, the primary prevention trial. Primary prevention trials require that the intervention occur early in childhood. Ideally, prevention trials should be designed to enroll participants with a greater than 95% risk of disease in the absence of treatment. Unfortunately, there are currently no biomarkers that can identify such a high-risk population, and therefore it is necessary to design a trial in which the target population has only a moderate risk of having the disease. For example, in the general population only 1% of children will have peanut allergy. However, in a population of children with severe atopic dermatitis, egg allergy, or both, 20% to 25% of children will have peanut allergy.³¹⁻³³ The workshop participants believed that prevention trials would be ethically justified only if safety concerns are minimal. Early phase I and II trials must maximize enrollment of high-risk subjects to power the study sufficiently for statistical significance while keeping the number of required participants as low as possible. The workshop participants also pointed out that it might be necessary to test new therapies not only with high-risk subjects but also with other subgroups, including low-risk subgroups. As an example, the issue of whether a food allergy immunotherapy will have the same effect in patients with or without atopic dermatitis should be addressed in such trials.

For prevention trials, additional data are needed to determine whether the goal is to prevent sensitization or to prevent the development of allergy. There are insufficient data on the precise relationship between serum IgE antibodies to food-positive reactions, skin prick test (SPT)-positive reactions, or both at a young age versus the risk of allergy. Some recent data suggest that sensitization to food allergens occurs at ages of less than 15

months in a high percentage of at-risk individuals,³⁴ and it is possible that only a subset of sensitized individuals will have clinical allergy. Thus the study might consider enrolling at-risk individuals who might already have serum IgE antibodies to a food allergen, a positive SPT response to a food allergen, or both but are not clinically allergic. Clinical trials to prevent food allergy should be careful in defining whether the strategy is aimed at preventing sensitization versus preventing disease, whether the study will enroll children with known positive test reactions for a food, and whether family histories will be used to identify a higher-risk group.

TREATMENT TRIALS

In treatment trials with participants who are already clinically allergic, it is necessary to define which populations of subjects with food allergy should be enrolled. The risks of a severe reaction to both food allergens as a therapy and oral food challenge with food allergen as an evaluative component of the trial are uncertain. Therefore participants with a prior history of severe and life-threatening anaphylaxis are believed to be at high risk and are often excluded in early safety studies, although these patients are precisely those for whom a new therapy might reduce the risk of a severe reaction. Treatment trials are also complicated by the fact that the majority of patients with life-threatening anaphylaxis to foods might not have a prior history of a severe reaction. Other factors might be used to classify subjects as being members of a high-risk group. For example, patients with asthma are at higher risk of life-threatening anaphylaxis. However, patients with asthma represent a large subset of individuals with food allergy. Although not unanimous, the workshop participants believed that asthmatic patients were a special case. If their asthma was poorly controlled or if they required a high continual dose of inhaled corticosteroids for control, they should be excluded from initial trials. Patients with milder forms of asthma might be studied relatively early. Patients with more severe asthma should be studied only in later trials. The trial design might need not only to include frequent associated and comorbid conditions, such as asthma, in study populations but also to use modified treatment regimens that minimize the potential for adverse reactions related to these associated and comorbid conditions. These modifications include wider dose-ranging studies and increased observation times after or between administration of a therapeutic agent.

Safety and efficacy in treatment trials

Safety considerations for clinical trials include the risks associated with the therapeutic dosing of food or other agents that might induce allergic reactions and the risks when oral food challenge is used as an evaluative component of the trial. These safety considerations will be discussed in detail below.

Safety of oral food challenges. Oral food challenges have traditionally been used for diagnostic testing. Titrated oral food challenges can be generally performed safely by trained physicians to unambiguously confirm a diagnosis of food allergy, which is especially important given that many foods suspected based on a patient's history and test results (SPT and food-specific IgE antibodies) do not trigger reactions to oral food challenge.³⁵ The risks associated with oral food challenge are reduced by performing the challenges only when it is not likely that the patients

will have a severe allergic reaction to the challenge food. One publication suggested that clinical practice can keep the expected risk of a severe allergic reaction to food challenge to less than 50%.³⁶ The clinical use of food challenges are often directed toward persons with a likelihood of tolerating the food. For clinical trials, the subjects might be selected based on a likelihood of reacting to the challenge food. Gradually increasing the doses of the challenge food is standard practice to minimize the risk of a severe reaction.

