SUBCUTANEOUS IMMUNOTHERAPY (SCIT) IS THE PREFERRED FIRST LINE METHOD OF ALLERGEN IMMUNOTHERAPY

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ALLERGIC RHINITIS IS A SIGNIFICANT PUBLIC HEALTH CONCERN

- Prevalence of AR has continued to rise over the last 50 years
- Worldwide, 10-30% of the population and up to 50% of children
- 6th leading cause of chronic illness in the US → Over 50 million Americans
- Allergic rhinitis accounts for:
  - 11.1 million office visits
  - 3.5 million lost workdays
  - 2 million missed school days
- 36% of patients report impairment in at-work performance due to AR
- Overall productivity impairment due to AR ~40%, similar to other chronic diseases (Depression, COPD, Arthritis)
- Excess of $18 billion in annual costs

SCIT IS SUPERIOR TO SLIT

• Long history of use
• SCIT leads to disease modification
• SCIT leads to disease prevention
• SCIT is effective
• SCIT is cost effective
• SCIT has better compliance than SLIT
• SCIT is safe
• SCIT is tailored to the patient
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OVER 100 YEARS OF PUBLICATIONS

• First SCIT article, Lancet 1911 “Prophylactic inoculation against hay fever”
  • Used eye drops made of Timothy grass pollen extract to elicit reactions, noted at very low dilutions in allergic patients
  • Patients given subcutaneous immunotherapy, demonstrating an increase in resistance to pollen extract

• SLIT therapy introduced in the 1970s
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SCIT LEADS TO DISEASE MODIFICATION

- SCIT results in immunologic tolerance characterized by:
  - Decreases in the sensitivity of end organs
  - Changes in the humoral and cellular immunity

- Successful SCIT \( \rightarrow \) generation of regulatory T cells, occurring within days or weeks
  - Continued SCIT \( \rightarrow \) immune deviation from Th2 to Th1 cytokine response

- Specific IgE levels initially increase then decrease

- Increase in allergen-specific IgG (especially IgG 4) levels \( \rightarrow \) blocks IgE-dependent histamine release and IgE-facilitated antigen presentation

SCIT LEADS TO SUPERIOR DISEASE MODIFICATION

- Review comparing SCIT and SLIT studies: “The greater effect of SCIT on immunologic and tissue threshold markers is striking”
  - Specific IgG4 rose significantly in the SCIT arm
    - Never equaled or exceeded by SLIT
  - Significant decreases in SPT observed only with SCIT
  - Nasal or bronchial challenge improved only with SCIT
  - Increased CD4⁺CD25⁺ T cells observed only with SCIT

- No studies in which immunologic results were significant only with SLIT
SCIT HAS LONG LASTING EFFECTS

- Year 1
  - Patients with continuing IT success: 2.7% (CI: 0.6-7.95)
  - Patients with increasing allergy symptoms

- Year 2
  - Patients with continuing IT success: 16.7% (CI: 9.7-26.7)
  - Patients with increasing allergy symptoms

- Year 3
  - Patients with continuing IT success: 30.6% (CI: 22.1-39.9)
  - Patients with increasing allergy symptoms

- Year 4
  - Patients with continuing IT success: 32.8% (CI: 21.9-45.4)
  - Patients with increasing allergy symptoms

EBNER C. ALLERGY 1994 JAN;49(1):38-42
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SCIT PREVENTS NEW SENSITIZATIONS

• 134 children (5-8 y) with mild-intermittent asthma monosensitized to dust mite
  • 75 SCIT / 63 control
  • SCIT for 3 years and followed for 6 years
• 123 completed the study
  • 75.4% (52/69) in SCIT group vs 33.3% (18/54) in control group showed no new sensitization

P<0.0002

75.4%
33.3%
SCIT PREVENTS PROGRESSION TO ASTHMA

- 205 children (ages 6-14) with grass and/or birch pollen allergy randomized to 3y SCIT vs control
  - 147 (ages 16-25) participated in 10 year follow up
  - 117/147 no asthma at baseline

- Continued significant improvements in rhinoconjunctivitis and conjunctival sensitivity

- Significantly fewer patients had developed asthma by clinical symptoms

- OR for no-asthma 4.6 95% CI (1.5–13.7) in favor of SCIT
  - Longitudinal treatment effect (P = 0.0075)
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SCIT IS EFFECTIVE

“This review has shown that **specific allergen injection immunotherapy** in suitably selected patients with seasonal allergic rhinitis **results in a significant reduction in symptom scores and medication use**” when compared to placebo

- Allergen injection immunotherapy for seasonal allergic rhinitis, Cochrane Review 2007
SCIT is more effective than SLIT

