

Commentary Article

Recommendations on Intralymphatic Immunotherapy (ILIT): Precision Medicine in Vaccination and Immunotherapy

Pål Johansen^{1,2*}, Stephan Flory¹, Lara Šošić¹, Thomas M Kündig^{1,2}, Claudia CV Lang²

¹Department of Dermatology, University of Zurich, Zurich, Switzerland

²Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

*Correspondence author: Pål Johansen, Department of Dermatology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland;
Email: pal.johansen@usz.ch

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Lead

Intralymphatic Immunotherapy (ILIT) offers a safe and efficient form of Allergen Immunotherapy (AIT) and is becoming increasingly important in clinical research and off-label use. Since its efficacy depends on precise injections, the lack of procedural standards poses a challenge to maintaining uniform treatment quality. By analyzing 173 injection videos, we critically evaluated key aspects of the ILIT method and provided a set of pragmatic recommendations for accurate and safe ILIT injections with greater ease and consistency. Considering the increasing use of ILIT, our empirically evaluated recommendations may provide a foundation for the establishment of procedural standards and the recognition of ILIT as a valid method for allergen immunotherapy.

Allergy and Immunotherapy

Allergies affect a significant proportion of the general population worldwide, with symptoms ranging from mild hay fever or itchy skin rash to life-threatening anaphylaxis [1]. With nearly 30% of people worldwide suffering from Allergic Rhinoconjunctivitis (ARC) and its prevalence on the rise, the only potentially curative treatment is Allergen Immunotherapy (AIT). Through repeated administration of allergens, the immune system can be modulated towards tolerance. Various established application modes exist, including the conventional Subcutaneous Immunotherapy (SCIT), used for ARC, asthma and venom allergies, the more recent Sublingual Immunotherapy (SLIT) for ARC and asthma and the rather experimental Oral Immunotherapy (OIT) for some IgE-mediated food allergies [2-4]. However, all AIT methods require long treatment durations, which may hinder patient adherence to the protocols. Consequently, less than 7% of potential AIT patients in Germany commence AIT treatment and fewer than 30% of those who start actually complete the treatment [5]. Another challenge is the dose-dependent trade-off between efficacy and safety.

Intralymphatic Immunotherapy

Intralymphatic Immunotherapy (ILIT) is a novel approach that addresses some of the challenges of traditional AIT. Clinical trials have shown symptom alleviation in patients through ultrasound-guided injections of allergen extracts into lymph nodes [6-9]. Fig. 1 illustrates the ILIT procedure with ultrasound monitoring. Since lymph nodes are rich in antigen-presenting cells and antigen-responsive lymphoid cells, ILIT enhances the probability of initiating allergen-specific immune responses compared to SCIT. Studies in mice also showed that ILIT led to stronger immune responses at 100-fold lower doses than SCIT [10]. Thus, ILIT holds the potential for stronger immune induction, shorter treatment durations and the use of lower doses, offering a solution to the problem of allergic side effects, and poor patient compliance and lower treatment costs [11]. Moreover, ILIT may be effective in treating patients with severe allergic manifestations, including asthma triggered by dust mites, animals and molds. Several studies have demonstrated effective symptom relief for ARC with just three ILIT injections over two months, with mild and mostly local side effects [12-17]. One study showed that three ILIT injections in two months were as safe and effective as 54 SCIT injections administered over three years for treating grass pollen-associated ARC [16]. ILIT could meet many unmet needs of allergy patients who have not been offered or opted for AIT.

In SCIT, only a small amount of the allergen reaches a draining lymph node, a limitation that ILIT overcomes by directly releasing the allergen into the target lymph node [18]. This improvement in targeting is critical for the efficacy of ILIT. The acquisition of ultrasound skills is also expected to correlate with ILIT treatment efficacy, the more accurate the injections, the better the outcomes. While one study reported lymph node hit rates of 75-80%, another study demonstrated a lower overall hit rate of 37% during the learning process for ILIT injections [17,19].