At experienced centers, the risks of severe reactions to oral food challenges are very low, and there have been no deaths reported among the thousands of oral food challenges that have already been performed. However, in clinical practice most of those challenges have been of lower risk than in a clinical trial setting. High levels of IgE antibody do correlate with increased risk of an allergic reaction to a food allergen, although these levels do not predict the severity of the reaction.³⁷ Some workshop participants believed that subjects with high levels of IgE anti-food antibodies should not undergo oral food challenges because of this higher risk of reactions. Currently, there are only a small number of experienced centers able to meet the safety requirements for food allergy clinical trials. Recent experimental approaches have used oral food challenges as an end point to demonstrate the ability of subjects to tolerate increasing amounts of food. The optimal design for oral food challenge is currently being investigated in several ongoing food allergy clinical trials. The workshop participants discussed the possibility of encapsulating the food for oral challenge. Encapsulation of food can improve blinding in double-blind, placebo-controlled (DBPC) food challenges but might also result in increased risk because absorption of food might be delayed. Also, encapsulation shields the oral mucosa from the food, thereby preventing oral mucosal responses. Together, these effects might give rise to the false clinical impression that subjects have not reacted to an encapsulated test dose. As a result of this false impression, in an escalating-dose challenge protocol the next higher dose can be given, and the ultimate allergic reaction could then be quite severe. The workshop participants believed that, on balance, encapsulation of food was not recommended in oral food challenge studies. Although food allergens can also be blinded by preparing them in a food matrix, rather than using encapsulation, this issue was not discussed at the workshop.

Safety of food allergens as therapy. It appears that administration of food allergens as immunotherapy carries a greater risk of adverse and potentially severe allergic reactions compared with the administration of inhalant allergens. At present, the precise mechanisms by which subcutaneous food allergen exposure places patients at higher risk for a reaction is unknown. Based largely on the clinical experience published in European trials on the safety of sublingual immunotherapy with inhalant allergens,²⁸ on data from one published trial on sublingual immunotherapy with food allergens,³⁸ and on data from limited trials in Europe and the United States on oral immunotherapy with food allergens,^{29,39-42} there is a general impression that food allergen exposure through the oral or sublingual routes is less risky than through the subcutaneous route. The workshop participants pointed out, however, that this perception has yet to be definitively demonstrated, and subjects with food allergy might still be at higher risk for reactions when these alternative routes of administration are used. Controlled therapeutic trials with foods have been performed only in the last few years, and

therefore the risk of oral or sublingual food treatment regimens cannot be compared directly with the risk of oral food challenge used in the evaluative arm of a study. The workshop participants noted that the same precautions to anticipate anaphylaxis should be applied to both food allergen therapy and oral food challenges.

Precautions during administration of food allergens.

The workshop participants noted that some of the measurements, such as those of pulmonary function by means of spirometry and blood pressure measurement, performed during both administration of food allergens as therapy and during oral food challenges might not be reliable determinations of reactions to food allergens in children. Thus inexperienced investigators might rely too heavily on these measurements. It was also noted that “soft signs” of a reaction to a food allergen are often evident only to experienced investigators. For example, changes in a child’s behavior, such as stopping play and clinging to a parent, might signal an impending adverse reaction. These soft signs should result in a pause in dosing, a repeating or decreasing of the subsequent administered dose, or both. The workshop participants estimated that a full understanding of all aspects of oral food allergen challenge, including the soft signs, requires training and previous investigator experience with approximately 50 to 100 oral food challenges.

