Sublingual and epicutaneous immunotherapy for food allergy

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Sublingual (SLIT) and Epicutaneous (EPIT) Immunotherapy:

In sublingual immunotherapy (SLIT), a food allergen extract is kept in the mouth for 2-3 minutes and then spit out or swallowed. It is generally better tolerated and utilizes significantly lower doses as compared to OIT, but appears to have inferior clinical effects of desensitization.\(^1\) Clinical trials of food SLIT have been reported for milk, peanut, hazelnut, and peach extracts [Table 1].\(^{1-8}\)

Epicutaneous immunotherapy (EPIT) utilizes a skin patch containing soluble allergen that is absorbed into intact stratum corneum. It is an attractive approach to non-invasive immunotherapy with minimal side effects, and studies have demonstrated that EPIT commonly causes local reactions but almost never induces serious systemic adverse events.\(^9\) Randomized multi-center clinical trials are currently underway for milk and peanut [Table 1].\(^{9,10}\)
Table 1 Selected Sublingual and Epicutaneous Immunotherapy Studies

<table>
<thead>
<tr>
<th>Study/Subjects</th>
<th>Success rate</th>
<th>Immunologic changes</th>
<th>Side effects/comments</th>
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<tbody>
<tr>
<td><strong>SLIT</strong></td>
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<td><strong>Milk</strong></td>
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<td><em>Keet et al, 2012</em></td>
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<td>n=30; age 6-17 years</td>
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<td>Randomized clinical trial comparing milk OIT and SLIT with challenge performed after 12 and 60 weeks.</td>
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<td>Goal maintenance dose:</td>
<td>SLIT: 7 mg daily</td>
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<td>Low dose OIT:</td>
<td>1000 mg</td>
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<td>High dose OIT:</td>
<td>2000 mg</td>
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<td>One of 10 subjects in the SLIT group, 6 of 10 subjects in the SLIT/low dose OIT group, and 8 of 10 subjects in the SLIT/high dose OIT group passed the 8 g milk protein challenge (P = 0.002, SLIT vs OIT). After avoidance, 6 of 15 subjects (3 subjects in each OIT group) regained reactivity, 2 after only 1 week off therapy.</td>
<td>Titrated milk SPT wheal diameter and basophil activity decreased in all groups. Milk-specific IgG4 increased in all groups. Milk-specific IgE and spontaneous histamine release decreased in only the OIT group.</td>
<td>OIT was more efficacious for desensitization than SLIT alone, but was accompanied by more systemic side effects. There were symptoms with 1,802 (29%) of 6,246 SLIT doses and 2,402 (23%) of 10,645 OIT doses. However, OIT had significantly more multisystem, upper respiratory tract, gastrointestinal, and lower respiratory tract symptoms as compared to SLIT.</td>
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<td><strong>Peanut</strong></td>
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<td><em>Fleischer et al, 2013</em></td>
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<td>n=40; age 12-37 years</td>
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<td>Randomized, double-blind, placebo-controlled multicenter trial comparing peanut SLIT and placebo after 44 weeks. Placebo treated patients were unblinded, then crossed over into a higher dose peanut SLIT for</td>
<td>After 44 weeks of SLIT, 14 of 20 subjects receiving peanut SLIT passed a 5 g peanut powder challenge (or ingested at least 10-fold more peanut powder than the baseline OFC), compared with 3 of 20 subjects receiving placebo (P &lt; .001). Seven of 16 crossover subjects passed a 5 g peanut powder challenge (or ingested at least 10-fold more peanut powder than the baseline OFC) after 44 weeks.</td>
<td>Peanut-specific IgE levels increased in SLIT group between baseline and week 44, but not in the placebo or crossover group. Peanut-specific IgG4 increased in SLIT and crossover group between baseline and week 44, but not in placebo group. Basophil activity decreased in SLIT group.</td>
<td>Of 10,855 peanut doses through the week 44 OFCs, 63.1% were symptom free; excluding oral-pharyngeal symptoms, 95.2% were symptom free.</td>
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### Hazelnut