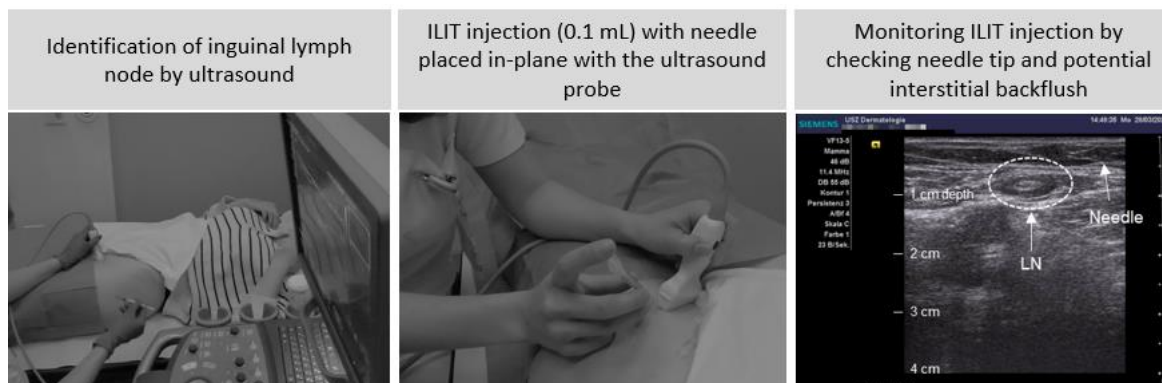


Figure 1: Photographic scheme of the setting for ultrasound-guided Intralymphatic Immunotherapy (ILIT) into an inguinal lymph node in human. The ILIT is done by a single clinician and the whole procedure typically takes 2-4 minutes. For allergen ILIT, the patients is typically released within 10 minutes upon arrival but has remain at the allergy ward for another 30-60 minutes for safety monitoring, as after Subcutaneous Immunotherapy (SCIT).

Guideline for Correct ILIT Injections

Research on ILIT has mainly focused on efficacy and safety, but no procedural standards or recommendations have been formulated for ILIT injections. Johansen and co-workers aimed to critically appraise ILIT and deliver recommendations for lymph node selection and improved injection techniques [20]. In the study, 60 patients with grass pollen ARC in an ILIT trial were included based on defined clinical criteria, e.g. skin prick tests and rhinitis symptom score. All patients received three ILIT injections with CA. 4-week intervals and each injection was document by recording the injection using a Siemens ACUSON X300 ultrasound system and linear transducer model VF13-5 with breast tissue presetting. The recordings of 6-18 seconds were started just before the injection started and stopped after content release from the syringe. The recordings were analysed using software ImageJ (v1.8.0_351) by two practitioners. Out of 180 recordings, 7 were rejected due to poor quality. By evaluating the remaining 173 ultrasound-guided injections from the ILIT trial, injections were graded based on three key criteria: injection location, static needle visibility and dynamic needle detectability. Injection location referred to the accuracy of the injection within the lymph node, with the highest scores given for injections into the lymph node cortex. Static needle visibility was the ability to distinguish the needle from surrounding tissue in a static ultrasound image, while dynamic needle detectability referred to the clarity of needle movement through tissue during the injection.

Of the 173 injections analyzed, 95% successfully released the AIT substance intranodally, although 35% showed some backflush into the interstitial space. Static needle visibility was achieved in 51% of injections, while dynamic needle detectability was achieved in 76%. The quality of the injection, in terms of location, was closely linked to the quality of needle visibility and detectability. Better visibility and detectability significantly improved the accuracy of injections, and injections with backflush into the interstitial space were often associated with poor static visibility and dynamic detectability.

The depth of the lymph node and the angle of the needle to the probe influenced the injection accuracy. Superficial lymph nodes, which allowed for smaller needle-to-probe angles, resulted in clearer needle visibility and more accurate injections. The width of the lymph node cortex also played a role in determining injection accuracy, with a wider cortex making it easier to release the allergen intranodally and avoid backflush. Patient characteristics, such as Body-Mass Index (BMI) and age, did not significantly affect the accuracy of the injections, though higher BMIs were associated with slightly lower static visibility.

Training was found to have a significant positive impact on injection accuracy, with practitioners showing improvement in static visibility, dynamic detectability and injection location as they gained experience. Technical skills, such as aligning the needle

with the ultrasound plane and maintaining clear needle visibility throughout the procedure, were critical to successful injections. The use of advanced ultrasound technology, careful selection of lymph nodes and proper needle-probe handling also contributed to better outcomes.