Desensitization versus tolerance

One critical issue in food allergy clinical trials is whether the therapeutic goal of the trial should be desensitization, induction of tolerance, or both. The workshop participants noted that there are currently no precise mechanistic definitions of desensitization or tolerance resulting from food allergen therapy. Desensitization is observed clinically as the ability to tolerate a food while ingesting regular doses of that food. It is believed that this phenomenon is rapidly reversible and is mediated by altered signaling pathways in key effector cells, including mast cells and basophils. Tolerance is clinically defined as the ability to tolerate food after a significant period of time has elapsed since last ingesting that food. Tolerance to food is believed to reflect an immunologic response involving regulatory T cells or other T-cell subsets, as well as allergen-specific anergy and clonal deletion. Tolerance is expected to persist for at least months or years after the food therapy has ended. Desensitization is measured by performing oral food challenge while a subject is eating regular doses of a food. By comparison, tolerance is tested only after discontinuing the food ingestion for a period of time, at least 2 to 4 weeks or more, and then performing an oral food challenge.

Several publications suggest that desensitization to foods can be achieved by means of therapeutic oral administration of food allergens, although it is unclear whether tolerance can also be achieved through such allergen administration. The appropriate regimen and dosage of food allergen treatment required to maintain a desensitized or tolerant state are presently unknown. Once achieved, the duration of a symptom-free state is also unknown. It is believed that tolerance to food allergens is a long-lasting state but not necessarily a permanent one. For example, most patients who become “tolerant” after several years of immunotherapy with grass pollen or with insect venom maintain their tolerance for several years but eventually lose it.¹¹ For individuals who had milk or egg allergy and became spontaneously tolerant, these persons generally maintain their tolerant state indefinitely. Among individuals who had peanut allergy but spontaneously became tolerant to

peanuts, the majority are able to maintain this tolerant state indefinitely. It should be noted that less than 10% of individuals lose this tolerant state, and those who lost their tolerant state all ate peanuts less frequently than monthly. The conclusions are based on a very small number of subjects who lost their tolerance.⁴³ It is not known whether the individuals who lost their tolerant state were truly tolerant or only desensitized.

One potentially useful biomarker for spontaneous tolerance is a reduction in the level of food-specific serum IgE antibody levels. However, the utility of reduced IgE antibody levels to food allergen as a biomarker for the induction and maintenance of tolerance induced by food allergen immunotherapy has not been fully evaluated. It is not known whether any of the current experimental approaches to the treatment of food allergy will alter the levels of IgE antibodies to food allergen.²⁹ As discussed in the “Safety of oral food challenges” section, the workshop participants did not reach a consensus as to whether patients with high levels of food-specific IgE antibodies should undergo oral food challenge because of the increased risk of IgE-mediated reactions.

The workshop participants identified potential clinical benefits in inducing both a desensitized state and a tolerant state. Desensitization to food allergen is clinically valuable in that it could protect a patient with food allergy against unintentional ingestion of the food. Therapy that induces tolerance to food might be more valuable clinically in that it potentially protects a patient with food allergy in circumstances such as travel or illness, during which it might be difficult for the patient to continue to eat the food to maintain a desensitized state. Based on clinical impressions, it has also been postulated that certain illnesses, particularly viral infections, might increase reactivity to foods if individuals are desensitized but is less likely to alter reactivity in tolerant individuals.

Risky behavior as a consequence of clinical trials

The workshop participants discussed whether risky behavior by study participants influences the results of food allergy clinical trials. Most deaths from food allergy–induced anaphylaxis occur mainly in adolescents and young adults, and it has been speculated that risky behavior in this age group, such as ingesting foods to which the individuals are allergic, accounts for the higher death rate. Indeed, there are adolescents and young adults who engage in risk-taking behavior.⁴⁴ Thus during a clinical trial, the temporary induction of desensitization to a food could encourage risky behavior if young patients believe that they have now been fully protected against a reaction to ingestion of the food. The panel was unable to reach definitive conclusions about whether participation in a therapeutic trial would increase risk-taking behavior. This is a difficult aspect of food allergy clinical trials that requires careful patient and family education by the investigative team.

