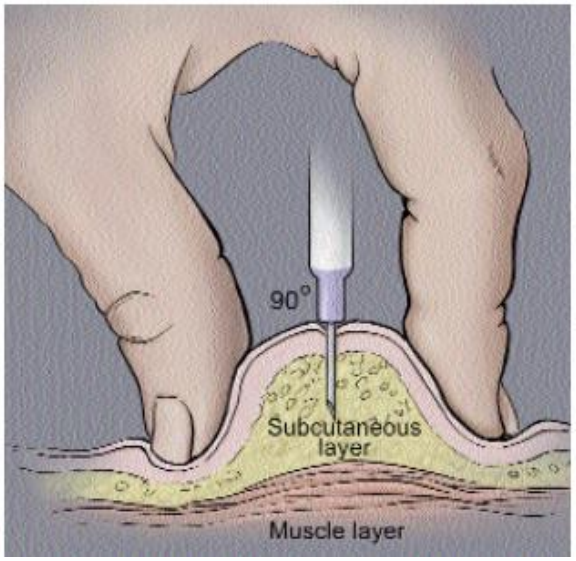
SUBLINGUAL IMMUNOTHERAPY

Objectives

- Discuss the details of subcutaneous immunotherapy
- Overview sublingual immunotherapy, including its mechanism of action, approved products, safety, efficacy and clinical approach
- Compare and contrast subcutaneous immunotherapy with sublingual immunotherapy

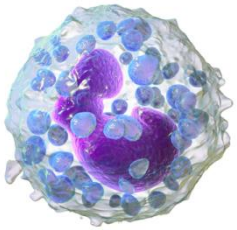
Immunotherapy Background

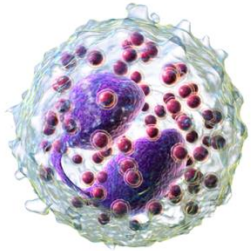
- Allergen Immunotherapy is an established therapeutic modality for the treatment of allergic diseases, including allergic rhinitis and asthma
- Traditional Immunotherapy has been administered via subcutaneous route