One of the key challenges in ILIT is avoiding backflush of the allergen into the interstitium, which can occur when the needle is not inserted deep enough into the lymph node. Ensuring that the entire needle bevel is inserted into the cortex or hilum is essential for preventing this issue. Additionally, needle misalignment can lead to misinterpretation of the needle's position, increasing the risk of errors. In such cases, practitioners should retract the needle, adjust the probe or needle and attempt reinsertion. Based on our experience with allergen ILIT, we believe that interstitial backflush may significantly impact treatment efficacy, as such injections may function more like subcutaneous rather than intralymphatic delivery. Given that SCIT typically requires dozens of higher-dose injections over several years to achieve efficacy, interstitial backflush during ILIT may indeed compromise therapeutic outcomes. Additionally, dose release outside the lymph node could raise safety concerns, as the allergen would have direct access to mast cells in the connective tissue, potentially triggering degranulation and resulting in local or systemic allergic reactions. However, because ILIT doses are generally 10- to 100-fold lower than SCIT doses, the severity of allergic reactions associated with an ILIT backflush is expected to be significantly lower than those observed with SCIT.

The study by Flory et al. also highlighted the importance of technical considerations in optimizing the ultrasound image, such as adjusting the frequency and dynamic range of the ultrasound machine to enhance needle visibility [20]. Selecting a suitable lymph node with sufficient cortex width and depth further contributed to injection success. For patients with higher BMIs or deeper lymph nodes, lowering the ultrasound frequency may improve image quality and allow for injections that are more accurate. The study also emphasized the importance of standardized training and procedures for ILIT. More accurate injections were associated with fewer adverse events, suggesting that both the safety and efficacy of ILIT may benefit from improving injection quality. As ILIT becomes more widely used, the development of standardized protocols and clinical skills training programs will be essential for ensuring consistent and high-quality treatment.

In closing, the described study by Flory, et al., provides practical recommendations for performing ILIT in allergy patients, focusing on selecting appropriate lymph nodes, optimizing ultrasound settings and improving needle handling techniques [20]. With proper training and adherence to these recommendations, ILIT injections can be performed quickly and accurately, offering an effective treatment option for patients with allergies. Once expertise is developed, the selection of a suitable inguinal lymph node and the administration of ILIT can be completed in approximately five minutes per patient, making it a potentially time-efficient alternative to traditional AIT.

ILIT in Dermatology and Future Directions

Beyond its application in treating IgE-mediated allergies, ILIT is being explored for several other dermatological and oncological conditions, although most of these studies have been performed in pre-clinical models. In the future, ILIT may, however, find application in various immune-related skin disorders such as Atopic Dermatitis (AD) and autoimmune skin disorders. In AD, a chronic inflammatory skin condition with a significant allergic component, ILIT may help to induce tolerance to specific triggers of AD, such as environmental allergens. Early studies in dogs are exploring whether ILIT can reduce symptom severity and reliance on topical or systemic immunosuppressants [21-23]. ILIT may also be considered for autoimmune diseases such as psoriasis and vitiligo, where an imbalanced immune response leads to inflammation or autoimmune activity against skin cells. General vaccination have been shown to trigger cutaneous side effect, such as the exacerbation of psoriasis [24], while vitiligo is a frequent side effect of checkpoint immunotherapy [25]. In autoimmune skin diseases, ILIT should therefore modulating the immune system in similar way as in allergy, namely by dampening immune responses and autoimmune attacks on skin tissue through induction of immune tolerance. Likewise, ILIT might induce tolerance against hair follicle antigens in alopecia areata. While these applications are still in the exploratory stages, ILIT's precise immune-modulating potential makes it a candidate for clinical trials in autoimmune dermatology [26].

ILIT has of course also gained interest in cancer immunotherapy, specifically for skin cancers such as melanoma [27,28]. By delivering tumor-associated antigens directly into lymph nodes, ILIT can potentially train the immune system to recognize and target cancer cells more effectively [29]. Moreover, when coupled with immune checkpoint inhibitors or other immunostimulatory agents, ILIT may enhance the recruitment of T-cells against tumor antigens [30]. This approach is

particularly attractive in melanoma due to the immune system's ability to recognize melanoma cells.

Research is ongoing to determine the best protocols, antigen types and combinations for ILIT in treating dermatological diseases and cancers. This includes the use of modified mRNA, tumor-specific peptides and adjuvants that enhance immune response. Studies are also assessing the longevity and specificity of immune tolerance induced by ILIT, as well as its efficacy when combined with existing immunotherapies.

Conflict of Interest

The authors declare they do not have conflicts of interest.

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