An Update on Allergen Immunotherapy

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Disclosures

- Consultant: Genentech
- Speaker’s bureau: Genentech, Teva
Outline

- Immunologic response
- Indications
- Route and schedules
- Special considerations
- Random musings
- Real world questions
Immunologic Response

- **Very early basophil tolerance**
  - Early decrease in mast cell and basophil activity for systemic anaphylaxis

- **Induction of Treg and Breg cells**
  - Suppression of Th2-Th1 cells

- **Decreased allergen-specific lymphocyte proliferation**

- **Decreased numbers of tissue mast cells and eosinophils and release of their mediators in nasal mucosal biopsies of allergic rhinitis patients.**
  - Decreased skin late-phase response in parallel to decreased lymphocyte and eosinophil infiltration

- **Type I skin test reactivity**

- **Early increase in specific IgE**
  - Followed by a late decrease in specific IgE

- **Increase in specific IgG4 and in some studies IgA and IgG1**

Indications

- Allergic rhinitis
- Allergic conjunctivitis
- Asthma
- Stinging insect hypersensitivity
- Atopic dermatitis
- Food pollen syndrome
- IgE mediated food allergy
Allergic Rhino-conjunctivitis

Allergen injection immunotherapy for seasonal allergic rhinitis (Review)


Authors’ conclusions

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. Injection immunotherapy has a known and relatively low risk of severe adverse events. We found no long-term consequences from adverse events.

Appropriate selection of patients is the key to success!

Patient Selection

- Evaluation
- Single allergen versus multi-allergen IT
- House dust mite versus pollen
- Molds
- Cockroach
Prevention of New Sensitizations

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Polysensitized T1 (%)</th>
<th>Polysensitized T2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup A1 (rhinitis)</td>
<td>2938</td>
<td>620 (21.10)</td>
<td>702 (23.89)</td>
</tr>
<tr>
<td>Subgroup A2 (asthma and rhinitis)</td>
<td>4244</td>
<td>1086 (25.59)</td>
<td>1234 (29.07)</td>
</tr>
<tr>
<td>Group A (total)</td>
<td>7182</td>
<td>1706 (23.75)</td>
<td>1936 (26.96)</td>
</tr>
<tr>
<td><strong>DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup B1 (rhinitis)</td>
<td>499</td>
<td>318 (63.72)</td>
<td>356 (71.34)</td>
</tr>
<tr>
<td>Subgroup B2 (asthma and rhinitis)</td>
<td>715</td>
<td>508 (71.05)</td>
<td>576 (80.56)</td>
</tr>
<tr>
<td>Group B (total)</td>
<td>1214</td>
<td>826 (68.04)</td>
<td>932 (76.77)</td>
</tr>
</tbody>
</table>

Prevention of Asthma - PAT Study

SCIT for Asthma

- Included 88 trials
- SCIT directed at house dust mites, pollen, animal dander, mold, and cockroach
- Significant decrease in asthma symptoms
- Significant decrease in utilization of asthma medications
- Significant decrease in bronchial hyperreactivity
- Must account for risk of local or systemic reaction

Stinging Insects

- Yellow jacket
- Yellow hornet
- White-faced hornet
- Honeybee
- Wasp
- Fire ant
A CONTROLLED TRIAL OF IMMUNOTHERAPY IN INSECT HYPERSENSITIVITY

Kevin J. Hunt, M.D., Martin D. Valentine, M.D., Anne K. Sobotka, Ph.D., Allen W. Benton, Ph.D., Frank J. Amodio, M.D., and Lawrence M. Lichtenstein, M.D.

Table 2. Summary of Sting Challenges with Venom (Group I), Whole-Body Extract (Group II) and Placebo (Group III).

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PATIENTS TREATED</th>
<th>PATIENTS STUNG</th>
<th>SYSTEMIC REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19</td>
<td>18</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>11</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>12</td>
<td>7 (58%)</td>
</tr>
</tbody>
</table>
Venom Immunotherapy

- **Indications**
  - History of systemic reaction in the setting of appropriate IgE sensitization
  - Generalized urticaria
    - > 16 years of age: yes
    - < 16 years of age: generally no
  - Large, local reactions are generally not an indication

Venom Immunotherapy

- **Special considerations**
  - No increased risk of systemic reaction with accelerated protocols
  - Maintenance dose of q8 weeks is efficacious, and possibly q12-16 week, but not at q6 months
  - Lab evaluation: serum tryptase

- **Suggested course:** 5 years

- **Indications to consider indefinite course**
  - Severe initial reaction
  - Systemic reaction to VIT or while on VIT
  - Honeybee allergy
  - Elevated serum tryptase

