SLIT IS the Preferred First-line Immunotherapy to SCIT

Allergy/Immunology Fall Journal Club
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Why debate about immunotherapy administration?

- Affects 30-60 million people annually in the US
- Societal cost of $11 billion in 2005
- Total cost of allergic rhinitis exceeded those associated with asthma, diabetes, and migraines
- Literature and practice has demonstrated clinical superiority of immunotherapy compared to pharmacotherapy
  - Induces immunologic tolerance
  - Decreases risk for development of asthma
- ...but what about SLIT vs SC IT?

New Options for AIT Are Beneficial for Both the Clinician and Adult Patient*

50M have allergic disease¹

Approximately 24M diagnosed with AR²

Approximately 10M are candidates for AIT³

Approximately 3.5M initiate AIT³

Factors Influencing Patients' AIT Initiation²,⁴
- Age
- Concurrent health problems
- Change of residence
- Inconvenience
- Cost

Factors Influencing Patients' Completion of AIT³
- Patients never return for their AIT appointment
- Patients discontinue treatment within the first 3 sessions
- Patients did not complete the recommended 3-year course of treatment

¹Adults >18 years of age in the US.
⁶Allergy Partners & Sherer. Three shots and they're out. AAAAI-Annual Meeting 2009.

Republished in Yahoo! Finance.
**SLIT in the USA Today**

- **4 FDA approved SLIT (tablets):**
  - Timothy grass - Grastek
  - Five-grass mixture - Oralair
  - Short ragweed - Ragwitek
  - House dust mite - Odactra

- **AAAAI 2018 SLIT Practice Parameter statement regarding non-FDA approved SLIT preparation:**
  “Use of such products...is currently off-label, at a practitioner’s discretion and liability, and is without recommendation for any current particular indication in the US population” (Evidence: D)

- **Chronic Urticaria**
- **Oral Immunotherapy**

- **Creticos et al conducted RW-SAIL, a double-blind, placebo-controlled study with short ragweed extract and demonstrated comparable clinical efficacy to that of the approved SLIT ragweed tablet**

- **In Europe SLIT represents most of the new AIT prescriptions with 45% of AIT patients on SLIT (range 25-80%).**

SLIT IS the Superior first line immunotherapy to SC IT

- Efficacy
- Safety
- Cost
  - Patient
  - Your Practice
- Patient Adherence/Satisfaction
Efficacy

The effectiveness of SLIT for AR/C has been confirmed by several large-scale systematic reviews:

- In 2013 Lin et al. performed a systematic review of 63 aqueous SLIT RCTs with 5131 participants, including both pediatric and adult studies with strong evidence to support the use of SLIT for allergic asthma symptoms; moderate evidence supported the use of SLIT to decrease AR/C symptoms and medication use.

- A 2011 Cochrane review by Radulovic et al. of 60 pediatric and adult SLIT DBRCTs with 4589 patients found significant reductions in symptoms and medication requirements compared to placebo (grass, ragweed, trees, cat, hdm).

- Kim et al. reviewed 13 SCIT trials (920 children) and 18 SLIT trials (1583 children) and 3 trials comparing SCIT and SLIT and found more evidence to support the use of SLIT than SCIT in children for asthma and AR/C.

Efficacy - Grastek

Reduction in Total Combined Score Demonstrates Significant Benefit

Total combined rhinoconjunctivitis symptom and medication scores (median values)

Placebo (n=167)
Grass AIT (n=173)

Nolte et al. showed that HDM SLIT significantly decreased nasal and ocular symptoms after 24 weeks of treatment.

Significant decrease in nasal symptoms was observed at all time point assessed for the 12 SQ-HDM dose.

The 12 SQ-HDM dose showed the greatest decrease in symptoms.
Efficacy

World Allergy Organization (WAO) position paper 2013

“SLIT is clinically effective in rhinoconjunctivitis and asthma”

“The available meta-analyses are in favor of SLIT (rhinitis and conjunctivitis in adults; asthma and rhinitis in children)”

“The problem of comparing the efficacy of SCIT and SLIT is still open. The comparison is technically difficult, because head-to-head comparisons need a double-blind, double-dummy design, with a careful choice of outcomes and dosages.”

