Clinical Development of Allergen Immunotherapies for the Treatment of Food Allergy

Allergenic Products Advisory Committee Meeting

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Presentation topics

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

Introduction

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- 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

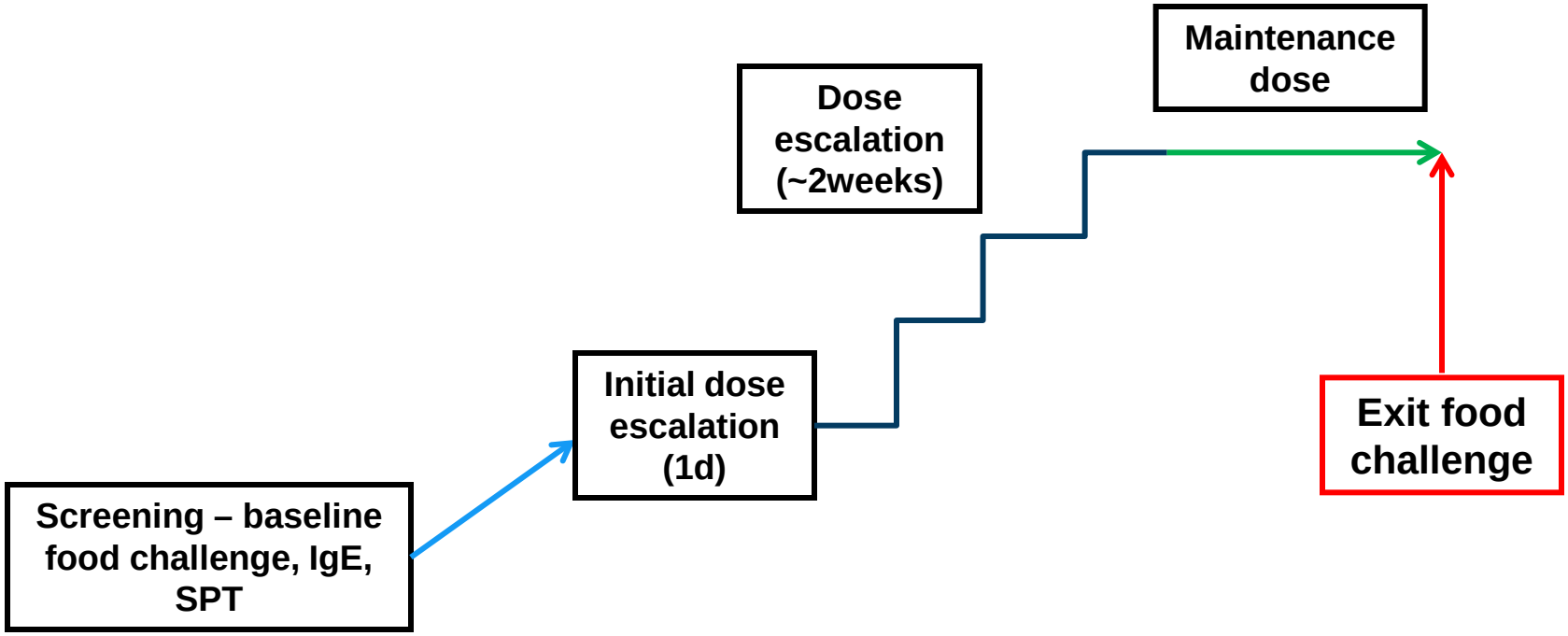
Desensitization

- *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



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, oropharyngeal 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

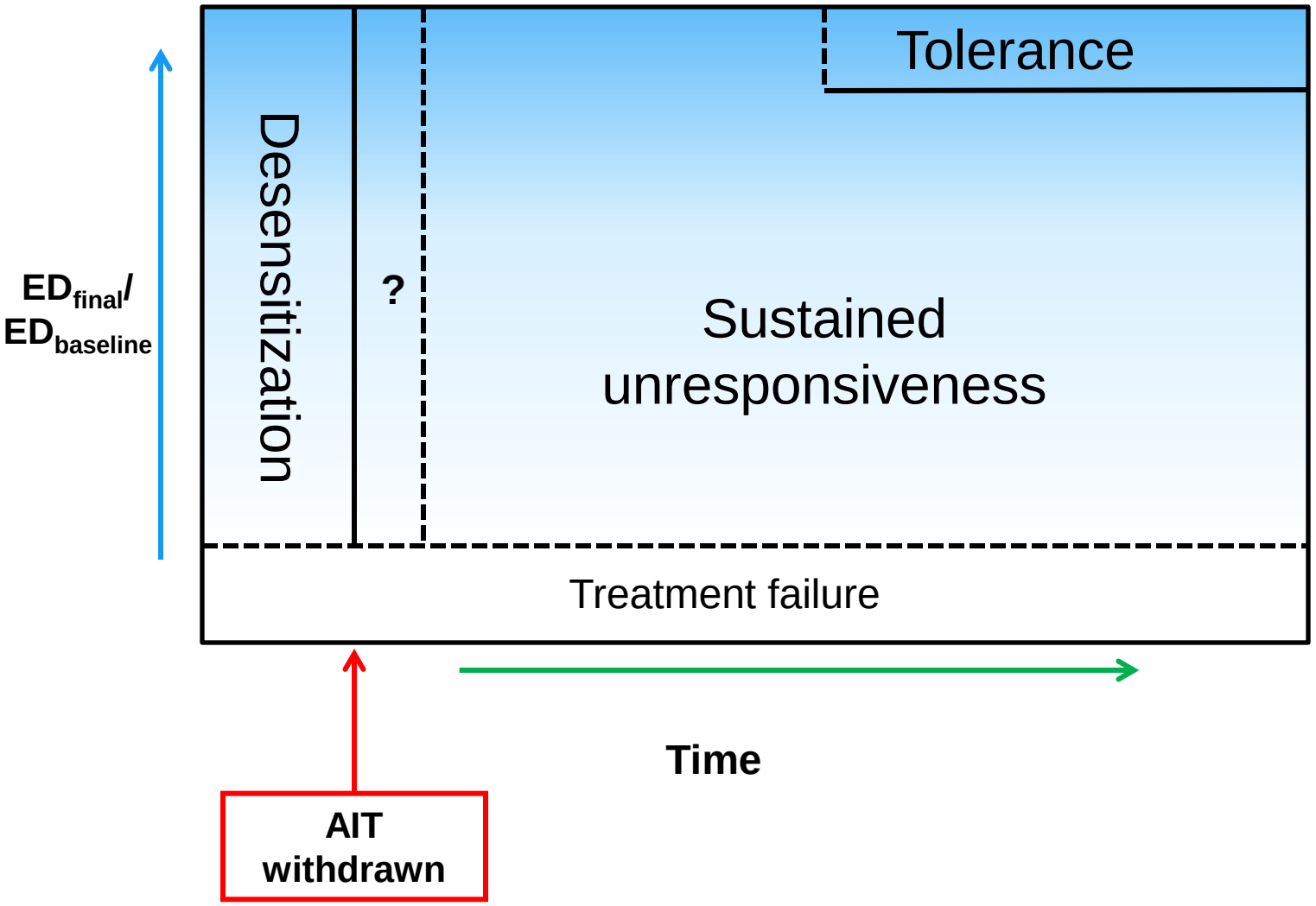
- The capacity to maintain desensitization to the food allergen after termination of therapy has been described as *sustained unresponsiveness*
- At various time points after termination of AIT, the ED is re-evaluated by DBPCFC
- The length of time after termination of AIT that defines sustained unresponsiveness 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



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