- Meta-analysis of 36 RCT (3014 patients; 2768 controls)
- Compared the Standard Mean Difference (SMD) between the 2 groups
  - Symptom score
    - SCIT: SMD, −0.92; 95% CI, −1.26 to −0.58
    - SLIT drops: SMD, −0.25; 95% CI, −0.45 to −0.05
    - SLIT tablets: SMD, −0.40; 95% CI, −0.54 to −0.27
  - Medication score
    - SCIT: SMD, −0.58; 95% CI, −0.86 to −0.30
    - SLIT drops: SMD, −0.37; 95% CI, −0.74 to −0.00
    - SLIT tablets: SMD, −0.30; 95% CI, −0.44 to −0.16
SCIT IS EFFECTIVE FOR ASTHMA

- Reduced asthma symptoms
- Reduced use of asthma medications
- Improved bronchial hyper-reactivity
- Benefit possibly comparable to inhaled steroids
- For every 100 asthma patients treated with SCIT
  - 30 patients will be prevented from having an attack (worse symptoms)
- NNT = 4
SLIT IS NOT EFFECTIVE FOR ASTHMA

“Therefore, this meta-analysis does not demonstrate a definitive result regarding the efficacy of SLIT for asthma treatment”

• Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method, Allergy 2006.

“Lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma, so we cannot comment on the safety of SLIT for those with moderate or severe asthma.”

• Sublingual therapy for asthma, Cochrane Review 2015
SCIT IS EFFECTIVE IN POLYSENSITIZED PATIENTS

- Polysensitization is more prevalent than monosensitization
  - Europe: 16-20% monosensitized vs 13-25% polysensitized
  - US: 16% monosensitized vs 40% polysensitized
- Combined treatment for grass/birch
  - Significant reduction in median symptom medication score for SCIT 5.70 vs placebo 7.07
  - Significant improvement in rhinitis quality-of-life scores
  - Increase in both birch and grass IgG4

P<0.05
SLIT IS NOT EFFECTIVE IN POLYSENSITIZED PATIENTS

“Clinical efficacy [of slit] may be reduced with the addition of multiple allergens, **limiting SLIT use in polysensitized individuals**”

- Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract, JACI 2009

“**No studies** found efficacy of multiple allergens administered as a mixture, there is a need for further investigations **to determine efficacy and optimal formulations and regimens for multiallergen SLIT**”

- Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update, Ann Allergy Asthma Immunology 2017
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SCIT IS COST EFFECTIVE

- Florida Medicaid study matched 2771 SCIT with 11,010 controls
- SCIT patients had significantly lower 18-month median per-patient:
  - Total health care: $1625
  - Outpatient exclusive SCIT: $1519
  - Outpatient inclusive SCIT: $795
  - Pharmacy: $208
- Difference in total health care costs was evident 3 months after SCIT initiation and increased through study
  - $248 → $1625

<table>
<thead>
<tr>
<th>Table 3. Differences in Health Care Costs between IT-Treated Patients and Matched Controls During 18-Month Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Cost category</td>
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<tr>
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<tr>
<td>Total health care costs, $</td>
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<tr>
<td>IT-treated patients</td>
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<td>Matched controls</td>
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<td>Inpatient costs, $</td>
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Abbreviation: IT, immunotherapy.

P < .001 at all time points

All costs are median and per patient.
SCIT IS MORE COST EFFECTIVE THAN SLIT

- SCIT (Allergovit) vs SLIT (Oralair) for 3yr treatment over 9yr period
- Total per-patient cost of treatment
  - Austria €1,368 vs €2,012
  - Spain €2,229 vs €2,547
  - Switzerland €1,901 vs €2,220
- SCIT with superior effectiveness in symptom-score based quality-adjusted life years (QALY)
  - SCIT 8.02 vs SLIT 7.98 vs Medication 7.90
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**SCIT has better compliance than SLIT**

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MORE PATIENTS ADHERE TO SCIT THAN SLIT

• Data from Italian manufacturers: less than 15% of patients initiating SLIT reach the 3rd yr of treatment
  • 43.7% → 27.7% → 13.2%

• Pajno 1998-2003: SCIT (n=1186) vs SLIT (n=806) → 22% of patients treated with SLIT prematurely discontinued treatment during the first 3 years vs 11% SCIT

• Kiel: Retrospective study of 6486 Dutch pharmacy claims SCIT (n=2796) vs SLIT (n=3690) → 93% of patients treated with SLIT discontinued treatment before 3 years vs 77% SCIT

![Graph showing adherence rates for SCIT and SLIT](image)

- **Graph**: Pajno, 2005: 22% SCIT, 11% SLIT, P<0.001
- **Graph**: Hsu, 2012: 45% SCIT, 41% SLIT
- **Graph**: Sieber, 2011: 49% SCIT, 64% SLIT
- **Graph**: Kiel, 2003: 93% SCIT, 77% SLIT, P<0.0005
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SCIT IS SAFE IN CHILDREN AND DURING PREGNANCY

