Non-IgE Mediated Food Allergy and Intolerances

Margaret Redmond, MD
Assistant Professor - Clinical
Division of Allergy-Immunology
Nationwide Children's Hospital
The Ohio State University College of Medicine

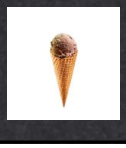
Case 1

- 24 year old female
- Reports that every time she drinks milk she develops bloating, flatulence and diarrhea
- She can tolerate live yogurt and small servings of cheese without symptoms
- She wants to know more about her milk allergy

Food Allergy?

A immunologic reaction that occurs reproducibly in response to exposure to a food

- Reactions can occur to small amounts of the food
- Reactions are not dose dependent
- Reactions occur with every exposure

Food Intolerance

- Non immunologic
- Severity correlates to amount ingested, not life threatening
- Symptoms are generally digestive or cutaneous



Food Intolerance Management

- Avoidance or Limitation of foods for comfort
  - Lactose Intolerance: Lactase enzyme replacement, ultra filtered milk, A2 milk
  - Fructose Intolerance: Improved with glucose. Do not combine with sorbitol.

Case 2

- 8 week old male
- Mother generally breast feeds, but has tried supplementing with formula
- She is concerned that her son may be allergic to his formula
- She reports that on the two occasions that she has attempted formula, he has had vomiting

Case 2

- Vomiting started 2 hours after the formula
- The vomiting was dramatic and recurrent, but did not persist for more than a few hours.
- He then had a few episodes of diarrhea

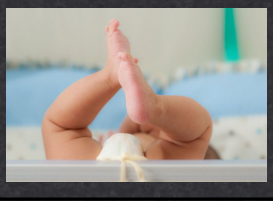
- She reports that she almost called 911 because he seemed lethargic, but then he started nursing and acting more like himself

Differential Diagnosis

- Pyloric stenosis
- Over feeding
- GERD
- Viral gastroenteritis
- Hirschsprungs
- Ileus
- Lactose intolerance
- Food allergy

Case 2

- Patient is growing well
- Patient has no issues with stooling
- Episodes of emesis have only occurred following cow's milk based formula exposure



Could it be Food Allergy?

- It is occurring reproducibly

BUT

- Mainly GI symptoms?
- Is two hours too delayed?
- Self-resolved?

Non IgE Mediated Food Allergy

- IgE mediated is what is classically thought of as food allergy
- Non IgE mediated food allergy
  - Incompletely understood, but involves activation of cellular and innate immune responses in the intestines following food protein exposure
  - Spectrum of manifestations

Food Protein Induced Allergic Proctocolitis

- Immune reaction to food protein effecting the rectum and colon
- Classically causes bright red blood in the stool of breast fed infants
- In contrast to other processes on the differential (IBD, infection, intussusception) these children are generally thriving and most are not even fussy.
  - Failure to thrive, fever, diarrhea, or significant emesis should push you to investigate other causes of rectal bleeding

Food Protein Induced Allergic Proctocolitis

- Laboratory Testing
  - Hemoccult of stool

- Food Triggers
  - Majority caused by cow's milk
    - Egg, soy, and corn have also been reported

Food Protein Induced Allergic Proctocolitis

- Management
  - If mother wishes to continue breastfeeding, she must eliminate all foods containing suspected food protein out of her diet
  - If formula fed:
    - 15% will also have symptoms with soy
    - Most will improve with an extensively hydrolyzed formula
    - Minority will require amino acid based formula
- Natural History
  - Nearly all infants will be able to tolerate trigger food by one year of age

Case 2

- Is it Food Protein Induced Allergic Proctocolitis?
- While this patient is growing well and is breast feed
  - No bright blood in the stool
  - Symptoms are not occurring with breastfeeding and mother's diet includes cow's milk, egg, soy, and grains

Food Protein Induced Enterocolitis Syndrome

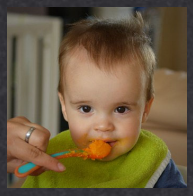
- Also called FPIES
- Immune reaction to food protein in the small intestine
- Can occur in either an acute or chronic presentation
- Cow's milk or soy generally cause symptoms in younger infants than solid food triggers