Placebo controls

The workshop participants believed that all food allergy clinical trials need to be placebo controlled, particularly because the data supporting the efficacy of current experimental food allergen therapy are incomplete. Unfortunately, because of the nature of food-induced allergic diseases, it is difficult to blind subjects as to whether they are being treated with food or placebo. For subcutaneous immunotherapy, it is possible to blind the

TABLE I. Key workshop findings**Food allergy clinical trials research in young children**

Food allergy in young children might represent a disorder that is distinct and more responsive to therapy than food allergy in older children and adults. Thus initial trials of a new therapy should be with older subjects, but once safety is established, later trials should consider testing young children.

Prevention trials: Inclusion criteria

For primary prevention of food allergies, early trials must maximize enrollment of high-risk subjects to power the study sufficiently while keeping the number of required participants as low as possible. Later testing must expand to other subgroups, including low-risk subgroups. Another consideration is whether prevention should target study subjects who are not sensitized versus those who have IgE antibody to a food allergen but no clinical disease.

Treatment trials

Comorbid conditions, such as asthma, might classify subjects as members of a high-risk group. Patients with milder forms of asthma can be studied relatively early because of the lower risk of severe allergic reactions. Subjects with more severe asthma are an important group and should be entered into later trials.

Precautions and safety considerations for administration of food allergens

Both a history of a prior severe reaction and high levels of IgE antibody to a food have been proposed to identify subjects who should not undergo oral food challenge, but neither these nor other biomarkers are proved predictors of risk to oral challenge.

Food allergen exposure through the oral or sublingual routes might be less risky than through the subcutaneous route, but this hypothesis has not been proved. Even for these alternative routes of administration, subjects with food allergy might still be at higher risk for allergic reactions to allergen than subjects who are allergic to inhalant allergens.

Some of the measurements performed during both administration of food allergens as therapy and during oral food challenges might not be reliable determinations of allergic reactions to food allergens in children (eg, spirometry and blood pressure), and "soft signs" must also be considered. A full understanding of all aspects of oral food allergen challenge, including the soft signs, requires training and previous investigator experience.

Desensitization versus tolerance

After therapy with a food allergen, the ability to eat increased doses of the food might result from desensitization (reversible once food is discontinued) versus tolerance (persists for a period of time after food is discontinued), and both end points are being explored. The appropriate dosage and duration of food allergen treatment required to induce a desensitized or tolerant state are presently unknown. Once achieved, the duration of a symptom-free state is also unknown.

Risky behavior as a consequence of clinical trials

The temporary induction of desensitization to a food could encourage risky behavior in subjects who believe that they have been protected against a reaction to ingestion of the food. This aspect of food allergy clinical trials requires careful patient and family education by the investigative team.

Placebo controls

It is difficult to find a substitute for oral food that will blind subjects as to whether they are being treated with food or placebo.

Several institutional review boards will not approve a placebo-controlled clinical trial in children unless placebo-treated children are offered the opportunity to cross over to the treatment group at the end of the trial.

Regulatory aspects of food allergy clinical trials

Investigators are strongly encouraged to discuss any proposed study with the FDA before requesting an exemption from IND or submitting an IND application. It is necessary to determine the amount of active allergen components in the therapeutic foods, the stability of the active allergenic components, and the dose range for safely using the therapeutic food. For phase III trials, there is a greater focus on efficacy, as well as safety, and there are more stringent requirements for the CMC section of an IND for efficacy evaluation of products.

End points

Assessing changes in the dose response to DBPC oral food challenges before and after therapy can provide statistically significant information about potential efficacy based on a relatively small number of subjects. Potential disadvantages of this approach include the risk of adverse reactions to the oral challenge.

Assessing changes in the number of allergic episodes during a longitudinal natural history/exposure study has an inherent advantage over the oral food challenge design because the longitudinal study mimics the real-world situation. Limitations of this approach include the need for relatively large cohorts to detect statistically significant differences in the rate or severity of allergic reactions.