- SCIT can be initiated in **children less than 5** if indicated
- SCIT (at maintenance) **can be continued pregnant** patients
- **No evidence of an increased risk** of prescribing or continuing SCIT for a mother while breastfeeding and **no risk** for the breast-fed child

COX L. JACI 2011 JAN;127
SLIT LIMITATIONS IN PEDIATRICS AND PREGNANCY

• Only 2 FDA-approved SLIT products for children
  • Grastek (age 5) and Oralair (age 10)

• Use FDA-approved SLIT products **very cautiously** in the pregnant or breastfeeding patient → **insufficient data** regarding the **safety of initiating or continuing SLIT** during either pregnancy or breastfeeding
SLIT IS NOT AN ALTERNATIVE FOR SCIT

• “Both patients had respiratory—that is, **systemic**—side effects. In the first patient, they even progressed from large local reactions with SCIT to **respiratory reactions with SLIT, thus increasing in severity**”
  • Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy, JACI 2009

• **SLIT tablet contraindications**: severe, unstable, or uncontrolled asthma; **any history of a severe systemic reaction to any form of immunotherapy**; a history of eosinophilic esophagitis (EoE); or hypersensitivity to any of the inactive ingredients of the preparation.”
  • Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update

COCHARD M. JACI 2009 AUG;124(2):378-9; GREENHAWT M. ANN ALLERGY ASTHMA IMMUNOLOGY 2017; 118:276-282
SLIT LIMITATIONS
SLIT LIMITATIONS

• **Only use FDA-approved SLIT products** for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition

• FDA approved SLIT products:
  - Grastek (Ages 5-65) – Timothy Grass
    • Start 12 weeks prior to grass season (March through September)
  - Oralair (Ages 10-65) – 5-grass mix (sweet vernal, orchard, perennial rye, timothy, Kentucky blue grass)
    • Start 4 months prior to grass season (March through September)
  - Ragwitek (Ages 18-65) – Ragweed
    • Start 12 weeks prior to ragweed season (August through October)
  - Odactra (Ages 18-65) – Dust mite (DF and DP)
    • Year Round
MISSING ALLERGENS

Tree Allergens:
- Oak, California Black Oak, California Live Oak, Coastal White (Valley Oak), Coastal White, Western White
- Pines, Ponderosa
- Walnut, Butternut (Hickory), Walnut, English
- Other Trees:
  - Acacia
  - Box Elder
  - Elm, George Washington Elm
  - Beach Poplar
  - Blackberry, White
  - Russian Olive
  - Sorrel, Western
  - Tamarisk, Salt Cedar

Animal Allergens:
- Grasses
- Tree Pollens
- Winds
- Other Pollens:
  - Bank, Yellow Grass, Spring
  - Perennial Grass

Grass Allergens:
- Hymenochloa, Indiarice, Lepidium, Lovegrass, Ryegrass, Festuca, Poa, Holcus, Lolium, Lolium multiflorum
- Couch Grass
- Johnson Grass
- Other Grasses:
  - Agrostis, Little Brome, Wheat

Molds Allergens:
- Fungi
- Mold
- Other Molds:
  - Alternaria, Aspergillus, Cladosporium, Dendrobatidium, Penicillium, Stachybotrys, Stachybotrys

References:
- COX L. JACI 2011 JAN;127(1 SUPPL):S1-55
- BAUER CS. JACI 2014 SEP;134(3):765-765.E2
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**SCIT is tailored to the patient**
SCIT IS TAILORED TO THE PATIENT

• Standardized extracts with effective dose ranges
• Wide range of extracts: pollens (trees, grasses, weeds), animals, and molds which can be tailored to the patient based on their sensitizations
• Many ways to build-up SCIT based on patient preference and tolerance
  • Rush and Ultra-Rush schedules to reach maintenance faster
• Maintenance dosing every 4-6 weeks, tailored to patient symptoms
• Administered in a monitored setting
  • Allows for patient evaluation at each visit to assess safety
  • Allows for dosing adjustments during high-pollen season
  • Allows for dosing adjustments based on prior reactions
  • Billable procedure with each administration

EPSTEIN T. JACI IN PRACTICE 2014 MAR-APR;2(2):161-7; COX L. JACI 2011JAN;127(1 SUPPL):S1-55
SLIT is **NOT** THE PREFERRED THERAPY

- Long history
  - 100+ years vs 45 years
- SCIT leads to disease modification
  - Superior immunologic responses in comparison studies with SLIT
- SCIT leads to disease prevention
- SCIT is effective
  - Effective for asthma treatment, no data for SLIT
  - Superior symptom and medication scores in comparison studies with SLIT
- SCIT is cost effective when compared to medication
  - More cost effective than SLIT in comparison studies
- SCIT has better compliance than SLIT
- SCIT is safe for use in children and pregnant/breastfeeding patients
- SCIT is tailored to the patient
SCIT IS STILL SUPERIOR TO SLIT
SCIT SAFETY CONTINUES TO IMPROVE