AAAAI/ACAAI Task Force Report 2006

“Majority of SLIT studies reviewed demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both”
Efficacy

Proportion of subjects experiencing asthma symptoms or asthma medication use reported summer visits

FIG 4. Proportion of subjects experiencing asthma symptoms, asthma medication use, asthma symptoms and asthma medication use, asthma symptoms and asthma medication use, and having a documented FEV1 reversibility ≥12%, asthma symptoms and inhaled corticosteroids use, and documented FEV1 reversibility ≥12% during the 2-year follow-up period.
Safety

- In the **2006 AAAI/ACAAI Task Force Report**, Cox et al comprehensively reviewed 104 SLIT articles with 4378 patients and **1,818,000 doses of SLIT**.
  - There were no serious life-threatening reactions reported
  - 2.7 AEs per 1000 doses, majority of reactions were local (oral/mucosal)
  - 14 systemic serious adverse events were reported (1 serious AE per 384 patient years)
  - Systemic reactions were found to be 0.6% for SCIT vs 0.056% for SLIT, with SCIT deaths of 3.4 deaths/year and no deaths reported for SLIT

  “By far the most common [reactions for SLIT] are local symptoms in the oral cavity; however, abdominal complaints, urticaria, and asthma have been reported, although all are uncommon. Anaphylactic reactions accompanied by hypotension and fatal reactions have not been reported.”

Safety

- In a 12 year survey sent to AAAAI member practices with 646 responders (25% response rate), Bernstein et al reported 41 fatalities associated with SCIT between 1990 and 2001; a rate of 1 death per every 25 million injections.

- Epstein et al conducted a survey of AAAAI/ACAAI physician members from 2008 and 2013 with 28.9 million injection visits, including 5.6 million injection visits and 344,480 patients in year 5.

  - 4 fatalities associated with SCIT

Systemic reaction (SR) rate per 10,000 injection visits

No (SRs) among 3,343 patients undergoing off-label sublingual immunotherapy (SLIT) from 2012 to 2013:

- 1.3%
- 1.1%
- 0.3%
- 0.03%
Safety

- In all Phase III trials of FDA approved SLIT tablets there were no fatal or life threatening reactions.
- In a 2013 systematic review of allergy immunotherapy that included 74 randomized controlled trials (RCTs) of SCIT and 60 RCTs of SLIT, Lin et al. examined adverse reactions from immunotherapy.
  - No anaphylaxis in the SLIT studies.
  - However, 4 SCIT studies reported severe anaphylactic reactions.
  - The range of local reactions in the studies reviewed were similar (0.6% to 54% for the SCIT studies, and 0.2% to 97% for SLIT).
- In a review of 29 SLIT trials (13 timothy grass, 5 short ragweed, 11 HDM) with approximately 14,000 patients and 891,000 SLIT tablets received, Nolte et al. reported only 16 epinephrine administrations for treatment-related events.
  - SLIT-tablet treatment-related events of 0.002% (16/891,057) or 1.80 administrations per 100,000 tablets.
  - There were no epinephrine administrations for events related to SLIT-tablet treatment in the 7 asthma trials.

Safety

**World Allergy Organization (WAO) position paper 2013**

“Sublingual immunotherapy (SLIT) appears to be better tolerated than subcutaneous immunotherapy (SCIT)”

“The majority of SLIT adverse events are local reactions (e.g., oromucosal pruritus) that occur during the beginning of treatment and resolve within a few days or weeks without any medical intervention (e.g., dose adjustment, medication).”

**AAAAI/ACAAI Task Force Report 2006**

“By far the most common [reactions for SLIT] are local symptoms in the oral cavity; however, abdominal complaints, urticaria, and asthma have been reported, although all are uncommon. Anaphylactic reactions accompanied by hypotension and fatal reactions have not been reported.”
Pokladnikova et al compared SLIT with grass pollen extract (drops) with SCIT over three years and found equal clinical improvement with favorable economics when comparing SLIT with SCIT:

- Third party payer cost: €416 with SLIT vs €482 with SCIT per patient (p < 0.001)
- Less out of pocket patient cost: €176 with SLIT vs €255 with SCIT
- Direct and indirect costs: €684 with SLIT and €1004 with SCIT (p < 0.001)
Cost

- Seiberling et al found that as soon as US insurance plans require patients to pay 20% or more of healthcare costs and/or required weekly co-pays for shot visits, the gap between SCIT and SLIT significantly narrows and even more so when indirect costs were factored in.