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Atopic Dermatitis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Treatment Total</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman et al.</td>
<td>1.7047</td>
<td>0.6703</td>
<td>26</td>
<td>26</td>
<td>13.5%</td>
<td>5.50</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Warner et al.</td>
<td>2.2336</td>
<td>1.0494</td>
<td>9</td>
<td>11</td>
<td>10.9%</td>
<td>9.33</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Glover et al.</td>
<td>-0.3409</td>
<td>0.8283</td>
<td>13</td>
<td>13</td>
<td>12.4%</td>
<td>0.71</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Leroy et al.</td>
<td>2.6847</td>
<td>0.87</td>
<td>12</td>
<td>11</td>
<td>12.1%</td>
<td>14.65</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Galli et al.</td>
<td>0.0588</td>
<td>0.7074</td>
<td>16</td>
<td>18</td>
<td>13.2%</td>
<td>1.06</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Silny et al.</td>
<td>3.5835</td>
<td>1.3176</td>
<td>10</td>
<td>10</td>
<td>9.2%</td>
<td>36.00</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Pajno et al.</td>
<td>-4.1359</td>
<td>0.6849</td>
<td>26</td>
<td>22</td>
<td>13.4%</td>
<td>62.55</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Novak et al.</td>
<td>0.1995</td>
<td>0.3332</td>
<td>107</td>
<td>55</td>
<td>15.3%</td>
<td>1.22</td>
<td>IV, Random, 95% CI Year</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>219</td>
<td>166</td>
<td>100.0%</td>
<td>5.35</td>
<td>IV, Random, 95% CI Year</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.34; Ch² = 41.00, df = 7 (P < .00001); I² = 83%
Test for overall effect: Z = 2.74 (P = .006)

FIG 4. Meta-analysis of 8 RCTs of patients with atopic dermatitis allergen-SIT vs control. A random-effects model was used to produce data.
Food Allergy - Oral Immunotherapy (OIT)

Dose Build-up:
Daily dosing with observed
dose increases q1-2 weeks
over 3-9 months

Screening and Baseline Challenge

Initial dose escalation day
(max 10-25 mg)

Home Maintenance x months – years
(doses 500 mg to 4000 mg)

6-12 Months
18+ Months

Repeat Challenges (5-10 grams)
Many studies also include a final
challenge off therapy to distinguish
transient desensitization from
sustained unresponsiveness

FIG 1. Schematic representation of the typical approach to OIT. For SLIT, the overall scheme is similar, with far lower goal doses and a somewhat more rapid dose build-up.
Epicutaneous Immunotherapy (EPIT)
Routes of Immunotherapy

Future Immunotherapy

Injection
- Standard Extract
  - Omalizumab
- TLR-9 agonist

Intralymphatic
- Without Allergen
- With Allergens

Chemical Modification

Modified Extract

Non-injection
- Bronchial
- Sublingual
- Epicutaneous
- Oral
- Nasal
- Recombinant Wildtype
- Recombinant Hypoallergenic
- Peptide
**Degree of Immune Response**

**TABLE III.** Differences and similarities in mechanisms of SCIT and SLIT

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>SLIT</th>
<th>SCIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early desensitization</td>
<td>Not known</td>
<td>+</td>
</tr>
<tr>
<td>T-cell tolerance</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Treg cell generation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Breg cell generation</td>
<td>Not known</td>
<td>+</td>
</tr>
<tr>
<td>Role of IL-10</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Role of TGF-β</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased tissue mast cell functions</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased tissue eosinophils and mediators</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Decreased IgE</strong></td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Increased IgG₄</strong></td>
<td>+/-</td>
<td>++++</td>
</tr>
</tbody>
</table>

*SCIT*, Subcutaneous immunotherapy.
# SCIT Versus SLIT

<table>
<thead>
<tr>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available for all aeroallergens</td>
<td>FDA approved for grass and ragweed only</td>
</tr>
<tr>
<td>0.1% risk of systemic reaction</td>
<td>Negligible risk of systemic reaction</td>
</tr>
<tr>
<td>Must be administered at a medical facility</td>
<td>Can be administered at home</td>
</tr>
<tr>
<td>Year round therapy</td>
<td>Co-seasonal therapy</td>
</tr>
</tbody>
</table>

![Diagram showing efficacy and safety comparison between SCIT and SLIT](image-url)

**FIG 3.** SCIT versus SLIT: a balance of efficacy and safety.

Schedules of Immunotherapy

- **Conventional**
  - Start at dilution of 1,000-10,000 fold – 1:1 for maintenance
  - Build up dosing q2-21 days
  - ~20-25 build up doses

- **Cluster**
  - 2-3 injections per visit
  - “Same or increased frequency of systemic reaction”
  - Premedication with antihistamines is indicated

- **Rush**
  - Reach maintenance dosing within 2-6 days
  - Associated with increased risk of systemic reaction for aeroallergens but not venom

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Schedules of IT

Premedication Regimens

- Antihistamines decrease LLR and possibly systemic reactions during cluster and rush protocol for both aeroallergens and venom
- Antihistamines have not been studied in conventional schedule for aeroallergens
- LTRA possibly decrease LLR with venom
- For rush for aeroallergens, systemic steroids/H1/H2 blockers decrease risk of systemic reaction
- Omalizumab