Clinical trials with combinations of 2 agents

The study sponsor should consult officials at both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research when considering the use of more than 1 agent. The study sponsor might elect to submit a Request for Product Jurisdiction to the FDA Office of Combination Products to determine which FDA center should conduct the IND review.

subject by treating with a histamine solution as placebo, which provokes a skin reaction, but there is no comparable placebo to reproduce the tingling sensation or pruritus that results from oral or sublingual food allergen exposure in subjects with food allergy. It should also be noted that several US institutional review boards will not approve a placebo-controlled clinical trial in children unless placebo-treated children are offered the opportunity to cross over to the treatment group at the end of the trial.

REGULATORY ASPECTS OF FOOD ALLERGY CLINICAL TRIALS

There are no absolute regulatory requirements for clinical trials in food allergy. However, if food is used to modify the immune

response in a clinical trial, then the investigator is expected to obtain either an investigational new drug (IND) application from the FDA or an IND exemption. Both the FDA and NIAID offer assistance to investigators in navigating the IND process. Although it is not a requirement in an NIAID-funded clinical trial, the NIAID can hold the IND for a study. The investigator might prefer such an arrangement because the burden of medical monitoring and safety-reporting responsibilities generally lies with the IND holder. Recent experience has shown that most food allergy clinical trials will require an FDA-approved IND. Investigators are strongly encouraged to discuss any proposed study with the FDA before submitting an IND application. Even though the foods used in clinical trials will probably not be licensed for therapeutic purposes, the results of the clinical trials will

undoubtedly influence contemporary medical care of patients with food allergy. Food allergens might be FDA approved for diagnostic skin testing, but these allergens are currently not approved for oral, sublingual, or other route of administration and are also not approved for therapeutic interventions. Overall, there is the need for regulatory review and oversight of all food allergy clinical trials.

When clinical trials are undertaken with an FDA-approved IND, investigators should recognize that there are extensive requirements associated with the IND approval process. It is necessary to perform measurements to determine both the amount of active allergen components in the therapeutic foods and the stability of the active allergen components. Because the material being administered can cause severe allergic reactions, it is important to determine the safe dose range. It is also critical to identify the dose range for performing both therapeutic food administration and oral food challenges in both prevention and treatment studies.

In clinical studies with Botanical Drug Products (<http://www.fda.gov/cder/guidance/4592fnl.pdf>), the chemistry, manufacturing, and controls (CMC) section might be waived because the product is already on the market and there is considerable experience with its use. In addition, an investigator brochure will be required but might be modified for foods already on the market. However, the CMC section of the IND required for regulatory approval of phase I and phase II clinical trials cannot be waived for food allergy clinical trials because of the risks of allergic reactions, although there might be options available to simplify this section. For phase III trials, there is a greater focus on efficacy, as well as safety, and there are more stringent requirements for the CMC section of an IND for efficacy evaluation of products. The FDA should always be consulted for guidance in the preparation of a phase III food allergy clinical trial. The workshop participants identified difficulties that need to be resolved, including whether there are alternate, less expensive approaches to packaging of food products and whether there are funds available to define safe dose ranges for therapeutic foods. The workshop participants noted that NIH study section reviews might give investigator-initiated dose-ranging studies relatively low priority. They also noted that local institutional review boards sometimes state that the food allergy trial does not require submission to the FDA. Nevertheless, the FDA should be consulted regardless of the local institutional review board opinion because the FDA is the ultimate regulatory authority for the conduct of food allergy clinical trials.

End points

The workshop participants emphasized the importance of accurate clinical descriptors and careful selection of clinical end points. The workshop participants discussed 2 possible end points: response to oral food challenge and response to natural (inadvertent, accidental, and unintentional) exposure. This workshop discussion was undertaken in the context of whether anti-IgE (omalizumab) could be a therapeutic agent to treat food allergy, but the potential strengths would be relevant to a variety of potential therapeutic agents. The discussion highlighted strengths and limitations of these potential end points but did not lead to specific conclusions about what designs would or would not be required for licensure of a product. These 2 potential end points are true regardless of the nature of the therapeutic approach

(ie, tolerogenic approaches vs approaches that do not induce immunologic tolerance).