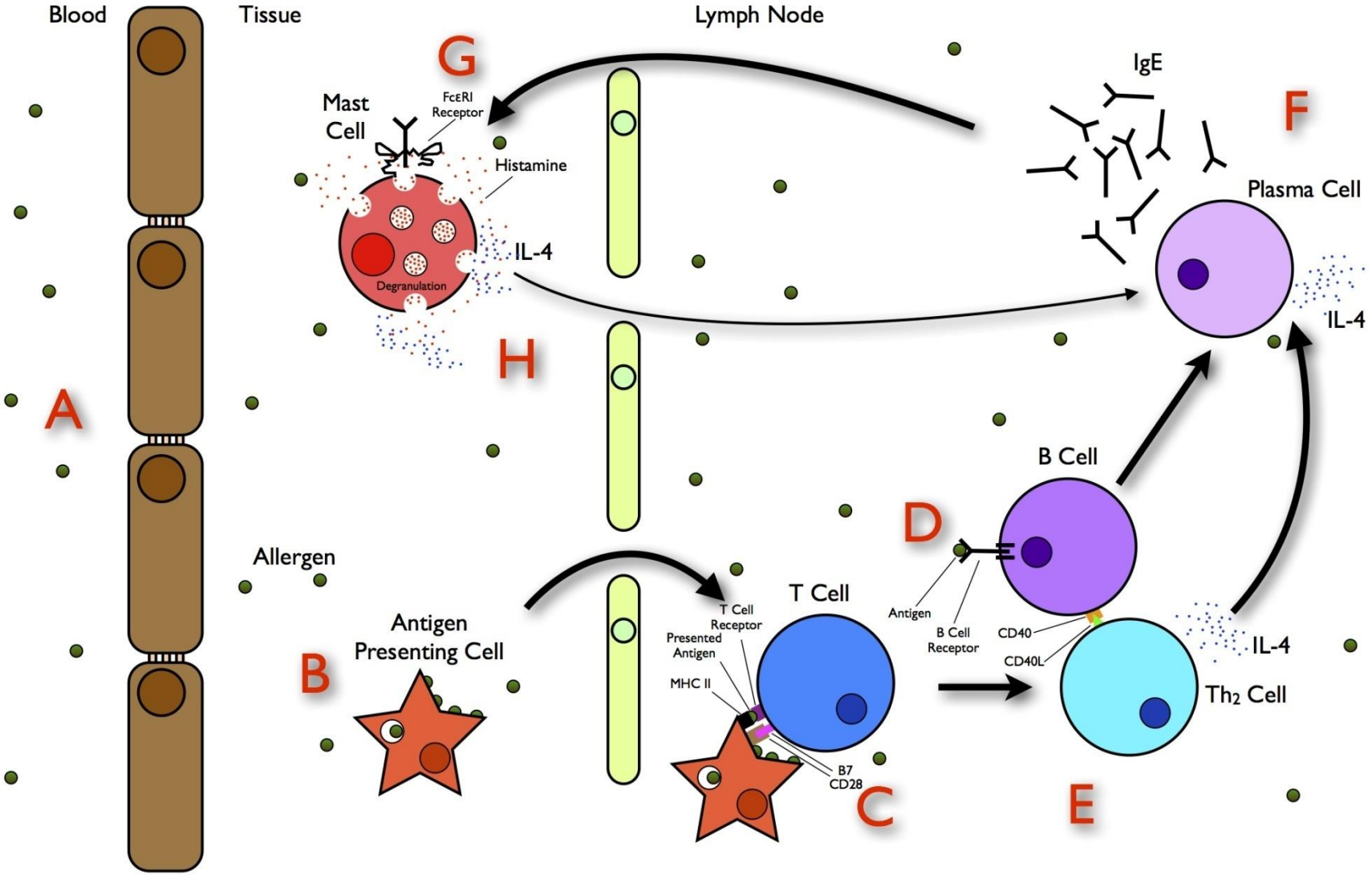
The Allergic Response

- Allergic patients exposed to an allergen often display a biphasic response
  - Early phase- involves release of mediators from local tissue mast cells and circulating basophils, including histamine, leukotrienes, prostaglandin D2, kinins, cytokines and chemokines
  - Late phase- these mediators stimulate cell recruitment to the area, leading to secondary influx of T lymphocytes, eosinophils, and additional basophils, which perpetuate the inflammation



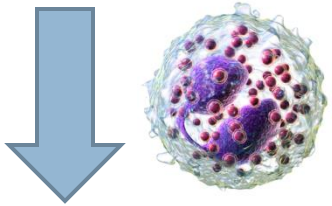


The Allergic Response



Immunotherapy

- Immunotherapy (SCIT or SLIT) alters the basic immunologic mechanisms resulting in
  - Suppression in the increase in eosinophila
  - Reduction in late-phase reactivity