• Reaction Rate: 9.4/10,000 injection visits

• Grade 1 (Urticaria, Upper respiratory symptoms): 6.6/10,000 injection visits

• Grade 2 (Asthma reactions with decreased lung function +/- GI symptoms): 2.6/10,000 injection visits

• Grade 3 (Anaphylaxis with severe airway compromise or upper airway obstruction): 0.4/10,000 injection visits

• Grade 4 (Adopted 2011 – respiratory failure or hypotension +/- LOC): 0.01/10,000 injection visits
LOCAL REACTIONS DO NOT LEAD TO DISCONTINUATION

- Analysis of 381 charts of patients who had stopped SCIT
  - Only 5.5% stated local reactions from SCIT as reason for discontinuation

- Survey of 249 SCIT patients
  - 96.6% would not stop allergen immunotherapy because of local reactions
  - 81.9% deemed local reactions not to be bothersome
SCIT FATALITY RATES ARE DECLINING

• Before 2002: 3.4 fatal reactions per year (1 in 2.5 million injection visits)
• Between 2008-2012: 1 fatality (1 in 23.3 million injection visits)
<table>
<thead>
<tr>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Established effective dose ranges</td>
<td>• Non-standardized dosing ranges</td>
</tr>
<tr>
<td>• Efficacy proven for pollen, animal allergens, dust mite, and mold/fungi</td>
<td>• FDA-Approved products include grass (timothy grass, sweet vernal, orchard, perennial rye, perennial rye, Kentucky blue grass), ragweed and dust mites</td>
</tr>
<tr>
<td>• Multi-allergen therapy</td>
<td>• No data for non-standardized allergy drops</td>
</tr>
<tr>
<td>• Customize dose amount (build-up and maintenance) to patient</td>
<td>• One standard dose (FDA-Approved products)</td>
</tr>
<tr>
<td>• Customize dosing interval to patient</td>
<td>• Daily dosing</td>
</tr>
<tr>
<td>• Safe to use in children 5 and under</td>
<td>• Missed dose (1-7 days) → contact health provider</td>
</tr>
<tr>
<td>• Ok to continue maintenance during pregnancy and breastfeeding</td>
<td>• 2 FDA-approved products for children: Grastek (age 5) and Oralair (age 10). Others are 18+</td>
</tr>
<tr>
<td>• Medical conditions that reduce the patient’s ability to survive systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy</td>
<td>• Use cautiously due to insufficient data on initiating or continuing during pregnancy or breastfeeding</td>
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<tr>
<td></td>
<td>• Contraindicated in:</td>
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<td></td>
<td>• EoE</td>
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<td></td>
<td>• Severe/unstable or uncontrolled asthma</td>
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<td></td>
<td>• History of severe systemic reaction to any form of IT</td>
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<td></td>
<td>• History of severe local reaction to SLIT</td>
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<tr>
<td>SCIT</td>
<td>SLIT</td>
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<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>• N/A</td>
<td>• Hold doses 24h after dental cleaning, 10-14 days after dental extraction and with oral lesions until healed</td>
</tr>
<tr>
<td>• Improves outcomes in patients with allergic asthma</td>
<td>• Lack of data to draw clinical conclusion per Cochrane Review 2015</td>
</tr>
<tr>
<td>• Prevents new onset of allergen sensitivities in monosensitized patients</td>
<td>• Conflicting data and use of non FDA-approved SLIT products</td>
</tr>
<tr>
<td>• Prevents progression from allergic rhinitis to asthma</td>
<td>• Conflicting data and use of non FDA-approved SLIT products</td>
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<tr>
<td>• More cost-effective in comparison studies</td>
<td>---</td>
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<tr>
<td>• Higher adherence in comparison studies with SLIT</td>
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</tr>
<tr>
<td>• Managed by board-certified Allergists and administered in clinic in observed setting</td>
<td>• Can be managed by PCP and ENT in addition to allergists.</td>
</tr>
<tr>
<td>• Billable procedure (95165)</td>
<td>• Taken at home, unable to bill aside from initial administration</td>
</tr>
<tr>
<td></td>
<td>• Risk of overdosing error at home</td>
</tr>
</tbody>
</table>
23. Bruggenjurgan B, Reinhold T. Cost-effectiveness of grass pollen subcutaneous immunotherapy (SCIT) compared to sublingual immunotherapy (SLIT) and symptomatic treatment in Austria, Spain, and Switzerland. J Med Econ. 2018 Apr;21(4):374-381.
THE END