FDA Briefing Document

Allergenic Products Advisory Committee

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Clinical Development of Allergen Immunotherapies for the Treatment of Food Allergy

1. Introduction

Food allergy arises from a failure of the immune system to generate or maintain tolerance to specific food proteins. IgE-mediated food allergy is a deleterious immune response to food proteins characterized by acute onset of symptoms generally within 2 hours after ingestion of or exposure to the protein [1]. The clinical presentation includes a range of symptoms from oral pruritus to acute urticaria/angioedema which can progress to more serious sequelae such as anaphylaxis, hypotension, and multiple organ dysfunction syndrome [1].

The most common food allergens are peanut, tree nut, milk, egg, soy, wheat, and shellfish [2]. These foods constitute more than 90% of food allergies in children [3]. Some food allergies (milk, egg, wheat, and soy) have an increased chance of resolving with age whereas others (peanut, tree nut, and shellfish) tend to be persistent over time [4].

Food allergy affects up to 15 million people in the U.S., approximately 6 million of whom are children. Prevalence has been increasing, particularly in children; the National Center for Health Statistics reports that the prevalence increased from 3.4% in 1997-1999 to 5.1% in 2009-2011 in individuals 0 to 17 years of age [5]. Quality of life in food-allergic individuals and their caregivers is often adversely affected due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods. The potential consequences of accidental exposure can be serious and life-threatening. About 50% of cases of anaphylaxis reported by emergency departments are due to a food allergen [6]. Fatalities due to anaphylaxis from food allergies are estimated at about 100 per year with most deaths occurring during early adulthood [7].

Allergen immunotherapy (AIT) has long been used to treat individuals with sensitivity to aeroallergens and hymenoptera venoms. A number of allergen extracts are available for use in subcutaneous immunotherapy (SCIT) for such individuals. Three products for sublingual immunotherapy (SLIT) were recently licensed by FDA for treatment of allergic rhinitis due to certain grass pollens (two products) and short ragweed pollen (one product). No licensed immunotherapy products are available for the treatment of food allergy. Investigators are pursuing the use of AIT for food allergy via several different routes of administration including oral, sublingual, and epicutaneous.

The APAC is being convened to discuss considerations regarding the clinical development of products intended for use in food allergic individuals. CBER will seek the Committee's opinion on, for example, study design for the development of investigational products, the performance of oral food challenge (OFC) protocols (particularly in children <5 years of age), effectiveness

endpoints to support potential indications for licensure, safety monitoring during clinical development, and safety data to support licensure applications.

2. Current standard of care

The diagnosis of food allergy is frequently made based on patient history and IgE testing. Oral food challenge (OFC) is typically done to rule out food allergy or to confirm that tolerance has developed in a patient with a history of allergic symptoms. A double blind placebo-controlled food challenge (DBPCFC) is considered the gold standard for diagnosing food allergy [3]. However, clinicians generally use unblinded OFCs, because in most clinical circumstances, ascertaining an accurate threshold of allergic sensitivity – the eliciting dose (ED) - is not necessary.

To prevent reactions, food-allergic individuals must maintain a strict avoidance diet. Treatment is limited to mitigating the symptoms of reaction after accidental exposure to allergens - either with immediate injection of epinephrine for suspected or confirmed anaphylaxis or with antihistamines for milder symptoms.

3. Investigational treatments

AIT for IgE-mediated food allergy is an active field of clinical research. An objective of AIT is to induce a state of desensitization in food-allergic individuals to prevent a catastrophic response following accidental exposure. Some of the published literature is briefly summarized below. The discussion is grouped by the different routes of administration that are being investigated.

3.1 Oral immunotherapy (OIT)

In OIT, individuals with confirmed IgE-mediated allergy to food ingest increasing amounts of the allergenic food protein. Typical protocols include an initial rapid dose escalation done in one day followed by bi-weekly dose increases until the maintenance dose is reached [9]. Subjects are usually instructed to ingest the maintenance dose daily while continuing to avoid the food allergen in their regular diet. Although the definitions and criteria for desensitization have not been uniform, several published studies have reported promising efficacy results in the induction of desensitization.

OIT is associated with a relatively high rate of adverse events, most commonly oral and gastrointestinal side effects. The inability to tolerate therapy leads to a subject withdrawal rate of 10-20% [10]. Serious events such as anaphylaxis, asthma exacerbations, and oropharyngeal edema have been reported with the use of OIT. Younger study participants such as infants and

toddlers may be at increased risk for systemic or serious reactions because they may not be able to communicate early symptoms of an allergen reaction such as oral itching or abdominal discomfort. Another safety consideration with the use of OIT is the possibility of the development of eosinophilic esophagitis (EoE) in participants. This has been reported in trials studying milk OIT [11, 12].

3.2 Sublingual immunotherapy (SLIT)

SLIT is similar to OIT in that the food to which the subject is sensitive is administered orally. In SLIT small amounts of food extract are placed and held under the tongue for 2-3 minutes, then spit out or swallowed [8]. While few studies have evaluated this route of administration for food AIT, the available data suggest that desensitization is less often achieved compared with OIT. However, these data also suggest that the safety profile may be improved relative to OIT [10, 13, 14]. As with OIT, EoE is a safety concern that must be monitored in SLIT studies.

