

Is epicutaneous immunotherapy only skin deep?

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Peanut food allergy is a major public health concern because of the increasing prevalence over the past decade, the low rate of spontaneous recovery, and the relatively high rate of fatal accidents. In addition to its burden on health care delivery, peanut allergy significantly reduces quality of life for both patients and their families.

Interestingly enough, the peanut food allergy epidemic is at least partially iatrogenic, enhanced by previous international recommendations to postpone the introduction of peanut to high-risk populations. Although new recommendations were recently published,¹ their implementation poses major cost and logistic challenges.² Thus it is possible that a continued increase in prevalence can precede the desired decrease.

For many years, avoidance was the only option and, together with carrying an epinephrine autoinjector, is still the standard of treatment. However, even with meticulous avoidance, frequent and potentially life-threatening reactions do occur. Since 2005, numerous articles describing various protocols of peanut oral immunotherapy (OIT) have been published.^{3,4} Peanut OIT has a high rate (70% to 85%) of full desensitization, which is defined as the ability to eat a dose of peanut protein that is considered safe for free peanut consumption. However, there are several concerning issues that render the OIT solution less than optimal.

First, the prevalence of adverse events (AEs) during treatment and even after reaching full desensitization is not insignificant. Although most AEs are mild and the frequency of these AEs decreases with time,⁵ more severe reactions requiring the use of adrenaline do occur.⁶

Second, the majority of successfully treated patients do not acquire sustained desensitization. Once they discontinue consuming peanuts regularly, their threshold to reaction decreases gradually.

Third, the process itself is long, time-consuming, and expensive to implement and requires medical supervision during the buildup phase.

Finally, the immunologic mechanisms responsible for the state of desensitization are not fully understood, and even some of the identified aspects tend to be temporary⁷ and do not necessarily parallel the clinical response.

In this issue of the *Journal*, Jones et al⁸ report the results of a multicenter trial using a novel type of immunotherapy modality, epicutaneous immunotherapy (EPIT). EPIT is based on epicutaneous delivery of antigen rather than through the oral or sublingual route. In the present study 2 doses of Viaskin Peanut (VP; DBV Technologies, Montrouge, France) were compared versus placebo in children and young adults with peanut allergy. The primary end point was a 10-fold increase in the successfully consumed dose over baseline at the end of 52 weeks of treatment. This end point was achieved in 45.8% and 48.0% of the VP100- and VP250-treated participants, respectively, but only in 12% in the placebo-treated subjects. However, a *post hoc* analysis revealed that by using a stricter definition of success, less than 15% of the treated patients both had a 10-fold increase in the successfully consumed dose over baseline and could tolerate at least 1044 mg of peanut protein. Furthermore, participants who were older than 11 years demonstrated no treatment success for any of the criteria.

Despite the limitations of EPIT, however, there are several encouraging take-home messages from this study. First, there were very few AEs, and of those, most were mild, consisting of local itching. No nonanaphylactic gastrointestinal AEs were recorded,⁹ although this might be reflective of the small number of subjects studied.

Second, in at least younger children, there was a significant increase in the threshold of reaction to peanut. The no-observed-AE level achieved by VP immunotherapy might provide some reassurance for children with peanut allergy from inadvertent contact with or consumption of peanut-tainted products. By itself, this might improve the social lives of children with peanut allergy and their families.

Third, because of the relatively mild and tolerable local side effects, VP immunotherapy achieved a high rate of adherence to treatment.

Finally, some of the immunologic changes induced by VP, such as increases in peanut protein-specific IgG₄ levels and IgG₄/IgE ratios and, to a lesser degree, some of the reduced T_H2 and basophil responses during treatment, are similar to those observed with oral OIT.⁸ A mouse model in which EPIT protects against anaphylaxis promises to provide a unique model to further elucidate its mechanisms of desensitization.¹⁰

A major limitation for EPIT is that its benefits are restricted to a younger age group, especially when other immunotherapy modalities are viewed from the same perspective. For example, it was recently demonstrated that in young subjects OIT has a higher rate of full desensitization with a relatively low rate of concerning AEs.¹¹ In older patients the issue of AEs can be minimized and the treatment protocol can be accelerated through addition of omalizumab during OIT.¹² Alternately, sublingual immunotherapy¹³ can be used at the expense of achieving a lower tolerable dose. In the final analysis, despite the potential morbidity from OIT, no AEs ended with permanent or residual damage, and the gastrointestinal eosinophilic esophagitis-type reactions were reversible on cessation of

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TABLE I. Relative frequencies of results in various OIT modalities

Parameter	Type of immunotherapy				
	OIT	SLIT	OIT + omalizumab	VP	
Clinical outcome					No data yet in
Full desensitization age <11 y	++++	++	++++	++	peanuts, but similar
Full desensitization age >11 y	+++	++	++++	0	approaches for egg
Partial desensitization age <11 y	++++	+++	++++	+++	and milk have been
Partial desensitization age >11 y	++++	+++	++++	+	reported.
Sustained unresponsiveness (tolerance?)	++	+*	++/+++†	NA	
AEs	++++	++	+	+‡	
AEs with permanent damage	0	0	0	0	

Results are graded from the most frequent (++++) to least frequent (+) or unreported result (0).

NA, Not available; SLIT, sublingual immunotherapy.

*Isolated cases.

†Effect of omalizumab.

‡Consisting of mild irritation.

treatment. In Table I the various food immunotherapy modalities are qualitatively compared to produce an overview of their strengths and weaknesses. Because of the differences in sample size, characteristics of the investigated patients (eg, age and inclusion and exclusion criteria), and lack of head-to-head comparisons, we estimated the frequency of each parameter among the various OIT treatments.

Several unsolved questions have to be answered before the merits of EPIT can be considered. Would higher doses of allergen immersed into the patches provide further benefit without the cost of more frequent or more severe side effects? The answer to this question based on the present study⁸ is likely no because there was no advantage of VP250 over VP100.

Would a longer duration of application yield a higher tolerable dose in the young participants and perhaps even induce a significant effect in the older patients? There is no definitive answer to this question, but there was a tendency toward improvement, even in the older subjects (see Fig 2, B, in Jones et al⁸). Even if the level of sustained achievement is better with OIT, a higher rate of compliance of EPIT over an extended period of time might compensate for this modality of treatment. However, if the long-term adherence to disturbing patches turns out to be problematic, then its use in the older group would be limited.

Finally, the cost/benefit ratio of EPIT versus OIT needs to be evaluated. The main drawback of OIT with omalizumab is its high cost, and a comparison with the expected long-term cost of EPIT needs to be assessed.

Despite the limitations of this treatment modality, EPIT is clearly an important addition to the growing armamentarium of peanut allergy treatments. Although this treatment modality might not achieve levels equal to those of OIT, it certainly could have a place in providing an initial treatment for patients with severe peanut allergy to increase their tolerable threshold. This might indeed save lives by avoiding anaphylaxis resulting from accidental exposure and could also enable admission into subsequent immunotherapy programs, such as OIT.

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