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EDITORIAL



Epicutaneous immunotherapy: the next step for food allergy desensitization

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1. Introduction

Food allergy is a global health problem affecting 5–8% of adults and children respectively [1]. The current standard of care for food allergy remains strict avoidance of the allergen, reading product labels, education, and appropriately treating any accidental exposures [1]. However, even with meticulous avoidance, frequent and potentially life-threatening reactions do occur [2]. In the past decade, significant advances have been made in the field of specific food immunotherapy, including oral (OIT), sublingual (SLIT) and epicutaneous immunotherapy (EPIT) [3]. Each of these approaches is intended to induce some level of desensitization with chronic or repeated exposure to the allergenic food protein, although the risks and potential benefits of each treatment differ significantly [4].

Desensitization depends on regular food exposure; when dosing is interrupted (e.g. due to illness or nonadherence), the protective effect of desensitization is lost. Permanent tolerance is defined as the ability to ingest food without symptoms despite prolonged periods of avoidance or irregular intake [5]. The dual-allergen-exposure studies emphasizes that skin as well as GI tract are seriously involved in food allergy and several studies of the involved molecular and cellular factors are ongoing [6]. Both routes of therapy for desensitization are studied, but combining both, for example, SLIT and EPIT, have never been examined.

OIT has been the most extensively studied form of therapy. Numerous single-center studies have been published; although they have demonstrated induction of varying degrees of desensitization, there is concern about significant risk of severe treatment-associated local and systemic adverse events [7]. Moreover, only a minority of treated patients achieve any measure of longer-term tolerance. Furthermore, SLIT has been studied in a smaller extent. SLIT efficacy is limited by allergen dose due to low concentration of the available extracts and the volume that can be held sublingually; however it is generally better tolerated than OIT with less severe adverse reactions [5].

2. EPIT

EPIT, a relatively novel therapy that is currently under investigation, uses an allergen absorbed patch (DBV Technologies, Montrouge, France), which in murine models has been shown

to deliver allergen to the epidermal layer of normal intact skin, where it is taken up by Langerhans cells and transported to the regional lymph nodes [8]. This novel alternative for OIT and SLIT with food allergens has garnered much interest as a potentially safer approach for treating food allergies [9].

In 2010, the first pilot was performed with cow's milk allergen patch and more recently, phase I, IIa and IIb studies have been performed with the VIASKIN® Peanut (DBV Technologies, Montrouge, France) [10,11]. In these studies, the VIASKIN Peanut of 100 and 250 µg were compared with placebo in children and adults and evaluated for clinical response, safety and immunologically effects in treating peanut allergy. The primary endpoint was a 10-fold increase in the successfully consumed dose over baseline at the end of 52 weeks of treatment.

In the phase 2b study, a significant absolute difference in response rates was observed at month 12 between the 250-ug and placebo patches (difference 25%; 95%CI, 7.7%–42.3%; $p = 0.01$), contrary with the 100-ug patch that showed no significant difference. An age effect has been noted, with improvements between the 250-ug and placebo patches seen primarily in children aged 6–11 (19.4%; difference, 34.2%; 95%CI, 11.1%–57.3%; $p = 0.08$). No meaningful differences between the peanut patch and placebo were observed in the adolescents/adults group ($p = 0.40$). Patients completing this phase 2b trial were invited to participate in a 2-year extension trial (phase 3) using the 250-ug patch to assess efficacy for up to 36 months [10].

3. Safety, efficacy and adherence.

EPIT demonstrates a high-safety profile, with majority of AE's being mild and localized to the skin patch site. Topical treatment with corticosteroids and/or oral antihistamines was sufficient to relieve symptoms. Unlike OIT and SLIT, no persistent GI symptoms or eosinophilic esophagitis has been reported with EPIT treatment [12]. Concerning efficacy, OIT is superior compared to SLIT and EPIT. Efficacy of SLIT is limited by the low dose of the allergen delivered sublingually, and EPIT has a modest treatment effect that is greater in younger children [5]. In unpublished data from the EPIT phase 2b extension trial, it has been suggested that longer duration of immunotherapy might lead to greater efficacy [10]. Further reasons for the

different response in adolescents/adults compared with children might be less permeable stratum corneum, smaller patch size relative to total body size and possibly less immunologic plasticity in older patients. In clinical studies, EPIT shows high rates of adherence (all > 96%) and a low rate of drop-outs (0.9%), most likely due to the easy-to-use patches and their limited side effect profile. So far, none of the therapeutic approaches have been proven to deliver a permanent cure of peanut allergy [13]. Combinations with other therapies have not been studied yet, but might be a plausible idea. Currently, VIASKIN® Peanut is one of the first products to reach development in phase 3 and assuming that the product is approved by the US Food and Drug Administration (FDA), the integrating of the product into clinical practice is expected by the end of 2019 [14].

4. Conclusions

EPIT represents an important addition to the growing options for treating food allergies and might indeed save lives by avoiding anaphylaxis resulting from accidental exposure. Several clinical trials of EPIT have been completed, showing favorable safety profiles and good tolerability leading to high adherence rates, but provides more modest levels of protection than many had hoped. Clearly, safety should remain the preeminent driving force in treatment options for peanut allergy. In that perspective EPIT might be the best treatment method for now and all efforts should be made to increase clinical efficacy by fine-tune duration, concentration and exposed surface area.

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