

The Clinical Utility of Epicutaneous Immunotherapy for Peanut Allergy

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Fleischer DM, Greenhawt M, Sussman G, Bégin P, Nowak-Węgrzyn A, Petroni D, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: The PEPITES randomized clinical trial. *JAMA* 2019;321:946-55.

BACKGROUND

Immunotherapy for peanut allergy is being explored via the sublingual, oral, and epicutaneous routes. A retrospective study, pooling data from 3 prospective studies of peanut oral immunotherapy (OIT), found that it was efficacious, but 80% of subjects experienced an adverse event (AE).¹ Although most AEs were mild, systemic reactions were reported in 42% of patients and 10% withdrew because of gastrointestinal symptoms. Treatments included antihistamines (59%) and epinephrine (12%).¹ A meta-analysis of allergen immunotherapy to foods found similar results.² In another OIT study, 95 systemic reactions requiring epinephrine occurred in 352 treated patients, and OIT success rate, defined as reaching the maintenance dose set by the study center, was 85%.³ A phase 2 trial of standardized peanut OIT and an OIT meta-analysis found OIT effective but with significant risks of systemic reactions.^{2,4} There are fewer studies in the literature for sublingual immunotherapy (SLIT), but the data available suggest that SLIT is less effective than OIT.^{5,6}

In a phase 1 trial of epicutaneous immunotherapy (EPIT), only 2 of 80 patients reported systemic symptoms.⁷ Although 52% of patients on treatment experienced AEs, most were mild and none required epinephrine. In a phase 2b peanut EPIT trial, 50% of treatment patients showed response, defined as a posttreatment food challenge eliciting dose of 10 times or more greater than the pretreatment eliciting dose and/or 1000 mg or more of peanut protein, versus 25% of placebo patients.⁸ Although most AEs were

local skin reactions, 1 patient had moderate anaphylaxis “possibly related to therapy” and 3 of 221 trial patients, 2 on 50- μ g patch and 1 on the 250- μ g patch, reacted after accidentally ingesting peanuts. Three of 165 peanut patch-treated patients discontinued the study because of AEs.⁸ Based solely on safety data thus far, EPIT may be a more attractive method of immunotherapy because it avoids oral allergen delivery. However, more data to support clinical decisions are needed.

METHODS

Fleischer et al⁹ performed a phase 3, multicenter, randomized, double-blind, placebo-controlled peanut EPIT trial. A total of 356 children aged 4 to 11 years with positive double-blind placebo-controlled food challenges to peanut were randomized to receive treatment with a peanut or placebo patch. Patients were stratified as low or high eliciting on the basis of the dose triggering objective symptoms during initial double-blind placebo-controlled food challenge with doses of 1, 3, 10, 30, 100, and 300 mg of peanut protein. Low-eliciting patients reacted at doses up to 10 mg, and high-eliciting patients reacted between 30 and 300 mg of peanut protein. Participants were then randomly assigned 2:1 to receive peanut or placebo patch. The patch was applied for 3 hours at the study site and then daily application was performed at home for 6 hours a day in week 1, 12 hours a day in week 2, and 24 hours thereafter.

After 12 months, subjects again underwent double-blind placebo-controlled food challenge. Response was defined as a posttreatment eliciting dose of greater than or equal to 300 mg in the low-eliciting subgroup and greater than or equal to 1000 mg in the high-eliciting subgroup. A predetermined threshold of 15% on the lower bound of the 95% CI was set and if met, would have resulted in a positive trial result and analysis of secondary outcomes. This threshold was selected after discussion with the Food and Drug Administration, because it has been used to study other new pharmaceuticals including SLIT for aeroallergens. There is no known meaningful clinical or biologic significance to this number, nor is there any criterion standard treatment to use for comparison of effect size.

Treatment emergent adverse events (TEAEs) were all assessed by blinded investigators and event severity was graded. Site investigators assessed the event relationship as related, probable, possible, unlikely, or not related to study drug.

RESULTS

The mean adherence rate, defined as the total number of patches applied in the treatment period divided by the number of days in

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that period, was 98.5%. Response rate in the treatment group was significantly higher, 35.3%, compared with 13.6% in the placebo; however, the CI was 12.4% to 28.9% and the predetermined threshold of 15% was not met. Intention-to-treat, per-protocol, and full-analysis results all significantly favored treatment. Supplemental analysis shows that 62.6% of the treatment group and 28% of the placebo group had an increased eliciting dose at trial completion. The median cumulative reactive dose in the treatment group increased from 144 mg at baseline to 444 mg at 12 months. The low-eliciting subgroup response rate had a 95% CI of -6.4 to -38.4 . The number needed to treat to have one person's response rate above placebo was 5.

TEAEs occurred in 95.4% of treatment and 89% of placebo groups. These events consisted mostly of local application-site irritation and mild to moderate skin reactions. There was a trend toward increasing grades of skin reactions as time progressed. There were 4 serious TEAEs, categorized as moderate anaphylaxis, all in the peanut patch group. Two participants discontinued participation because of TEAEs. There were no trial-related gastrointestinal TEAEs.

CRITICAL APPRAISAL

The study was well designed, had excellent adherence, patient retention, and favorable safety profile, and showed a statistically significant response rate and increase in cumulative reactive dose compared with placebo. This increase may confer significant risk reduction from most accidental exposures due to cross-contamination.¹⁰ The lack of gastrointestinal TEAEs combined with low rates of TEAEs requiring epinephrine show that EPIT avoids many major pitfalls of OIT.

A notable issue with the study is the lower than expected number of enrollees in the low-eliciting subgroup, with lower than expected response rate and higher than expected placebo response rate within this subgroup. Although the high placebo response may be due to an unusual number of patients with natural resolution of disease, no explanation is given for these findings. Because the low-eliciting subgroup appears phenotypically different from the high-eliciting subgroup, it would be beneficial to study these patients separately, in a large cohort with increased power and more focus on predictors of response. Understanding how the low- and high-eliciting subgroups differ in terms of natural history of disease and response to therapy would also allow for proper patient selection.

Patients who had severe anaphylaxis to peanut were excluded from the study because of ethical and safety concerns from study-required food challenges and therefore these results cannot be applied to this cohort. However, because of the potential severity of their reaction, these patients would be the most likely to benefit from effective immunotherapy and associated risk reduction. Thus, the safety of EPIT in this cohort should be studied.

RECOMMENDATION

Although the study did not reach the predetermined threshold for a positive result, it did demonstrate a significant response rate to peanut EPIT. Reports for peanut OIT show greater efficacy, but these studies also have greater numbers of patients experiencing gastrointestinal effects and anaphylaxis and electing to

withdraw from treatment.^{3,11,12} There is currently no comparable therapy with a similar safety profile as EPIT and therefore clinicians should still consider its use. Alternatives such as SLIT show less efficacy than OIT without reduction in gastrointestinal side effects.⁵ This argues for the use of EPIT in the right cohort of patients including those with baseline predictors of adverse events to OIT and those who cannot tolerate OIT because of side effects. There is currently no formal trial that compares EPIT, OIT, and SLIT head to head. Studies with head-to-head comparisons of SLIT and OIT have suffered from low numbers of patients. The field would greatly benefit from a large trial comparing these methods.

There is an ongoing peanut EPIT study that will provide additional information about the high-risk patients excluded from the present study.¹³ This study will also investigate whether a longer duration of therapy may increase therapeutic benefit.^{9,13} These upcoming results, combined with data on predictors of response and adverse events to OIT and EPIT, will be crucial for clinicians when selecting appropriate patients to receive peanut EPIT.

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