*Costs include fee for the serum vial, multiple injection fee, weekly co-pay, and deductible

Cost

**TABLE 5. Cost of SLIT according to allergy practice and antigens mixed into the SLIT vial**

<table>
<thead>
<tr>
<th>Allergy practice</th>
<th>≤10 antigens</th>
<th>15 antigens</th>
<th>20 antigens</th>
<th>25 antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>950</td>
<td>1100</td>
<td>1250</td>
<td>1500</td>
</tr>
<tr>
<td>2</td>
<td>1200</td>
<td>1500</td>
<td>1800</td>
<td>2100</td>
</tr>
<tr>
<td>3</td>
<td>960</td>
<td>1140</td>
<td>1300</td>
<td>1500</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>1200</td>
<td>1500</td>
<td>1500</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>1100</td>
<td>1150</td>
<td>1200</td>
</tr>
<tr>
<td>6³</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7³</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>500</td>
<td>1000</td>
<td>1300</td>
<td>1420</td>
</tr>
<tr>
<td>9³</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>1000</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>11³</td>
<td>700</td>
<td>700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12³</td>
<td>540</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13³</td>
<td>900</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 6. Cost of SCIT vs SLIT for treatment of 15 allergens with several insurance options**

<table>
<thead>
<tr>
<th>Insurance coverage</th>
<th>SCIT ($)</th>
<th>SLIT 15 antigens ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%/30 co-pay</td>
<td>2143.60</td>
<td>700.00-1500.00</td>
</tr>
<tr>
<td>80%/0 co-pay</td>
<td>1167.20</td>
<td>700.00-1500.00</td>
</tr>
<tr>
<td>80%/20 co-pay</td>
<td>2207.20</td>
<td>700.00-1500.00</td>
</tr>
<tr>
<td>90%/10 co-pay</td>
<td>1103.60</td>
<td>700.00-1500.00</td>
</tr>
<tr>
<td>Medicare 80%/no co-pay</td>
<td>1167.20</td>
<td>700.00-1500.00</td>
</tr>
</tbody>
</table>

Cost

HDM SLIT-tablets Motivated More Patients to Initiate AIT in Germany

- New Patients 2015*: 30,721
- New Patients 2016*: 28,864
- New Patients 2017*: 28,015

Used with permission from DP Skoner
Patient Adherence/Satisfaction

- Incorvaia et al found higher noncompliance rates in patients undergoing SCIT (11%-50%) vs SLIT (3%-25%) due to more convenient administrations
  - Time of day
  - Decreased travel to and from allergist office
- In a retrospective study comparing SLIT (vials) and SCIT attrition rates, Hsu et al found that SCIT patients tended to withdraw from therapy earlier than SLIT patient with the most common reason being inconvenience.
- Penagos et al conducted a meta-analysis of 73 studies with 441 patients on the efficacy of SLIT for treatment of asthma in pediatric patients and found a significant reduction in symptoms and medication use.
- In a RCT Marogna et al found that in everyday clinical practice, SLIT reduced the onset of new sensitizations and mild persistent asthma and decreased bronchial hyperreactivity in children with respiratory allergy.

Patient Satisfaction
**Summary**

**TABLE 1. Comparison of different forms of allergy immunotherapy**

<table>
<thead>
<tr>
<th></th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness for allergic rhinitis</strong></td>
<td>Supported by systematic reviews of randomized, controlled trials</td>
<td>Supported by systematic reviews of randomized, controlled trials</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Deaths: 1 per 2.5 million injections</td>
<td>No reported deaths, anaphylaxis has been reported</td>
</tr>
<tr>
<td></td>
<td>Epinephrine autoinjection device prescription recommended</td>
<td></td>
</tr>
<tr>
<td><strong>Rate of systemic reactions</strong></td>
<td>0.06% to 0.9%</td>
<td>0.0566%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Administered in physician’s office, typically once weekly first year</td>
<td>Typically daily administration at home</td>
</tr>
<tr>
<td></td>
<td>First dose of SLIT tablet should be administered in physician’s office</td>
<td>SLIT tablet dosing preseasonal and co-seasonal</td>
</tr>
</tbody>
</table>

**FDA status**

<table>
<thead>
<tr>
<th></th>
<th>FDA approved</th>
<th>SLIT aqueous FDA “off-label” use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLIT tablets approved by FDA 2014; limited number of allergens available for treatment (Timothy, grass mix, ragweed)</td>
<td></td>
</tr>
</tbody>
</table>

**Socioeconomic**

- **CPT code exists for SCIT vial preparation and injections**
- **Covered by most insurance plans, but patient co-pay varies widely by insurance**
- **No CPT code exists for SLIT aqueous preparation.**
- **SLIT aqueous not covered by most insurance plans, out of pocket expense.**
- **SLIT tablet insurance coverage to be determined by individual insurance carriers.**
SLIT IS STILL Superior to SC IT