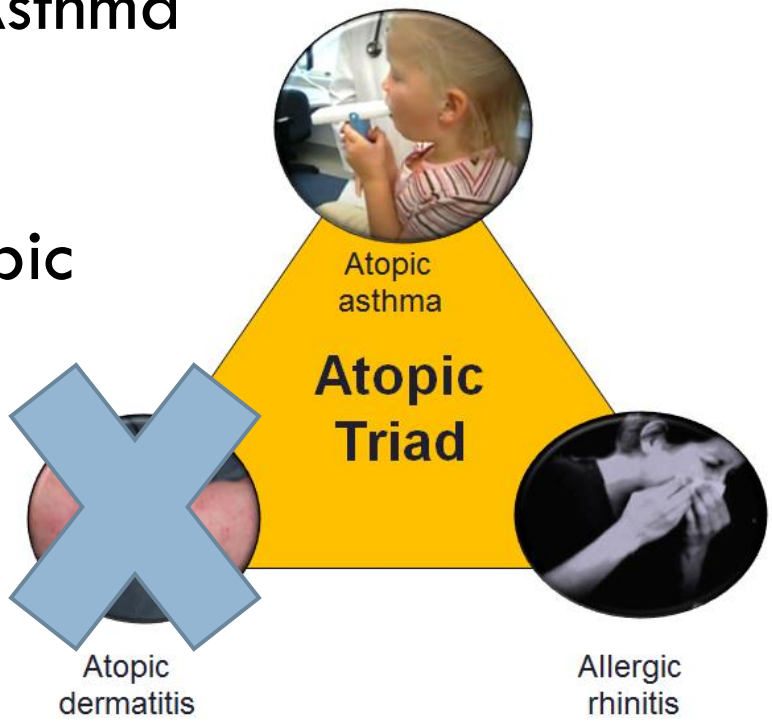


- Immunotherapy was previously thought to suppress allergen response by increasing the production of IgG antibodies (IgG4 subtype), which have an allergen-blocking effect at the mast cell/APC level
- More recent data has proven that tolerance to a particular allergen is achieved through generation of allergen-specific T regulatory cells, through IL-10 and TGF-β

SCIT Indications

- Allergic Rhinitis, with or without conjunctivitis
- Allergic Asthma
- Allergic Rhinitis + Allergic Asthma

- No established data to support use of SCIT for Atopic Dermatitis, Chronic Sinus Disease, or Aspirin-Exacerbated Respiratory Disease

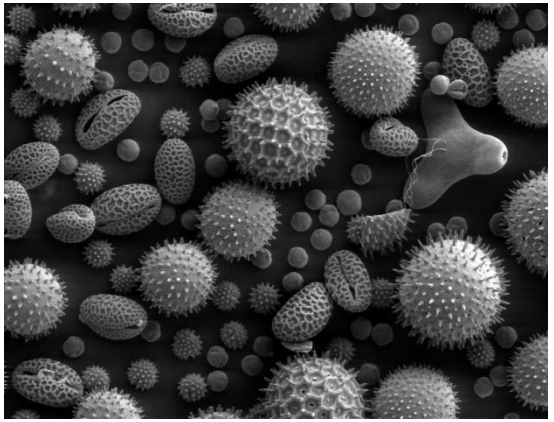


Immunotherapy: When do I treat?

- Patients are only candidates for immunotherapy if a clinically important allergic component exists to their disease
- Must establish both of the following:
  - Symptoms upon natural exposure to the antigen
  - IgE specific to the allergen present (via skin or serum testing)
- Clinician should ensure patient has maximized environmental control measures and is on optimal medication regimen (confirming compliance)

SCIT Efficacy

- Allergic Rhinitis
  - A 2007 Meta Analysis evaluated 51 double-blind placebo controlled trials from 1950-2006 assessing the efficacy of pollen immunotherapy for the treatment of allergic rhinitis in 2871 patients
    - Patients receiving immunotherapy experienced significant reductions in both symptom scores and medication use
- Allergic Asthma
  - A 2003 Meta Analysis evaluated 75 trials including 3188 patients with allergic asthma given immunotherapy to various aeroallergens, including house mites, pollen, animal dander, mold, and multiple allergens
    - Significant reduction in symptom scores, medication use and improvement in bronchial hyperreactivity

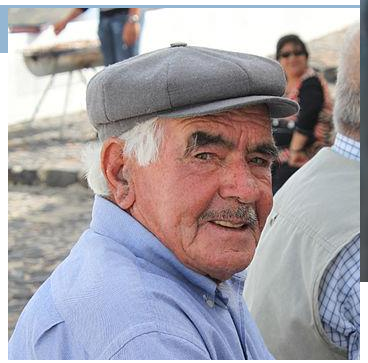


SCIT for specific antigens

- Placebo-controlled trials have shown SCIT to be effective in the treatment of the following inhalant allergens:
  - Tree Pollens (Birch and Mountain Cedar)
  - Grasses (Timothy and Grass Mixes)
  - Weed Pollens (Ragweed and Parietaria)
  - Animal Danders (Cat and Dog)
  - Dust Mites (Dermatophagoides pteronyssinus and D. farinae)
  - Molds (Alternaria and Cladosporium)
  - Cockroach

- Although other allergens are used in SCIT, their use not confirmed with placebo-controlled trials, but rather justified by analogy with proved extracts

