

ORIGINAL ARTICLE

Immunotherapy concepts under investigation

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Abstract

Allergen-specific immunotherapy (SIT) is effective, but used by only 5% of allergy patients, partly because it requires several years. Intralymphatic immunotherapy (ILIT) administers allergen directly into a subcutaneous lymph node and requires only three injections and a lower allergen dose than subcutaneous administration. ILIT was further improved using a recombinant allergen with enhanced uptake and decreased degradation by antigen-presenting cells. Another interesting route is transcutaneous/epicutaneous immunotherapy (TCIT, EPIT), which administers allergen by a skin patch. Clinical trials show that TCIT, EPIT is safe and comparably effective to conventional immunotherapy. Implementation of these new methods would increase the spectrum of SIT options, allowing greater individual choice of SIT.

Allergen-specific immunotherapy (SIT) has a success rate of 80–95% for insect venom and 70–80% for pollen allergy. It is the only causal treatment for allergy, and it stops disease progression and has long-term effects. It is preferable to symptomatic therapy, but only 5% of allergy patients undergo SIT because it takes 3–5 years, requires many injections in the case of subcutaneous immunotherapy (SCIT), and causes injection site side effects. When looking at allergen extracts as protein-based vaccines, it is unclear why numerous injections are needed for SIT, whereas typically three vaccine injections are sufficient for lifelong protection, e.g. against childhood diseases.

Direct injection of allergen into lymph nodes

Conventional SCIT injects allergen extract into subcutaneous fat, but immune effects are mediated in the subcutaneous lymph nodes, and <1% of subcutaneously injected proteins drain into the lymph nodes (1). Therefore, we hypothesized that introducing allergen directly into lymph nodes might have greater immunological effects.

We compared allergen administration routes in mice, with three injections of allergen administered as SCIT, Intralymphatic immunotherapy (ILIT), or intraperitoneally (Fig. 1). With ILIT, we could use 1000-fold less allergen than SCIT and still get an antibody response that was more than 10 times stronger. This translates into a >10 000-fold increase in immunological efficacy. The polarization of the immune

response was unchanged, as we found ILIT to enhance interferon- γ , interleukin (IL)-2, IL-4 as well as IL-10 production.

In humans, the groin has an average of 10–15 lymph nodes. Larger ones are approximately 1.5 cm long and only a few millimeters under the skin surface, so that they are readily found by ultrasound. A pain survey showed that ILIT caused less pain than a blood draw by venous puncture. Lymph nodes have no innervation, and we use small insulin hypodermic needles. Thus, ILIT is no more painful than SCIT.

First, we performed a clinical trial (ZU-BV-001) with bee venom on eight highly allergic patients. We administered three injections of 10 μ g into the lymph nodes at 2-week intervals. Protection was tested by sting provocation. Before treatment, all patients had grade 3 reactions, and after ILIT only one patient still had a grade 3 reaction. The other seven were protected. This was repeated in a larger, multicentre trial with 23 patients receiving four intralymphatic injections of 10 μ g and 22 patients receiving 20 μ g. Dose-dependency was seen. Three lymph node injections of 10 μ g protected 65% of patients and three injections of 20 μ g protected 82% of patients against sting challenge. This is close to what is achieved with SCIT.

We next tried ILIT with grass pollen in 165 patients. One study arm received 3 years of perennial treatment with subcutaneous Alutard[®] amounting to 56 injections with a maintenance dose of 100 000 SQ units each. The other arm received ILIT amounting to three injections of 1000 SQ units each.

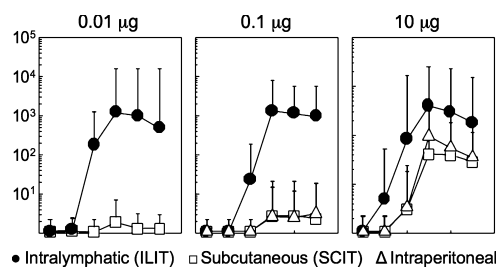


Figure 1 Specific antibody titers following different allergen administration routes.

Follow-up was over 3 years. Nasal provocation was the primary outcome. ILIT with three injections resulted in an 8-fold rise in the threshold after 3 months, which was maintained over the 3 years. No effect was seen with SCIT at 3 months, but patients improved as treatment continued. Overall, no significant difference in nasal tolerance was observed after 3 years between ILIT and SCIT, so ILIT produced the same results, but achieved them much faster.