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## Efficacy - Comparison

Table 2: Direct comparisons of SLIT and SCIT for efficacy

<table>
<thead>
<tr>
<th>Author, year design</th>
<th>Ages (y)</th>
<th>Treatment</th>
<th>Dropouts</th>
<th>Allergen</th>
<th>Duration</th>
<th>Cumulative doses</th>
<th>Disease</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eifan, 2010 [27]</td>
<td>5–12</td>
<td>16 SCIT</td>
<td>2</td>
<td>Mite</td>
<td>1 y</td>
<td>SCIT 111 mg Der p 1/156 mg Der f 1</td>
<td>RA</td>
<td>Significant reduction of total rhinitis and asthma score, medication score, VAS, and skin reactivity $P &lt; 0.05$ versus pharmacotherapy for both SCIT and SLIT. No difference between routes of administration.</td>
</tr>
<tr>
<td>Randomized, open, controlled</td>
<td></td>
<td>16 SLIT</td>
<td>1</td>
<td></td>
<td></td>
<td>SLIT 295.5 mg Der p 1/f 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 CON</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keles, 2011 [24]</td>
<td>5–12</td>
<td>15 SCIT</td>
<td>2</td>
<td>Mite</td>
<td>18 mo</td>
<td>Der p 1: 53 mcg SLIT and 42 mcg SCIT</td>
<td>A</td>
<td>Decreased asthma attacks and use of steroids at 4, 12, 18 mo for SCIT and SCIT+SLIT, at 12 mo only for SLIT. No change in VAS for asthma with SCIT or SIT alone.</td>
</tr>
<tr>
<td>Double blind, double dummy, controlled</td>
<td></td>
<td>15 SLIT</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 SLIT</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yukselen, 2012 [62]</td>
<td>7–14</td>
<td>10 SCIT</td>
<td>1</td>
<td>Mite</td>
<td>1 y</td>
<td>173,733 TU (86,866.5 TU D pt and 86,866.5 TU Df)</td>
<td>RA</td>
<td>Significant reduction in symptom and medication score versus baseline with both treatments. SCIT better than SLIT versus placebo.</td>
</tr>
<tr>
<td>Double blind, double dummy, placebo controlled</td>
<td></td>
<td>10 SLIT</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 PLA</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparative Efficacy

- Chelladurai et al. reviewed 4 RCTs with only 2 of them had SCIT and SLIT comparative arms direct comparisons were not carried out.

- DiBona et al. performed an indirect meta-analysis of 36 RCTs and found increased efficacy for SCIT mostly within studies not across studies.

- WAO: The problem of comparing the efficacy of subcutaneous immunotherapy (SCIT) and SLIT is still open. The comparison is technically difficult, because head-to-head comparisons need a double-blind, double-dummy design, with a careful choice of outcomes and dosages.

- In 2017, Dhami et al. showed in a large meta-analysis of 160 studies showed short-term improvement in symptom scores, medication scores, and combined symptom and medication scores when SLIT was compared to SCIT but no significant difference between the two modalities.
Efficacy

- In another randomized, double-blinded trial in European adults and adolescents (14 years old) with HDM allergic asthma, Mosbech showed a significant decrease in daily ICS dose vs placebo after 1 year of treatment with HDM SLIT tablet 6 SQ-HDM.

- In a randomized double-blinded trial of European adults with HDM allergic asthma not well controlled by inhaled corticosteroids (ICS), Virchow et al showed that HDM SLIT tablet 6 and 12 SQ-HDM significantly lowered the risk of experiencing a moderate or severe asthma exacerbation vs placebo during the ICS lowering period.
Safety in Asthma

- In another large study (N = 834) of MK-8237 in subjects with asthma not well-controlled with ICS, the HDM SLIT tablet decreased the risk of experiencing a moderate or severe exacerbation during a 6-month ICS reduction period.

- Furthermore, in an assessment of 4 ragweed SLIT tablet (MK-3641, Merck/ALK) trials for AR/C, it was concluded that treatment with the SLIT tablet did not lead to acute asthma worsening and did not increase the frequency of TEAEs or AEs of concern (ie, severe allergic swellings) in adults with asthma vs subjects without asthma.
Clinical Efficacy of Dual SLIT Drops

Children and adults with allergies to TG and DM were enrolled in a single-center, randomized, double-blind, phase I study. Subjects received either TG and DM dual SLIT (n=20) or placebo (n=10) for 12 months. Maintenance daily doses were self-administered at the same time, from separate bottles. Results during the GPS following SLIT completion:

Conclusion: Pilot study suggests that dual SLIT could be an effective means to treat subjects with sensitivities to a variety of allergens.
## Safety