*Enrique et al., 2005*

- **n** = 23; age 19-53 years
- Randomized, double-blind, placebo-controlled trial comparing hazelnut SLIT (with standardized hazelnut extract) and placebo after 8-12 weeks.
- **Goal maintenance dose:** 22 mg daily

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<th>Median successfully consumed doses of peanut powder increased with duration of SLIT.</th>
<th>Twenty-two subjects reached their planned maximum dose after 4 days.</th>
<th>IgG4 and IL-10 levels increased after immunotherapy in only the active group.</th>
<th>A total of 1466 doses were administered: 309 during the buildup phase and 1157 during maintenance. Systemic reactions were observed in only 0.2% of the total doses administered, and they appeared only in the buildup phase. A follow up study showed that beneficial effect increases with a long-lasting period of hazelnut SLIT, and even after treatment interruptions, the beneficial effects seem to persist.</th>
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<td>Mean hazelnut quantity provoking objective symptoms increased from 2.29 g to 11.56 g in the treated group (P = .02) versus 3.49 g to 4.14 g in the placebo group (not significant). Almost 50% of subjects who underwent treatment reached the highest dose of hazelnut (20 g) during the DBPCFC, as compared to 9% of placebo subjects.</td>
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### Peach

*Fernandez-Rivas, 2009*

- **n** = 49; age 18-65 years
- Randomized, double-blind, placebo-controlled trial comparing peach SLIT (with standardized)

| All 33 subjects in the SLIT group tolerated at least 3 times (3-9 times) more peach in the DBPCFC after 6 months of SLIT. | Pru p 3 specific IgE and IgG4 increased in the SLIT group. The SLIT group had a decrease in SPT. | No serious adverse events were reported. Systemic reactions were mild, and observed with a similar frequency in both groups. Local reactions were significantly more frequent in the active group (three times), and 95% of them were restricted to the |
and placebo after 6 months.

**Goal maintenance dose:**
10 mcg of Pru p 3 three times a week

**EPIT**

**Milk**
Dupont et al, 2010
n= 19; age 10 months-7 years
Double-blind, placebo-controlled bicenter trial comparing milk EPIT (patch with milk powder) and placebo after 3 months.

**Goal maintenance dose:**
1 mg three times a week

After 90 days, EPIT treatment tended to increase the cumulative tolerated dose, from a mean ± SD of 1.77 ± 2.98 mL at day 0 to 23.61 ± 28.61 mL at day 90 (P = .18). Mean cumulative tolerated dose did not vary in the placebo group (4.36 ± 5.87 mL at day 0 vs 5.44 ± 5.88 mL at day 90).

The mean cumulative tolerated dose increment was 12-fold in the active group versus 8% in placebo group (P = .13).

Milk-specific IgE did not increase in the EPIT group.

Typically, local erythema occurred at the site of patch application and remained visible during 4 to 14 days.

Local adverse events were reported for 4 subjects in the active group and 2 in the placebo group.

Among the ITT population, 24 systemic adverse events occurred in the active group and 8 in the placebo group, with no anaphylaxis.

The mean cumulative tolerated dose increment was 12-fold in the active group versus 8% in placebo group (P = .13).

**Peanut**
Dupont et al, 2014
n= 54; age 5-17 years
Multicenter study evaluating 18 months of daily peanut EPIT (patch with peanut protein), as well as a second regimen

Twenty-five subjects receiving eighteen-month EPIT showed a treatment response of 40% overall.

The subgroup of 15 subjects aged 5-11 years receiving eighteen-month EPIT showed a 67% response rate. Cumulative reactive dose for this group

In the 5-11 year age group receiving eighteen-month EPIT, a progressive IgG4 was seen over time.

(Abstract, study not yet published).
of placebo for 6 months followed by 12 months of daily peanut EPIT. Goal maintenance dose: 100 mcg peanut protein daily increased constantly over time; at baseline, it was 24.27 ± 29.98 mg peanut protein, and by 18 months it was 357.7 ± 542.9 mg peanut protein (P < 0.001 between serial values).

Abbreviations: SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy; SPT, skin prick test; OFC, oral food challenge; DBPCFC, double-blind placebo-controlled food challenge; ITT, intention to treat.

References: