Clinical Development of Allergen Immunotherapies for the Treatment of Food Allergy

Allergenic Products Advisory Committee Meeting
January 21, 2016

Kathleen S. Hise, MD
FDA/CBER/OVRR/DVRPA
Presentation topics

• Introduction
• Investigational treatments
• Demonstration of efficacy
  • Food challenges
  • Study models
• Safety monitoring
• Summary
Introduction
Introduction

• Allergen immunotherapy (AIT) is used to treat sensitivity to aeroallergens and hymenoptera venoms

• No licensed immunotherapy products are available for food allergies.

• Several different routes of AIT for food allergy are being investigated
Epidemiology & natural history

• Food allergy affects up to 15 million people in the U.S.
  • ~ 6 million children

• Prevalence has increased
  • 3.4% in 1997-1999 to 5.1% in 2009-2011 in ages 0 to 17 years (National Center for Health Statistics)

• ~50% of anaphylaxis reported by emergency departments is due to a food allergen

• Fatalities are estimated at ~100 per year
  • Data suggest those in early adulthood are at higher risk
Epidemiology & natural history

- A few foods constitute 90% of food allergies in children
  - Peanut, tree nut, milk, egg, soy, wheat, and shellfish

- Some allergies tend to resolve with age
  - Milk, egg, wheat, and soy

- Some allergies tend to be persistent over time
  - Peanut, tree nut, and shellfish
Current standard of care

• Diagnosis is usually made by clinical history and specific IgE

• No specific therapy is available

• Clinical management is limited to
  • Strict avoidance diet
  • Treatment of reactions with epinephrine or antihistamines for milder symptoms
Investigational treatments
Desensitization

- *Desensitization* is the ability to tolerate increased amounts of the food allergen during AIT
Protocol design

• Typical protocol designs include
  • Screening - entry food challenge, specific IgE, skin prick test
  • Dose escalation period
  • Pre-specified treatment period (maintenance dose)
  • Exit food challenge to assess desensitization
Typical protocol design

1. Screening – baseline food challenge, IgE, SPT
2. Initial dose escalation (1d)
3. Dose escalation (~2 weeks)
4. Maintenance dose
5. Exit food challenge
Oral immunotherapy (OIT)

• Typical protocols in published literature include:
  • Initial rapid dose escalation (usually done in 1 day)
  • Bi-weekly dose increase
  • Maintenance dose

• Subjects continue to avoid the food allergen in their diet
Oral immunotherapy (OIT)

• Some studies have reported ~50-60% desensitization
  • Criteria for desensitization vary across studies

• Some studies include an oral food challenge as an entry criterion in addition to specific IgE and skin prick testing

• Maintenance phase ranges from 4 weeks to 5 years

• Maintenance dose ranges from 500mg to 4000mg of food protein
Oral immunotherapy (OIT)

• High rate of adverse events → 10-20% subject withdrawal

• Serious adverse events
  • anaphylaxis, asthma exacerbations, oropharyngal edema

• Younger study participants may be at increased risk for serious reactions
  • Unable to communicate early symptoms of a reaction
  • Smaller caliber airway

• Eosinophilic esophagitis (EoE) is a particular concern
Sublingual immunotherapy (SLIT)

- Food extract is placed and held under the tongue for 2-3 minutes, then spit out or swallowed
- Few studies have evaluated this form of AIT
- Data suggest SLIT has lower efficacy than OIT
- Some investigators assert safety profile may be more favorable
Epicutaneous immunotherapy (EPIT)

• Food allergen is placed directly on intact skin through a patch

• One study published evaluating EPIT for treatment of milk allergy
  • Safety profile was reported to be reassuring
  • Therapy did not appear to be successful in inducing desensitization
Subcutaneous immunotherapy (SCIT)

- Limited data suggest ~50% subjects experience some degree of desensitization

- Relatively high rates of adverse events reported
  - Systemic reactions during the build-up phase
  - One fatality due to inadvertent administration of SCIT
Demonstration of efficacy
Treatment goals

• Induce a state of desensitization

• Protect against a serious allergic reaction following accidental exposure

• Clinically meaningful reduction in the risk of serious reaction
Food challenge studies to demonstrate efficacy

• Often used to assess
  • Degree of sensitivity at beginning of study
  • Efficacy at end of study

• Two types
  • Double-blind, placebo-controlled food challenge (DBPCFC)
  • Unblinded oral food challenge (OFC)
Food challenge studies to demonstrate efficacy - desensitization

- Before treatment is initiated, a DBPCFC is performed to identify the eliciting dose (ED)

- The ED is the lowest amount of food that elicits objective signs or symptoms

- After a defined period of treatment with AIT, the degree of desensitization is evaluated by the change in ED by a DBPCFC
Food challenge studies to demonstrate efficacy – sustained unresponsiveness

• The capacity to maintain desensitization to the food allergen after termination of therapy has been described as *sustained unresponsiveness*.

• At various time points after termination of AIT, the ED is re-evaluated by DBPCFC.

• The length of time after termination of AIT that defines sustained unresponsiveness has not been established.
Food challenge studies to demonstrate efficacy - tolerance

- *Tolerance*: currently defined as *complete* and *permanent* resolution of clinical response following exposure to any amount of the allergenic food after termination of therapy

- The length of time off therapy to claim tolerance has not been established
Possible endpoints

- Desensitization
- Tolerance
- Sustained unresponsiveness
- Treatment failure

- \( ED_{\text{final}} \) / \( ED_{\text{baseline}} \)
- AIT withdrawn
- Time
Potential alternatives to food challenge studies – field trial

• Randomized, controlled field trial
  • The primary endpoint: reduction of rate and/or severity of reactions to accidental food exposures in the treated group versus the control group

• Limitations of field trials have been noted including
  • Large cohorts and long study durations needed to detect statistically significant differences
Potential alternatives to food challenge studies - biomarkers

• Biomarkers as surrogate endpoints in clinical studies
  • Allergen specific IgE and IgG4 levels
  • Cytokine (IL-2, IL-4, IL-5, IL-13) production

• None have been well-established to support efficacy
Safety
Safety considerations

- In most food AIT studies, subjects incur two sets of risks
  - Use of the investigational product
  - Food challenge
- Risks include anaphylaxis, abdominal pain, asthma exacerbations, oropharyngeal edema, death
- Risks are substantially different for the different routes of administration.
- Surveillance, counseling, and follow-up must mitigate the risks of reactions, especially those that occur outside of a clinical care setting.
Summary
Summary

• Food allergy is a serious public health issue

• Potential risks and benefits vary according to the route of AIT administration

• To support labeling, agreement is needed between the applicant and the FDA on the study design, study population and clinical parameters for demonstrating desensitization, sustained unresponsiveness, and/or tolerance