SCIT recommendations



- Age of administration
  - No defined age limit
- Pregnancy
  - Not traditionally started during pregnancy, however can be continued in pregnant patient
- Beta Blocker Use
  - Patients receiving Beta Blockers are at risk for having poor outcome if they have anaphylactic reaction
  - Risk-benefit should weighed for switching Beta Blocker to alternative agent vs. continuing while on SCIT

SCIT Cost Effectiveness

- SCIT found to be cost effective in European and American studies
  - Significant healthcare cost benefits were demonstrated in both adults and children with Allergic Rhinitis within 3 months of SCIT initiation in one American study

SCIT Convenience

- SCIT requires time commitment, with multiple visits to healthcare provider
  - Build-up phase generally takes 3-6 months, with patients coming to receive injection a minimum of every two weeks and often multiple times per week
  - Once maintenance phase of injections is reached, visits are required every 2-4 weeks for the remainder treatment period
- Perfect compliance, however, may not be essential for improved clinical outcome
  - A study of 3000 low income children demonstrated significant pharmaceutical use 6 months following immunotherapy compared with pre-immunotherapy pharmaceutical use, despite sub-optimal compliance

SCIT Duration of Therapy

- No optimal duration of therapy is known, however consensus is duration of therapy should last a minimum of 3-5 years
  - One prospective study showed significant decrease in relapse rates in patients receiving at least 3 years of immunotherapy, than patients receiving 3 years or less

SCIT Safety

- Local Reactions- very common
  - Redness, pruritis, swelling at injection site
  - Can range from very small reaction to encompassing large portion of patient's arm

- Systemic Reactions- uncommon
  - Involve organ systems distant from injection site
  - Can range from cutaneous manifestations (at locations other than injection site) to anaphylaxis
  - Risk of systemic reactions varies with type of allergens, potency of injected allergens, modes of preparation, and dosing protocols

SCIT: Incidence of Systemic Reactions

- AAAAI(American Academy of Allergy, Asthma and Immunology/ACAAI (American College of Allergy, Asthma and Immunology) cosponsored an annual service project to track anaphylactic reactions with SCIT
  - Data gathered on 23.3 million injection visits
  - 1 confirmed fatality in 2009
  - Systemic reaction rates were 0.1%
  - World Allergy Organization Grade 4 systemic reaction rates were 1 in 1 million injections

Sublingual Immunotherapy Background

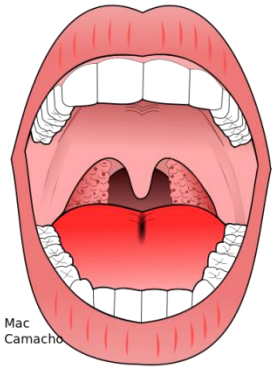
- Sublingual Immunotherapy (SLIT) has long been proposed as a method of allergy treatment and has been used in European countries for many years
- Trials performed in the 1980s demonstrated therapeutic response with specific aeroallergens
- In 2009 the World Allergy Organization published approval of SLIT as an acceptable alternative to SCIT and encouraged continual investigation for optimal techniques

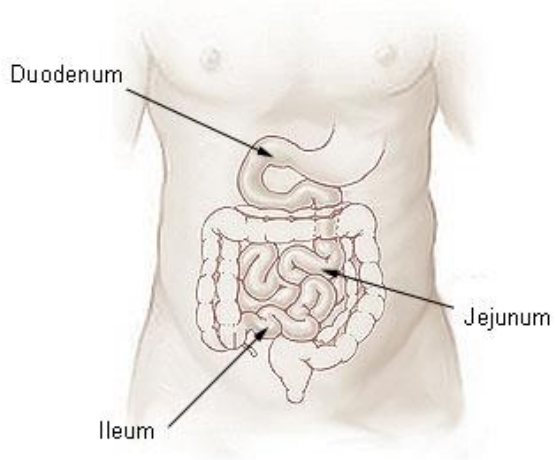
SLIT Delivery Systems

- Two main types of SLIT have shown promise in allergy therapy
  - Sublingual Allergen Tablet (SLIT-tablets)
    - Allergen formulated into a rapidly-dissolving tablet that is held beneath tongue until completely dissolved
  - Sublingual aqueous or glycerinated liquid allergen extracts (SLIT-drops)
    - Aqueous or liquid held under tongue for a period of time, then allowed to swallow remainder