Chronic FPIES

- Intermittent vomiting
- Chronic watery diarrhea
- Dehydration
- Weight loss
- Failure to thrive

Acute FPIES

- Repeated vomiting 2-6 hours after ingestion
- Diarrhea only after ingestion
- Hypotension
- Hypothermia
- Dehydration



FPIES

- Laboratory testing
  - Acute: Thrombocytosis, metabolic acidosis, methemoglobinemia
  - Chronic: Anemia, hypoalbuminemia, eosinophilia, metabolic acidosis, methemoglobinemia
- Clinical Diagnosis
  - Improvement with elimination of food protein
  - If history is unclear, can confirm with oral food challenge

FPIES

- Acute Management
  - Epinephrine will not improve symptoms in a FPIES reaction
  - Ondansetron may improve symptoms, but IV fluid replacement is often necessary
- Long Term Management
  - Avoid the causative food
  - Extensively hydrolyzed versus amino acid based formula
  - Introduce green vegetables and fruits before grains (low evidence)
- Natural History
  - Typically outgrown by 3 years of age, serial food challenges to assess

IgE-Mediated Food Allergy

Benjamin T. Prince, MD, MSCI
Assistant Professor of Pediatrics
Division of Allergy-Immunology
Nationwide Children's Hospital
The Ohio State University College of Medicine

Case

A 12 month old boy presents with hives and increased work of breathing that began 20 minutes after eating scrambled eggs for the first time.

His parents report that they gave him diphenhydramine by mouth, but he vomited shortly afterwards. They noticed that he was breathing more rapidly and brought him in for evaluation.

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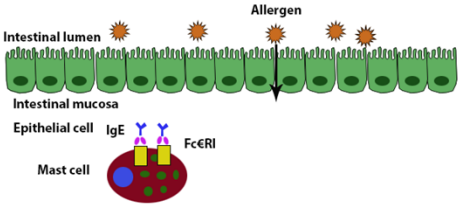
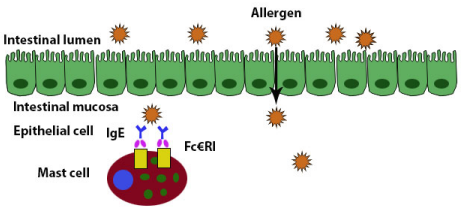
Questions:

1. Is this history consistent with IgE-mediated food allergy?
2. How do you diagnose anaphylaxis?
3. What is the next best step in management of this patient?

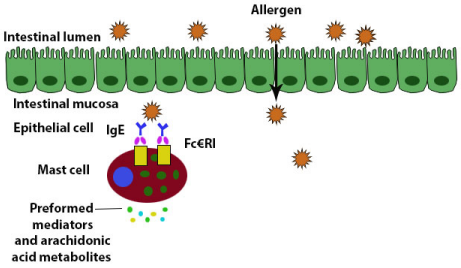
IgE-Mediated Food Allergy: Pathophysiology



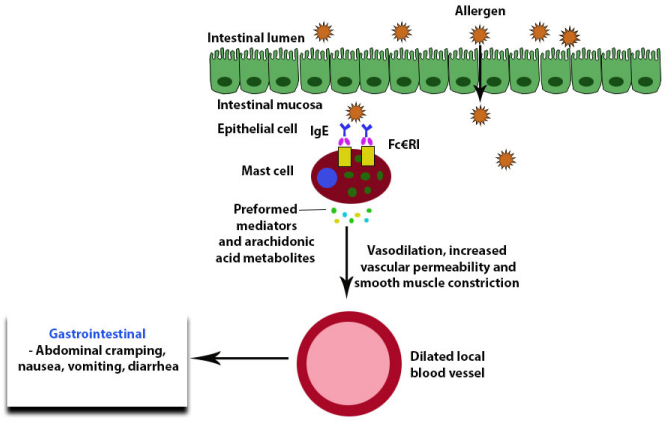
IgE-Mediated Food Allergy: Pathophysiology