A comparison of the dose response to DBPC oral food challenges before and after therapy would be expected to provide statistically significant information about potential efficacy based on a relatively small number of subjects. Other advantages of this approach include the opportunity to (1) gradually escalate exposures and define thresholds for clinically significant reactions and (2) monitor, record, and treat adverse events in well-equipped and staffed clinic/research facilities. Potential disadvantages of this approach include the fact that subjects are put at risk of adverse reactions to the oral challenge, particularly because in a typical study design all subjects would be expected to have an allergic response on baseline challenge, as would those in the untreated/placebo group after sham treatment. Furthermore, many potential subjects decline to participate in studies that involve a baseline oral food challenge, particularly when there is a placebo group. Other limitations include the fact that oral food challenges are generally performed with food extracts containing only a subset of the components present in a meal or diet consumed in a natural exposure setting. Food extracts used in oral challenges are sometimes encapsulated, eliminating or minimizing the potential to elicit oral, esophageal, or airway reactions that can occur after natural exposure. As noted above, the workshop participants recommended not using encapsulated allergens in oral food challenges. Although DBPC oral food challenges have the potential to be highly informative, allergic reactions that occur in this setting have not been validated as a surrogate biomarker of reactions after natural/accidental exposure. Although the exact symptom complex might not be replicated in a DBPC oral food challenge compared with a natural reaction, it should be noted that natural reactions do not necessarily manifest identical sets of symptoms with each exposure. Furthermore, on rare occasions, a subject with a negative DBPC oral food challenge result will react to food in a natural setting.⁴⁵ Taken together, these factors might constitute a “high bar” to licensure of a product based solely on oral food challenge studies.

An observational, longitudinal natural history study would typically enroll subjects at risk of unintentional ingestion of a food or foods to which they are sensitized. This design has an inherent advantage over the oral food challenge design because it mimics the real-world situation and has the potential to be highly informative regarding safety and efficacy. Nonetheless, the panel noted several limitations of this approach. Relatively large cohorts would be required for extended times to detect statistically significant differences in the rate or severity of allergic reactions. It might be difficult to recruit and retain such large numbers of subjects. The reactions to unintentional food allergen exposure occur, for the most part, in less than ideally controlled settings, and it might be difficult to obtain reliable data on the frequency, severity, and clinical management of such events. Another potential confounding factor is the possibility that subjects who believe they are in the experimental arm might engage in “risk-taking behavior,” increasing their chances of exposure to food allergens. Finally, it is estimated that there are only 15,000 to 30,000 food-induced anaphylactic events per year in the United States and perhaps 150 or fewer deaths per year. It is likely that a longitudinal natural exposure study would be dominated by mild and moderate reactions, even though protection from life-threatening reactions would be of greatest interest. Thus if natural exposure is necessary to prove protection against

the most severe reactions, only phase IV postmarketing studies could be powered to determine whether a therapy protects against the most severe reactions. The FDA might, however, consider DBPC, randomized, graded food challenges in determining whether therapy protects against these reactions.

Clinical trials with combinations of 2 agents

Combinations of 2 agents in a food allergy clinical trial raise several additional issues. The workshop participants noted that the adverse effects of the 2 agents might not be easy to separate, so that attribution to one agent versus the other might be impossible. When 1 or more of these products are to be used in an investigational manner, the study must be conducted under an IND. The workshop participants believed that investigators proposing such studies would benefit from consultation with the NIAID (or other sponsor) and the FDA in advance of submitting such proposals. If a combination study involving both drugs and biologic agents is planned, the investigators and sponsors should seek input from both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. The study sponsor might elect to submit a Request for Product Jurisdiction to the FDA Office of Combination Products to find out its views on which FDA center should conduct the IND review.

SUMMARY

The 2008 NIAID-FDA Workshop participants identified numerous challenges to the design of clinical trials in food allergy research (Table I). The workshop participants were able to recommend several approaches to overcome these difficulties. A critical aspect of this issue brought out by the workshop participants was the need for investigators to work closely with both FDA and NIAID staff in the design of a food allergy clinical trial, especially in situation in which investigators anticipate eventually seeking licensure for their therapeutic agent.

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APPENDIX 1

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