SLIT Mechanism of Action

- The gut immune system is comprised of secretory IgA, gut-associated lymphoid tissue (GALT), lymphoid organ and physical barriers
- Within the GALT, the tonsils, Peyer's patches of the duodenum, jejunum, and small intestine are essential for immunologic response to oral immunotherapy





SLIT Mechanism of Action

- Sublingual allergens are taken up by dendritic cells in the mucosa and presented to T cells in the lymph nodes
- Once in lymph node tissue the production of blocking IgG antibodies and T cell lymphocytes with suppressive function play a significant role in successful allergen immunotherapy
  - Similar to SCIT, the blocking IgG antibodies produced are of the IgG4 subtype and antagonize the antigen receptors that would typically bind IgE, setting off that allergic cascade
  - T regulatory cells also play a critical role in increased suppression of allergic response through increased T cell tolerance and increased production of blocking antibodies

SLIT: Approved Products

- *Oralair*: Indicated for the treatment of allergic rhinitis associated with any one of 5 grasses
  - Timothy
  - Orchard
  - Perennial Rye
  - Kentucky Blue Grass
  - Sweet Vernel

- Approved for ages 10-65 years old
- First dose to be administered at physician's office, followed by 30 minute observation period
- Dosing units expressed as Index of Reactivity (IR)
- Ages 10-17- Day 1 one 100 IR tablet, Day 2 two 100 IR tablets, Day 3 and every day thereafter 300 IR tablet
- ≥ Age 18- Start 300 IR tablet Day 1 and continue daily
- Begin therapy 16 weeks prior to grass season and continue through grass season

SLIT: Approved Products

- *Grastek*: Indicated for the treatment of allergic rhinitis associated with Timothy grass or cross-reactive species of grass (sweet vernal, orchard/cocksfoot, perennial rye, Kentucky blue/June grass, meadow fescue, or redtop)
- Contains 2800 bioequivalent allergy units of Timothy grass
- Approved for ages 5-65 years old
- First dose administered at physician's office, followed by 30 minute observation period
- Start 12 weeks prior to grass season and continue throughout the entire season

SLIT: Approved Products

- *Ragwitek*: Indicated for the treatment of Allergic Rhinitis associated with short ragweed pollen
  - There is extensive cross-reactivity between ragweed species (short, giant, false and western)
- Each tablet contains 12 Amb a 1 units (equivalent to 12 mcg) of short ragweed pollen
- Approved for ages 18-65 years old
- First dose administered at physician's office, followed by 30 minute observation period
- Start 12 weeks prior to grass season and continue throughout the entire season

SLIT: Efficacy

- A systemic review of 60 randomized trials, involving 2300 adults and children receiving SLIT treatment showed a statistically significant reduction in symptoms and medication requirements
  - Most studies involved single pollen (mostly grasses) or house dust mite preparations
- Multiple randomized double-blind placebo-controlled trials were performed to confirm the efficacy of SLIT, and demonstrate dose-effect relationship
- In 2009 the World Allergy Organization published a position paper after gathering all data relating to SLIT therapy
  - WAO stated that SLIT is a viable alternative to SCIT for the treatment of allergic rhinitis associated with specific allergens

SLIT: Safety

- Local adverse reactions are common with SLIT, especially in the build-up phase
- Most common local adverse reactions were oral pruritis, throat irritation, ear pruritis, and mouth edema
- Systemic adverse reactions were less common an included gastrointestinal symptoms, rhinoconjunctivitis, urticaria, or combination of these symptoms
- In 38 placebo-controlled trials, involving 1688 patients and 282,894 doses of SLIT, 21% of patients reported adverse events, however AEs accounted for withdrawal in only 3%

SLIT: Safety

- Serious adverse reactions- extremely rare
- In the SLIT comprehensive review of 3984 patients and 1,019,826 doses, 14 probable SLIT-related serious adverse reactions occurred
  - 7 were asthmatic reactions, 3 were abdominal pain/vomiting, 1 was uvular edema and urticaria lasting 48 hours
- There are no fatalities that have been reported with SLIT to date
- According to the WAO position paper update in 2013, there had been 6 total report cases of anaphylaxis to SLIT
  - 2 cases were after first dose of SLIT, and 2 cases had previous anaphylaxis to SCIT