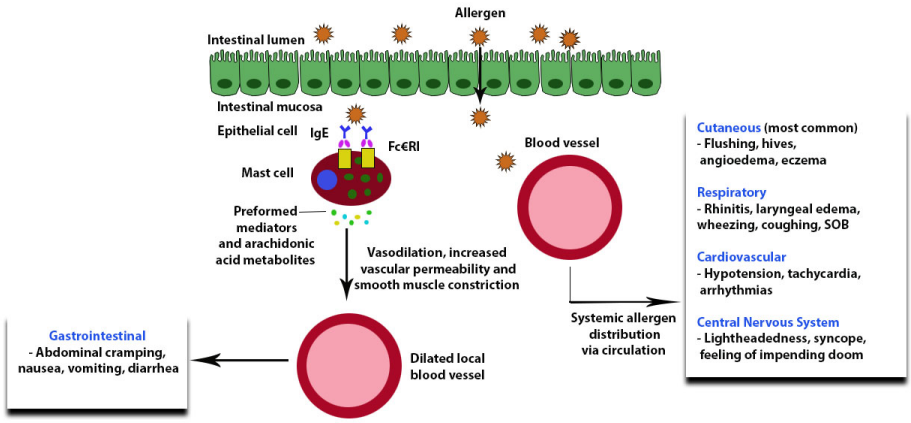
IgE-Mediated Food Allergy: Pathophysiology



IgE-Mediated Food Allergy: Pathophysiology



IgE-Mediated Food Allergy: Pathophysiology



IgE-Mediated Food Allergy: Epidemiology

Perceived Prevalence

- 20-25% of the population report food allergies

True Prevalence

- Adults: 2-5%
- Children: 6-8%
- Recent data from the US Centers for Disease Control and Prevention have demonstrated a 50% increase in prevalence from 1999 to 2011.
- Geographic variability in specific food allergens and overall prevalence.

Branum AM, *et al.* Pediatrics 2009;124:1549-55.
Sicherer, *et al.* J Allergy Clin Immunol. 2014;133:291-5.

Most Common Causal Foods in the US

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Milk/Egg

- Most common food allergens in children
- 70% can tolerate baked form
- 80% will outgrow by teenage years

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Peanut/Tree nuts

- Peanut allergy slowly surpassing milk and egg allergy in prevalence
- Most common cause of fatal anaphylaxis
- 40% cross-sensitization between peanut and tree nuts
- 20% of individuals outgrow peanut and 10% outgrow tree nuts

Most Common Causal Foods in the US

Soy/Wheat

- Affects 0.4% of children
- 5% Soy/Peanut cross-reactivity and 20% wheat/grain cross-reactivity
- 70% will outgrow by adulthood

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Fish/Shellfish

- More common in adults then children
- 50% cross-reactivity between different fish species
- 75% cross-reactivity between shellfish species
- Generally life-long allergy

Routes of Exposure

Ingestion

- Most common exposure in producing in producing systemic reactions
- Severity of symptoms related to amount consumed and other factors

Inhalation

- Possible only if food is aerosolized
- Most commonly when cooking fish/shellfish
- Symptoms are typically respiratory, but can be systemic in severe allergy

Contact

- Symptoms are typically local and cutaneous.
- Unlikely to induce anaphylaxis unless food is indirectly ingested

Simonte S, *et al*. JACI 2003.

IgE-Mediated Food Allergy: Diagnosis

History (extremely important)

- **Symptoms**: consistent with IgE mediated food allergy
- **Timing**: onset within 1-2hrs of consuming food (often more immediate)
- **Duration**: typically resolved within 24hrs unless continued exposure
- **Remitting Factors**: Improved with antihistamines, IM epinephrine
- **Reproducibility**: subsequent exposure without a reaction rules out that food
- **Concurrent Factors**: exercise, medications, illness

Boyce JA *et al.* J Allergy Clin Immunol. 2010;126:S1-58.
Sampson HA *et al.* J Allergy Clin Immunol. 2014; 134:116-43.

IgE-Mediated Food Allergy: Diagnosis (cont.)