Improving allergens for intralymphatic delivery

For regulatory purposes, ILIT products are considered a new drug, even if SCIT-approved products are used. Because they were already considered a new drug, we improved the allergen for ILIT by adding an intracellular translocation sequence for enhanced uptake by antigen-presenting cells (APCs). Allergens enter APCs by pinocytosis and enter the endolysosomal pathway before being presented on the cell surface with major histocompatibility (MHC) II proteins. In this pathway, about 99% of allergen is digested. Therefore, we added a twin arginine translocation (Tat) sequence to bring the allergen into the cytoplasm. We also added part of a human invariant chain to target the molecule to MHC class II molecules in the endoplasmic reticulum. These so-called modular antigen transporter (MAT) molecules bypass endolysosomal digestion and therefore increase allergen presentation on MHC class II molecules by a factor of 100.

We found that it takes 100-fold more MAT allergen than Fel d 1 from cat dander extract or recombinant Fel d 1 to degranulate basophils from cat-allergic patients. This is probably because MAT allergen enters cells so rapidly, and it does not have time to crosslink IgE on basophils, a characteristic that should make MAT allergens safer. Also, the allergen dose required to induce skin hives in a titrated skin-prick test with MAT-Fel d 1 was about 100-fold higher than with Fel d 1, again suggesting the reduced allergenicity and increased safety of MAT allergen.

We investigated the clinical efficacy in a pilot clinical trial, in which 12 patients received intralymphatic injections with MAT-Fel d 1 in alum, and 8 patients received only alum. Injections were 1, 3, and 10 µg at 4-week intervals. We saw no drug-related adverse events in this double-blinded, placebo-controlled trial. Three injections of MAT-Fel d 1

resulted in an 8-fold induction of specific IgG₄ titers. No increase was found in the placebo group. IL-10-producing T cells were significantly induced in the treatment group but not in the placebo group, and IL-10-producing T cells correlated with IgG₄ levels. The primary endpoint was a nasal provocation test. We saw a highly significant 73-fold increase in nasal provocation threshold in the treatment group, comparable or even superior to what is typically achieved after 3 years of conventional immunotherapy. This suggests we have increased immunological efficacy. The treatment has been difficult to market, however, because the trend in immunotherapy is not toward more efficient, but rather toward more convenient methods, such as sublingual immunotherapy.

Transcutaneous immunotherapy (skin patch)

In an attempt to enhance convenience, we investigated transcutaneous/epicutaneous immunotherapy (TCIT, EPIT), an idea introduced by Blamoutier in 1959, who delivered pollen allergen onto scarified skin. Four uncontrolled trials (2) reported amelioration of hay fever symptoms. We conducted a trial (ZU-Skin-SIT-001) in 37 subjects using grass allergen in petroleum jelly on skin. The skin was pretreated by adhesive tape stripping, i.e., sticking a scotch tape onto the skin and removing it six times, which reduces the stratum corneum to make it more permeable for proteins and also activates keratinocytes. Mild eczema was induced in a small percentage of patients. We followed patients over the pollen season for 2 years. In the first season, a significant improvement was seen of 75% in the treatment group, and 25% in the placebo group. This effect lasted into the next season, even though treatment was not repeated.

We did a larger study of 132 patients (ZU-Skin-SIT-002), 33 each in placebo, low-, medium-, or high-dose groups. Regarding the number of adverse events, a dose response was observed. Adverse events, mainly pruritus under the patch, occurred three times more frequently in the treatment groups than the placebo group. Mild eczema was seen in 10% of the treatment group. In the first year, symptoms in the pollen season showed a 50% improvement in placebo and all treatment groups. In the second year, no patches were placed, and the placebo effect was lost, resulting in a dose-dependent, highly significant improvement of up to 70% in the treatment groups in the pollen season. After testing different methods, we predict the best skin preparation to be microneedles that puncture the epidermis. In contrast to sublingual immunotherapy, TCIT/EPIT more easily allows addition of adjuvants. In mice, adding adjuvant to TCIT/EPIT gave much higher IgG titers than SCIT.

Thus, SIT, like other vaccinations, can be reduced to three injections, but requires injection into lymph nodes. TCIT and EPIT are effective, but there is still room for improvement. As new delivery methods are developed, in clinical practice, the choice of therapy will be a matter of individual preference.

Conflict of interest

Thomas Kündig has received research grants from ImVisioN Therapeutics and Allergy Innovations, consultancy fees from

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