Omalizumab

TABLE II. Systemic and other adverse reactions reported on the day of RIT for all patients (0-7 hours postinjection)*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>OM + IT (n = 36)</th>
<th>OM (n = 37)</th>
<th>IT (n = 39)</th>
<th>PL (n = 37)</th>
<th>Total (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Flushing†</td>
<td>5</td>
<td>1</td>
<td>16</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Urticaria†</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Angioedema</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Mean drop of BP ≥ 15 mm</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Itching†</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Any reaction†</td>
<td>12 (33.3%)</td>
<td>11 (29.7%)</td>
<td>22 (56.4%)</td>
<td>7 (18.9%)</td>
<td>52 (34.9%)</td>
</tr>
<tr>
<td>Anaphylaxis†</td>
<td>2 (5.6%)</td>
<td>1 (2.7%)</td>
<td>10 (25.6%)</td>
<td>1 (2.7%)</td>
<td>14 (3.3%)</td>
</tr>
</tbody>
</table>
Medications

- **Beta blockers**
  - Risk factor for more serious systemic reaction
  - Risk factor for treatment resistance anaphylaxis
  - Consider discontinuation if other equally efficacious alternatives are available (HTN, migraine prophylaxis)
  - Antidote during anaphylaxis:
    - glucagon

- **ACEI**
  - Associated with increased frequency and severity to venom but not aeroallergens
  - Consider use of ARBs
Large, Local Reactions

- > 70% of patients experience LLRs during the course of IT
- < 5% of patients stop IT due to LLR
- LLR do not predict future LLR
- Prospectively, LLR are not predictive of future systemic reactions
- Retrospectively, in patients who have experienced a systemic reaction, up to 35% had experienced a previous LLR, compared to < 10% in a group with no history of systemic reactions

Management of LLRs

Premedication with antihistamines has been shown to decrease LLR during cluster and rush protocols but not studied with conventional schedule

Practice parameter: “dose reduction for most local reactions are unnecessary”

Systemic Reactions

- Prevalence ~0.1% for conventional IT
- Prevalence up to 34% for rush IT
- Prior to 2002, ~3 fatalities annually
  - Rate of 1 per 2.5 million injections
- 1 fatality between 2008-2012
- Nearly all severe reactions begin within 30 minutes
- Risk factor for severe reaction:
  - Poorly controlled asthma
  - Dosing error
  - History of previous systemic reaction

Seasonal Timing of Systemic Reactions

Pregnancy

- IT can be continued during pregnancy but is generally not initiated during pregnancy
- Doses should not be increased during pregnancy
- No evidence to support “cutting back” dose during pregnancy
- No evidence to suggest increased risk of prematurity, fetal abnormality, or any adverse outcomes in the mother
- Some evidence to suggest decrease risk of sensitization in the unborn child
Maternal AIT

A

allergen-specific IgG₁ binding

mother
cord blood

B

allergen-specific IgE binding

mother
cord blood

Maternal AIT

Dose adjustments

- LLR
  - No

- Systemic reaction
  - Yes

- Pregnancy
  - No

- AIT during peak pollen season
  - No
Mixing Guidelines

<table>
<thead>
<tr>
<th>Allergenic Extract</th>
<th>Insects</th>
<th>Fungi</th>
<th>Mites</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insects</td>
<td>ø</td>
<td>ø</td>
<td>ø</td>
<td>Whole-body insect extracts contain very high protease levels; susceptible to endogenous proteases unless stored in 50% glycerin</td>
</tr>
<tr>
<td>Fungi</td>
<td>ø</td>
<td>ø</td>
<td>ø</td>
<td>Fungal extracts do not appear to be adversely affected by proteases;</td>
</tr>
<tr>
<td>Mites</td>
<td>ø</td>
<td>ø</td>
<td>ø</td>
<td>Mite allergens resistant to insect and fungal proteases if stored in ≥ 10% glycerin.</td>
</tr>
<tr>
<td>Pollens</td>
<td>x</td>
<td>x</td>
<td>ø</td>
<td>Pollen extracts susceptible to insect and fungal proteases; compatible with mite extracts when stored in ≥ 10% glycerin.</td>
</tr>
<tr>
<td>Cat hair/epithelia</td>
<td>ø</td>
<td>ø</td>
<td>ø</td>
<td>Fel d 1 in cat extract is highly resistant to fungal and insect proteases</td>
</tr>
<tr>
<td>Dog hair/epithelia</td>
<td>ø</td>
<td>ø</td>
<td>ø</td>
<td>Dog allergens susceptible to most fungal extracts, but more stable when mixed with insect extracts.</td>
</tr>
</tbody>
</table>

Esch. JACI 2008; 122(3): 659.
Random Musings for IT

- No minimum or maximum age
- Can be considered in patients with immunodeficiency and malignancy
- FDA requires epinephrine auto-injector for patients on SLIT
  - ? Role of epinephrine auto-injector for patients on SCIT
- Potentially cost effective

Summary

- Indications
- Route and schedules
- Safety considerations
- Special considerations
Thank You

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