Skin Prick and Laboratory Specific IgE Testing

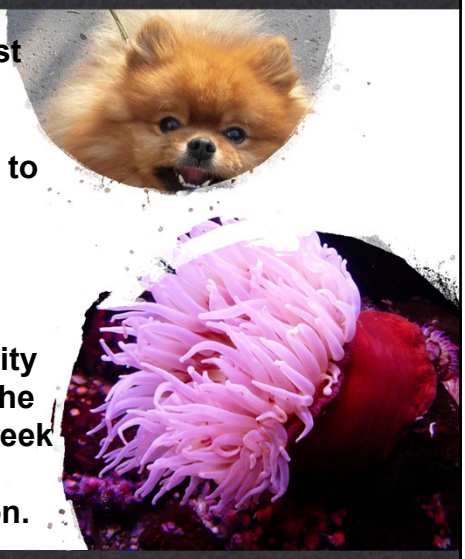
- High rate of false positives (40-50%)
- Directed testing can be helpful to confirm history
- Panels/broad screening should NOT be done

Oral Food Challenge (OFC)

- Gold standard of diagnosis
- Necessary when history and testing are inconclusive
- Performed to confirm resolution of allergy

What is anaphylaxis?

- The term anaphylaxis was first described in 1901 by Charles Richet and Paul Portier while attempting to immunize dogs to glycerine extracts from the venom of a sea anemone.
- They observed that the dogs developed increased sensitivity to the injections and coined the term anaphylaxis from the Greek "ana" meaning opposite and "phylaxis" meaning protection.



Anaphylaxis: Diagnostic Criteria

The presence of any 1 of these 3 criteria indicates that anaphylaxis is highly likely:

Simons FER *et al.* J Allergy Clin Immunol. 2011;127:587-93.

Anaphylaxis: Diagnostic Criteria

The presence of any 1 of these 3 criteria indicates that anaphylaxis is highly likely:

1. Acute onset of an illness (minutes to hours) involving skin, mucosal tissue, or both and at least one of the following:

- **Respiratory compromise**
- **Reduced blood pressure or associated symptoms of end-organ dysfunction**

Simons FER *et al.* J Allergy Clin Immunol. 2011;127:587-93.

Anaphylaxis: Diagnostic Criteria

The presence of any 1 of these 3 criteria indicates that anaphylaxis is highly likely:

2. Two or more of the following that occur suddenly (minutes to hours) after exposure to a LIKELY allergen for that patient:

- **Involvement of the skin-mucosal tissue**
- **Respiratory compromise**
- **Reduced blood pressure or associated symptoms of end-organ dysfunction**
- **Persistent gastrointestinal symptoms**

Simons FER *et al.* J Allergy Clin Immunol. 2011;127:587-93.

Anaphylaxis: Diagnostic Criteria

The presence of any 1 of these 3 criteria indicates that anaphylaxis is highly likely:

3. Reduced blood pressure **after exposure to a KNOWN allergen** for that patient (minutes to several hours).
   - In infants and children, reduced blood pressure is defined by a low systolic blood pressure for age or >30% decrease from baseline.
   - In adults reduced blood pressure is defined by a systolic blood pressure less than 90 mm Hg or >30% decrease from baseline.

Simons FER *et al.* J Allergy Clin Immunol. 2011;127:587-93.

Anaphylaxis: Acute Management

- **Intramuscular Epinephrine 0.01 mg/kg (1:1,000 solution)**
  - Delayed epinephrine administration associated with:
    - Increased risk of hospitalization
    - Increased morbidity
    - Death

- H1-antagonists (diphenhydramine, cetirizine)
- H2-antagonists (ranitidine)
- Beta-2 adreneric agonist (albuterol)

} Adjunctive Treatments

Anaphylaxis: Acute Management

Steroids?

- Although initially thought to prevent a biphasic reaction, more and more evidence shows that this is not true.
- May reduce the length of hospitalization in children admitted with anaphylaxis.
- I prescribe steroids in patients presenting with anaphylaxis and other comorbidities (poorly controlled asthma) as well as those requiring hospitalization.

Anaphylaxis: Observation

Current guidelines recommend observation for 4-24 hours

- Biphasic Reactions:
  - Historically thought to occur in up to 20% of individuals, but more recent studies closer to 4% (even less likely with foods).
  - Time of onset: 1-72 hours (median ~11hrs)
  - Factors associated biphasic reactions:
    - Delayed epinephrine or multiple epinephrine administrations
    - Severe anaphylaxis (hypotension, wheezing)
    - Prior anaphylaxis or unknown trigger
    - Diarrhea

Back to the case:

Epinephrine 0.01mg/kg was administered IM and an albuterol nebulizer treatment were administered. He was also given another dose of diphenhydramine.