3.3 Subcutaneous immunotherapy (SCIT)

Studies that evaluate SCIT for treatment of food allergy have reported relatively high rates of adverse events, particularly systemic reactions during the build-up phase, including one fatality that occurred when a subject received an injection of peanut SCIT [15]. The limited efficacy data from these studies indicate that among subjects who complete the regimen, ~50% experience some degree of desensitization [15, 16].

3. 4 Epicutaneous immunotherapy (EPIT)

In EPIT intact skin is exposed to small amounts of the food allergen, typically through the use of a patch [17]. The rationale for this approach is to present antigen to dendritic cells, which are thought to induce tolerizing pathways of the immune system. This route of administration has been studied for treatment of milk allergy [10]. The safety profile was reported to be reassuring; however therapy did not appear to be successful in inducing desensitization to milk [10, 18]. Studies using EPIT to treat other food allergies (e.g., peanut) are ongoing.

4. Food challenge studies to demonstrate effectiveness

One approach for demonstrating effectiveness of AIT is through a randomized, blinded, placebo-controlled study, in which the degree of desensitization is assessed by food challenge. Considerations regarding the design and conduct of such studies are discussed in this section.

4.1 Establishing sensitivity and assessing desensitization with food challenge protocols

In the investigational setting to evaluate the effectiveness of AIT, a DBPCFC may be performed before treatment is initiated in order to establish the precise quantity of the food allergen that evokes a reaction. The eliciting dose (ED) is defined as the lowest amount of the food that elicits objective signs or symptoms, such as urticaria, erythema, or oral angioedema [19]. The degree of desensitization achieved by a course of food AIT is evaluated by repeating the DBPCFC to assess the change in ED, if any, from baseline.

Establishing a precise ED may be challenging in children, particularly in infants and toddlers. Symptoms of allergic reactions in infants, such as drooling, vomiting, scratching or drowsiness, can be overlooked or mistaken for normal findings [20].

4.2 Effectiveness endpoints

A goal in the development of AIT products for food allergy is to protect the patient from a serious, life-threatening reaction in the event of accidental exposure. This may be accomplished through *desensitization,* which is the ability to tolerate increased amounts of the allergen (e.g., the amount that might be encountered in an accidental exposure) during maintenance therapy with the AIT product. Thus, in AIT studies using food challenge as the approach to demonstrating effectiveness, the primary objective is to demonstrate a degree of desensitization that translates to a clinically meaningful reduction in the risk of serious reaction to the food. Typically, the primary endpoint in these studies is the degree of desensitization in the treatment group compared with the placebo group.

Following cessation of therapy, the capacity to maintain desensitization to the food allergen is known as *sustained unresponsiveness.* The published literature defining and characterizing sustained unresponsiveness is not extensive [21, 22]. The length of time off therapy that would represent clinically meaningful benefit remains undefined. Therefore, the clinical parameters that should delineate sustained unresponsiveness and appropriate study endpoints to demonstrate it have not been established.

In the food-allergic individual, *tolerance* is the complete and permanent resolution of clinical response following exposure to any amount of the identified allergenic food. Tolerance has not been demonstrated in any controlled trial of food AIT to date. Similar to sustained unresponsiveness, the clinical parameters that should be used to demonstrate tolerance in clinical trials have not been established.

5. Alternatives to food challenge studies to demonstrate effectiveness

Although assessing the efficacy of food AIT by comparing the change in ED in treatment and placebo groups is one approach to demonstrate effectiveness, this clinical trial design has some

limitations. For example, subjecting severely food-allergic individuals to multiple OFCs entails risk to the study subjects and recruitment challenges for study sponsors. The following alternative designs avoid these concerns, but have limitations of their own.

5.1 Clinical field efficacy trials

One alternative to a food challenge study would be a randomized, controlled field trial in which the primary endpoint would be the rate and/or severity of reactions to food exposures encountered outside a controlled clinical setting. In the published literature, limitations of such an approach have been noted, such as the need for large cohorts and study durations long enough to detect statistically significant differences in the rate or severity of allergic reactions [23].

5.2 Status of biomarker development

Some published studies have collected biomarker data to evaluate possible correlations with response to AIT. These include allergen-specific IgE and IgG4, Th2-type cytokine (IL-2, IL-4, IL-5) production by peripheral blood mononuclear cells, and basophil activation tests [13,18,22,24,25]. The trends noted in these studies suggest that some biomarkers hold promise to evaluate response to therapy and to predict clinical efficacy. At this point, none appear to be well-established to the extent necessary to provide the primary support for effectiveness. However, a variety of laboratory and clinical parameters may be evaluated during food AIT clinical development programs to facilitate the development of biomarkers predictive of effectiveness for use in future studies.

6. Considerations regarding safety monitoring in food AIT studies

In most food AIT studies, subjects will incur not only the risks associated with use of the investigational product, but also the risk inherent in food challenge protocols. Sponsors should propose elements of surveillance and counseling (and an appropriate duration of follow up) necessary to mitigate these risks, particularly the risk of reactions that may occur outside of a clinical care setting.

As discussed in Section 3, the risks and specific safety concerns are substantially different for the different routes of administration. Surveillance and monitoring should be designed to address the relevant issues. For example, EPIT studies should pre-specify a group of solicited adverse events to provide detailed data to characterize local reactogenicity. For products intended for oral administration, the study protocol should address the risk of EoE, by including, for example, diagnostic and treatment algorithms, individual stopping rules for subjects with

suspected cases, and appropriate monitoring for incident cases, particularly among infants and toddlers.

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