Sublingual and epicutaneous immunotherapy for food allergy

Anna Nowak-Węgrzyn, MD

Associate Professor of Pediatrics, Icahn School of Medicine at Mount Sinai, Department of Pediatrics, Kravis Children's Hospital, Division of Allergy and Immunology, Jaffe Food Allergy Institute, New York, New York, USA

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

Study/Subjects	Success rate	Immunologic changes	Side effects/comments
SLIT			
Milk *Keet et al, 2012*[6] n=30; age 6-17 years Randomized clinical trial comparing milk OIT and SLIT with challenge performed after 12 and 60 weeks. <u>Goal maintenance dose:</u> SLIT: 7 mg daily Low dose OIT: 1000 mg High dose OIT: 2000 mg	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.	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.	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.
Peanut *Fleischer et al, 2013*[8] n=40; age 12-37 years 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	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 < .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.	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.	Of 10,855 peanut doses through the week 44 OFCs, 63.1% were symptom free; excluding oral-pharyngeal symptoms, 95.2% were symptom free.

44 weeks. <u>Goal maintenance dose:</u> Minimum dose of 165 mcg and maximum dose of 1386 mcg daily Crossover Group: Maximum maintenance dose of 3696 mcg daily	Median successfully consumed doses of peanut powder increased with duration of SLIT.		
Hazelnut *Enrique et al, 2005*[3] 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. <u>Goal maintenance dose:</u> 22 mg daily	Twenty-two subjects reached their planned maximum dose after 4 days. 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.	IgG4 and IL-10 levels increased after immunotherapy in only the active group.	A total of 1466 doses were administered: 309 during the build-up 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.[4]
Peach *Fernandez-Rivas, 2009*[5] 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

peach extract) and placebo after 6 months. <u>Goal maintenance dose:</u> 10 mcg of Pru p 3 three times a week			oral cavity.
EPIT			
Milk *Dupont et al, 2010*[9] 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. <u>Goal maintenance dose:</u> 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 estimated risk of local eczema was higher in the active group than in the placebo group.
Peanut *Dupont et al, 2014*[10] 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.

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