After injection of the epinephrine, he was breathing comfortably and his hives resolved over the next hour without re-emergence of symptoms.

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Questions:

1. How should the family proceed with food introduction?
2. What should the family receive prior to discharge?

Risk Factors for Food Allergy

- Eczema: start of the atopic march
- Personal history of food allergy
- Personal history of asthma
- Personal history of environmental allergies
- Sibling history of food allergy

Mastrorilli, et al. Pediatr Allergy Immunol 2017; 28(8):831-840.
Tram MM, et al. Ann Allergy Asthma Immunol 120 (2018) 115–119.

What's the Deal with Peanuts?

2000-2007: US clinical practice guidelines recommended the exclusion of allergenic foods from the diets of infants at high risk for allergy and from the diets of their mothers during pregnancy and lactation.

2008-2014: Recommendations for the avoidance of allergens withdrawn secondary to a lack of evidence that avoidance prevented allergy development.

2015: The LEAP (Learning Early about Peanut Allergy) study demonstrated that early introduction of peanut to high-risk infants was associated with up to an 86% relative risk reduction in the prevalence of peanut allergy.

2017: New guidelines published recommending early peanut introduction.

New Guidelines for Peanut Introduction

Infant with severe eczema and/or egg allergy
- Introduce peanut between 4-6 months of age
- Strongly consider peanut skin prick test or specific IgE and perform office oral food challenge if necessary based on result

Infant with mild-moderate eczema
- Introduce peanut around 6 months of age

Infant without eczema or food allergy
- Age-appropriate introduction of peanut according to family preference and cultural practices

Togias A, *et al.* J Allergy Clin Immunol. 2017;139(1):29-44.

IgE-Mediated Food Allergy: Management

All patients with IgE-mediated food allergy should receive:
- An epinephrine auto-injector Rx and education on use
- Education on allergen avoidance
- A food allergy emergency action plan
- A plan for arranging further evaluation with an allergist-immunologist

Epinephrine Autoinjectors

Autoinjector dosing:

- 7.5-15 kg: 0.1 mg (Auvi-Q Only)
- 15-25/30 kg: 0.15 mg
- >25/30 kg: 0.3 mg

Give IM in anterolateral, middle third thigh

- IM administration achieves peak plasma epinephrine concentration >4 times faster then Sub-Q.
- IM administration into the vastus lateralis muscle achieves a higher peak plasma epinephrine concentration compared to IM injection into the deltoid muscle.

Simons FE, JACI Suppl. 2010.
Rudders S, *et al*. Pediatrics 2010.
Kim JS, *et al*. JACI 2005.
Rudders S *et al*. Allergy Asthma Proc. 2010.

Epinephrine Autoinjectors

Always have 2 doses available

- 6-17% of individuals require >1 dose

Ideal temperature: 77° F

- Range: 59-86° F
- Do NOT leave in car

Always check viewing window

- Degradation can occur without discoloration or precipitation

Always check expiration date

- Expired autoinjector > no autoinjector

Sischerer SH *et al*. Pediatrics. 2017.
Rudders S, *et al*. Pediatrics 2010.
Kim JS, *et al*. JACI 2005.
Rudders S *et al*. Allergy Asthma Proc. 2010.

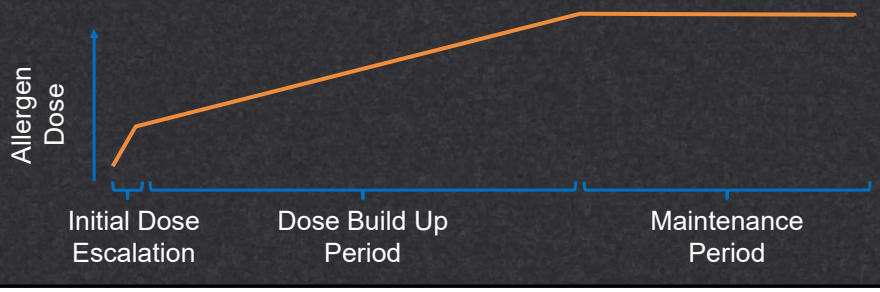
Epinephrine Autoinjector Video

Food Allergy: Finding a Cure

- Various therapies being studied on a research basis.
- Food oral immunotherapy (OIT) is the first to become FDA approved for the treatment of peanut allergy.