SLIT: Safety

- Pregnancy safety: Published data is lacking to address safety of SLIT in pregnancy
  - Oralair & Grastek- Category B
  - Ragwitek- Category C
- European manufacturers suggest an approach similar to SCIT, in which SLIT is not started in pregnant patient, however if women becomes pregnant during treatment, therapy can be continued provided no history of adverse reactions to SLIT in past

SLIT: Compliance

- Compliance rates varied significantly from study to study
- One US study reported attrition rate of over 40% in over 4 years
- Another European trial looked at drug sales figures, which showed SLIT prescription refills decreased from 100 percent to 44, 28, and 13 percent in years 1, 2, and 3 respectively

SLIT: Patients with concomitant asthma

- Multiple trials have examined the use of SLIT in allergic rhinitis patients with concomitant asthma
  - While many trials suggest SLIT is safe to use in milder asthma, published data is lacking for moderate to severe asthma as most studies for SLIT treatment of allergic rhinitis excluded those moderate to severe asthmatics
- Oralair, Grastek and Ragwitek manufacturers recommend avoiding use in patients with “severe, unstable, or uncontrolled asthma”

SLIT: Advantages

- SLIT appears to be safer
  - With no fatalities to date and very few anaphylactic episodes report, SLIT appear to have less incidence of serious adverse events
  - Comparing safety of SLIT with that of SCIT is difficult, as they are administered in two different settings
    - Since SCIT is administered in the medical setting and SLIT is administered in the home setting, there is considerable potential for inaccurate account of adverse events on the basis of patient's or family recall bias
  - 4 small studies with head to head safety comparisons between SLIT and SCIT were performed
    - One study found no local or systemic reactions in either (23 total patients)
    - One study found minor SEs in the SCIT group only (20 total patients)
    - One study found bronchospasm and nausea in two SCIT patients only (36 total patients)
    - One study found more Grade 3 and 4 reactions occurred in SCIT group (58 total patients)

SLIT: Advantages

- SLIT is more convenient and comfortable for patients
  - Self-administration by patients (or caregiver) at home allows avoidance of frequent office visits for injections
  - Duration of treatment with sublingual immunotherapy encompasses only the 12-16 weeks prior to and throughout the respective grass or ragweed season as opposed to year-round treatment, as is standard with SCIT
  - Beneath the tongue ingestion allows for a pain-free and much more comfortable route of administration compared to subcutaneous injection of serum

SLIT: Disadvantages

- SLIT is only approved for monoallergen therapy of allergic rhinitis associated with mixed grass or ragweed
  - In Europe the predominant view is that polyallergy does not always constitute a clinical problem and therefore the most troublesome allergy should be treated with the corresponding monoallergen SLIT
  - In the US, however, polyallergy is more common and the predominant view is to treat as many of the patient's allergies as possible with mixtures or separate extracts
  - Many common allergens (Trees, Mite, Mold, Dog, Cat) would be left untreated and would have the potential to cause significant allergic symptoms, despite treatment with the approved SLIT medications

SLIT: Disadvantages

- Combining SLIT treatments does not have FDA approval
  - Appropriate studies have not been performed to evaluate the combination of multiple SLIT treatments
  - For example, if a patient was found to be allergic to both Grass and Ragweed, the treatment periods would overlap and both SLIT treatments would have to be taken daily for that period of overlap
  - Studies have not clearly defined the affect of combining SLIT treatments on absorption, local irritation, etc. and therefore it is not recommended at this time

SLIT: Disadvantages

- SLIT is not approved for the treatment of allergic asthma
  - While SCIT can effectively be used for allergic rhinitis, allergic asthma, or both conditions, SLIT does not yet have approval for asthma treatment
  - Despite promising studies showing effectiveness in asthma, definitive data has not proven a clear role for SLIT in the treatment of asthma
  - SLIT should also be avoided in severe, unstable, or uncontrolled asthma

Questions?