**Table 6 Characteristics of the SLIT-induced anaphylaxis reported in literature**

<table>
<thead>
<tr>
<th>Author, year [reference]</th>
<th>Sex (age)</th>
<th>Allergen (producer)</th>
<th>Phase</th>
<th>Onset</th>
<th>Description</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Groot, 2009 [79]</td>
<td>M (13)</td>
<td>Grass (Grazax, ALK-Abelló)</td>
<td>First dose</td>
<td>15 min</td>
<td>Generalized urticaria, swelling of tongue</td>
<td>No</td>
</tr>
<tr>
<td>De Groot, 2009 [79]</td>
<td>F (27)</td>
<td>Grass (Grazax, ALK-Abelló)</td>
<td>First dose</td>
<td>5 min</td>
<td>Abdominal cramps, asthma, generalized itching, hypotension</td>
<td>Yes (SC)</td>
</tr>
<tr>
<td>Blazowski, 2008 [80]</td>
<td>F (16)</td>
<td>HDM (Storal, Stallergenes)</td>
<td>Maintenance overdose (60 drops)</td>
<td>10 min</td>
<td>Hypotension-collapse, flushing, urticaria</td>
<td>Yes (IM)</td>
</tr>
<tr>
<td>Eifan, 2007 [81]</td>
<td>F (11)</td>
<td>Mixture (dust mite + grass pollen mix (Stallergenes))</td>
<td>Maintenance</td>
<td>3 min</td>
<td>Abdominal pain, chest pain, fever, nausea</td>
<td>Not specified</td>
</tr>
<tr>
<td>Dunsky, 2006 [82]</td>
<td>F (31)</td>
<td><em>Alternaria</em>, cat, dog grass, ragweed, (Greer)</td>
<td>2nd day of updosing</td>
<td>5 min</td>
<td>Angioedema, dizziness, dyspnea, generalized itching</td>
<td>No</td>
</tr>
</tbody>
</table>
### Summary

<table>
<thead>
<tr>
<th></th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>Physician office visits for repeat injections required, 3- to 5-y</td>
<td>Patient may administer sublingual drops at home, &gt;5-y treatment period likely most effective.</td>
</tr>
<tr>
<td></td>
<td>treatment period effective.</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local reactions</strong></td>
<td>Local reactions (skin pruritus) reported in up to 58% of patients or 10% of injections.</td>
<td>Local reactions (pruritus, floor of mouth edema) reported in up to 97% of patients.</td>
</tr>
<tr>
<td><strong>Systemic reactions</strong></td>
<td>Systemic reactions (respiratory symptoms) may occur in up to 71% of patients or 27% of injections. Fatalities may occur in up to 1 in 25 million injection visits.</td>
<td>One case of anaphylaxis reported in 1 billion administrations. No fatalities reported.</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Evidence from systematic reviews to support improved symptoms, medication scores, and quality of life.</td>
<td>Evidence from systematic reviews to support improved symptoms, medication scores, and quality of life.</td>
</tr>
<tr>
<td>Allergic rhinitis and rhinoconjunctivitis</td>
<td>Evidence from randomized controlled trials to support dust mite SCIT in the treatment of allergic asthma in children.</td>
<td>Little evidence to support use of SLIT for treatment of adult asthma. Evidence from systematic reviews and meta-analyses to support improved symptom and medication scores, and decreased asthma severity with dust mite SLIT in children.</td>
</tr>
</tbody>
</table>
Efficacy

- Five year studies of Timothy and five-grass SLIT tablets (3 years of treatment, 2 years follow up) showed
  - Timothy - 36% improvement during third year (compared to placebo) with continued improvement of 34% and 27% in the follow up years
  - Five-grass - 39% improvement during third year with continues improvement of 30% and 28% in the follow up years

Durham et al. JACI. 2012; Didier et al. Clin Transl Allergy. 2015
Scaddling et al. JAMA 2017

- 2 years is not enough for SLIT but neither was SCIT and not powered to compare

Case reports of anaphylaxis 20 and 21. Twelve nonfatal cases of systemic allergic reactions described as anaphylaxis because of SLIT have been published [20,21]. Epinephrine was not used in all of these cases. Furthermore, some of these deviated from the standard clinical practice with use of nonstandardized extracts, allergen mixtures, rush protocols, overdose, and patients who had previously discontinued SCIT because of serious adverse reactions [20]. Makatsori

- A recent systematic review of head-to-head studies of SLIT and SCIT found low-grade to moderate-grade evidence supporting that SCIT is more effective for allergic asthma and allergic rhinoconjunctivitis, but the authors cautioned that more studies are required to strengthen the evidence base.48