Food OIT Basics

- Patients with known IgE-mediated food allergy started at a low dose of allergen ingested by mouth and slowly increased over a build up period to a predefined maintenance dose.
- Maintenance dose then continued daily for a defined period of time.



Food OIT Basics

- While on daily maintenance therapy, the majority of patients are able to tolerate accidental exposures to their allergen with minimal to no symptoms (desensitization).
- After discontinuation of OIT for a period of time (typically 4-8 weeks), only 30-40% of patients will continue to remain unresponsive with oral food challenge (sustained unresponsiveness).
- Most patients will experience an adverse reaction during OIT.
  - The majority are mild, but anaphylaxis can occur.
  - Gastrointestinal symptoms are the most common.

Food OIT Benefits

- Protection against IgE-mediated symptoms with accidental exposure.
- Some patients will achieve sustained unresponsiveness and be able to continue to maintain the food in their diet ad lib.
  - Younger children seem to have more mild adverse reactions during therapy and have a higher rate of sustained unresponsiveness.
- Improved quality of life in patients receiving OIT.

Vickery BP, et al. J Allergy Clin Immunol 2017; 139(1):173-181.
Epstein-Rigbi, et al. JACI in Practice 2019; 7(2):429-436

Peanut OIT

- At the end of the study period, the majority of patients could tolerate about 2-3 peanuts
- Mild adverse reactions occurred in approximately half of participants
- In all studies looking at various OIT there is a 25-30% drop out rate

Peanut OIT Meta-Analysis

- Patients on OIT are:
- 3 times more likely to have anaphylaxis
- 2 times more likely to use epinephrine
- 2 times more likely to have serious adverse events

Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy:a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019;published online April 25. http://dx.doi.org/10.1016/S0140-6736(19)30420-9.

Risk Factors for OIT Anaphylaxis

- Higher serum specific IgE level
- Larger skin prick test
- Taking the food on an empty stomach
- Exercising within two hours of dose
- Viral Illness
- NSAID use
- Menstruation

M. Vazquez-Ortiz, M. Alvaro-Lozano, L. Alsina, M.B. Garcia-Paba, M. Piquer-Gilbert, T. Giner-Munoz, *et al.*Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test Clin Exp Allergy, 43 (2013), pp. 92-102
V. Cardona, O. Luenga, T. Garriga, M. Labrador-Horrillo, A. Sala-Cunill, A. IzquierdoCo-factor-enhanced food allergy Allergy, 67 (2012), pp. 1316-1318

Quality of Life In Food Immunotherapy

- RCT for peanut OIT (31% drop out rate, but 95% desensitization in those who remained)
- Parents reported lower QoL at baseline compared to patient report
- In the treatment group, the parental QoL improved
- Patients in OIT group had no difference to controls

Stensgaard, A., Bindslev-Jensen, C., Nielsen, D., Munch, M., DunnGalvin, A. Quality of life in childhood, adolescence, and adult food allergy: Patient and parent perspectives. *Clinical & Experimental Allergy*, 2017 (47) 530– 539
Reier-Nilsen T et al. Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial. Pediatr Allergy Immunol. 2019 Apr 23.

What is the goal of therapy?

- Oral immunotherapy is not a cure
- Patients have to continue to read labels, be careful in social food settings, and carry epinephrine auto-injector
- OIT has limitations on lifestyle
- OIT increases risk of anaphylaxis to peanut

Food OIT Summary

- OIT is the first FDA-approved therapy for individuals with IgE-mediated peanut allergy.
- Has a high success rate of desensitization, but less patients will go on to have sustained unresponsiveness.
- Is associated with frequent side-effects during therapy.
- May be safer and have higher success rates in younger children.
- May be a good treatment option for some but not all patients.