Novel Delivery Routes for Allergy Immunotherapy

Intralymphatic, Epicutaneous, and Intradermal

Gabriela Senti, MD[a], Thomas M. Kündig, MD[b,*]

KEYWORDS

• Epicutaneous allergy immunotherapy • Transcutaneous allergy immunotherapy
• Respiratory allergy • Food allergy

KEY POINTS

- Subcutaneous immunotherapy deposits the allergen in the fat rather than stimulating the immune system. Therefore numerous injections are required to ameliorate symptoms.
- The ideal route for AIT contains dense APCs to enhance effects but few mast cells and blood vessels to reduce local and systemic side effects.
- Lymph nodes contain the highest density of APCs with only few mast cells and blood vessels, making ILIT highly efficient.
- Similar to mucosal epithelium, the epidermis has dense APCs with no mast cells or blood vessels. EPIT should therefore be as safe as SLIT.
- Allergen administered to the epidermis rapidly diffuses to the dermis. We expect diffusion toward blood vessels to be safer than injection into vascularized tissue.

INTRODUCTION

Today, up to 30% of the population in industrialized countries suffers from IgE-mediated allergies, which have therefore become an important socioeconomic burden. Pharmacotherapy with local and oral antihistamines and nasal corticosteroids ameliorates IgE-mediated symptoms efficiently,[1] but cannot stop progression of the causative immunologic imbalance, and therefore progression of rhinoconjunctivitis to asthma and to cross-reactive food allergies. The only disease-modifying treatment that also has a long-term effect is allergy immunotherapy (AIT).[1,2] More than a century ago, Noon[3] introduced subcutaneous allergen-specific immunotherapy (SCIT). However, despite its high efficacy and long-lasting symptom amelioration, less than 4% of allergy patients choose to undergo such AIT, mainly because it has two major

[a] Clinical Trials Center, University Hospital Zurich, Moussonstrasse 2, Zurich 8044, Switzerland;
[b] Department of Dermatology, University Hospital Zurich, Gloriatrasse 31, Zurich 8091, Switzerland
* Corresponding author.
E-mail address: thomas.kuendig@usz.ch

Immunol Allergy Clin N Am 36 (2016) 25–37
http://dx.doi.org/10.1016/j.iac.2015.08.006 immunology.theclinics.com
0889-8561/16/$ – see front matter

disadvantages. First, AIT is time consuming because it requires 30 to 70 visits to a medical practice. Second, subcutaneous allergen injections are associated with local and systemic allergic side effects.[4–6] Thinking generally, these two drawbacks may be addressed by the following strategies.

Measures to Reduce the Number of Allergen Administrations in Allergy Immunotherapy

To reduce the number of injections, immunogenicity of the allergen administration has to be enhanced, for instance by increasing the allergen dose. AIT has a clear dose effect,[7] but allergic side effects strongly limit the dose that can be given. Making allergens hypoallergenic by chemical modification to allergoids,[8] recombinant modification,[9] or by using non-IgE-binding peptides[10–12] may also permit increased allergen doses, but the modifications often negatively affect allergen immunogenicity. A reduction of injection numbers may also be achieved by replacing the classically used aluminum salts with a more T helper (Th) 1 promoting adjuvant, such as the Toll-like receptor (TLR) ligands CpG oligoeoxynucleotide[13] or monophosphoryl lipid A, a detoxified version of lipopolysaccharide.[14–16] The number of injections may also be reduced by changing to a more efficient route of allergen delivery. Ideally this route would be characterized by a high density of antigen-presenting cells (APCs). The latter are present at highest density in secondary lymphatic organs, such as lymph nodes, and indeed, when allergen is intralymphatically, the number of injections could be reduced to only three.[17–20] Intralymphatic immunotherapy (ILIT) is discussed in detail later.

Measures to Improve Allergy Immunotherapy Safety

To improve safety of AIT, inadvertent allergen delivery to the blood vasculature must be avoided, ideally by delivery of the allergen to nonvascularized tissue. Sublingual immunotherapy (SLIT) fulfills this criterion, because allergen is delivered to the oral mucosa, which is covered by a multilayered epithelium. The allergen diffuses down into deeper mast cell containing layers, and this diffusion is responsible for the frequently observed local oral side effects.[21,22] The layer below the epithelium also contains a high density of blood vessels. However, it seems that when there is no microtrauma to this vasculature, it rarely happens that significant amounts of allergen reach the circulation, for which reason SLIT has proved safe in terms of systemic allergic side effects.[21,22] The same should hold true for epicutaneous allergy immunotherapy (EPIT), where allergen is administered to the nonvascularized epidermis. An advantage of EPIT over SLIT is that keratinocytes can additionally be activated by physical irritation, such as abrasion or adhesive tape stripping, or also by adding adjuvants.[23] Such epithelial irritation increases the expression of proinflammatory cytokines, such as interleukin (IL)-1a, IL-6, and tumor necrosis factor-α, thus skewing the immune response toward Th1,[24] and also activating Langerhans cells (LCs). Therefore, EPIT may not only reduce side effects by minimizing the risk of allergen inadvertently reaching the blood vasculature, but also shorten treatment duration by increasing immunogenicity. We have also observed that epicutaneously administered allergen rapidly and efficiently diffuses down into the dermis.[25] Interestingly, another group has recently demonstrated that intradermal administration of even extremely low doses of allergen was able to induce tolerance.[26]

INTRALYMPHATIC ALLERGEN-SPECIFIC IMMUNOTHERAPY

The concept that antigen localization is a key parameter that determines the strength of the immune response was pioneered in Zurich by the work of Rolf Zinkernagel,