

The Fast Track: Curing Common Allergies Quickly and Effectively

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Introduction

Subcutaneous immunotherapy has long been the most effective way to end persistent and severe allergic reactions. However, such an approach requires 50-70 injections over a two-year period, causing issues on patient compliance and costs. Even when used, such treatment carries an ongoing risk of severe adverse reactions. Therefore, subcutaneous immunotherapy is only rarely used. This article reports here on a novel allergen immunotherapy that is safer, more effective and very much faster than traditional methods.

Introduction

Allergies are the result of inappropriate immune responses to normally harmless substances. Although allergic symptoms have been described for almost 200 years as a rare disease, over the last decades changes in life style and environmental circumstances have resulted in a tremendous increase in allergies. Numerous substances in every day life have the potential to act as allergens triggering allergic reactions. Allergens like pollen or cat dander are taken up through the respiratory system. Alternatively, some allergens generate a reaction by coming into direct contact with the skin or mucous membranes such as latex, poison ivy or oak. Some allergens generate a reaction through injection (bee venom) or by being swallowed (peanuts).

Contact with the allergen can cause a variety of symptoms ranging from sneezing, runny nose, burning eyes and nasal congestion through to extremely severe and life-threatening reactions like tissue swelling in the airways and anaphylactic shock, which can cause death. It is also worth noting that allergies are a leading cause of chronic diseases such as asthma. In 2005, nearly 30 million people living in the US suffered from asthma. About half of all Americans test positive for at least one of the 10 most common allergens, such as cat dander, house dust mite or peanuts (Matricardi *et al.*, 2002), and allergies are the sixth leading cause of chronic disease in the US, costing around US\$18 billion annually for national health care systems.¹

¹ American Academy of Allergy, Asthma and Immunology (AAAAI).

How Allergies Arise: The Immunological Process of Sensitisation

The human immune system is normally very efficient at identifying and eliminating external particles entering the body. In most cases, these particles are threatening like bacteria, viruses or toxic pathogens; however, allergies arise when the immune system mistakenly identifies a harmless substance as a threat and becomes sensitised to the substance.

The process starts by an exposure of the individual to the allergen, i.e. the substance later causing the allergy. The allergen is taken up by specialised cells, so called antigen-presenting cells (APCs), broken down into smaller peptides and the peptide fragments are presented to the immune system. These resulting peptides are presented to T cells (T helper cell type 2 – Th2), which release cytokines (e.g. IL-4, IL-5, IL-13) inducing B cells to produce allergen-specific E-type immunoglobulins (IgE). These IgE molecules then bind to high-affinity receptors on basophils and/or mast cells in a process called sensitisation (*Figure 1*). When the sensitised individual is re-exposed to the same allergen, IgE molecules recognise and bind these allergens. A quick reaction cross-links those IgE molecules that are bound to mast cells or basophils and activate them to release mediators such as histamines, prostaglandins, and leukotrienes. The release of these mediators results in the production of allergic symptoms in the different organs.

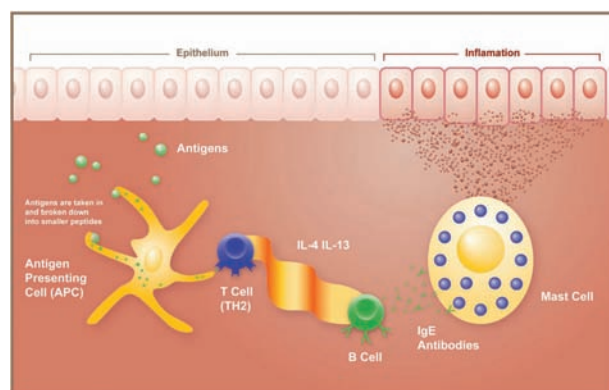


Figure 1 – The Immunological Process of Sensitisation.

If the allergen cross-links to IgE bound to basophils in the blood, these mediators can cause anaphylactic shock. The released mediators affect also the blood vessels, mucous glands and bronchial tubes of the patient and usually cause tissue swelling. This step is called the immediate hypersensitivity or early-phase reaction and it occurs within minutes of re-exposure to the allergen and usually resolves within one hour.

Treatment of Allergies

Allergies and their symptoms can be treated in three ways. The simplest therapeutic approach is the complete avoidance of the allergen. In most cases, this is not practicable and manageable in everyday life and there is a constant risk of sudden allergic shock in unexpected situations. The most common approach is to treat the symptoms of the allergic reaction with pharmacotherapy. The success of such a therapy depends on a well-timed and exactly dosed uptake of drugs over the period of allergen contact. In cases of perennial allergies, such as cat dander or house dust mite allergy, the time of treatment could be extended, even all year long. Corticosteroids, antihistamines, bronchodilators and decongestants are very effective and, therefore, frequently used to treat the symptoms, but they also have unwanted side-effects especially related to a long term use. In general, these drugs are just symptomatic treatments and do not have impact on the cause of the allergy.

In order to truly cure an allergic disease, the only current option is to use allergen-specific immunotherapy. Standard immunotherapy involves the subcutaneous injection of gradually increasing doses of the allergen extract to which the person is allergic. The incremental increase of the allergen dose results in a decreasing sensitivity of the immune system to the substance. This is accomplished by modulating the allergen-specific immune response, shifting the balance of T-lymphocyte subsets from a Th2 towards a Th1 phenotype with increased IFN-gamma and decreased IL-4 and IL-5 production. Also, production of IL-10 by allergen-specific regulatory T cells is observed, and serum levels and affinity of allergen-specific IgG antibodies, especially IgG4, increase.

One widely accepted theory explains the effect with the induction of "blocking" IgG antibodies, which bind to the allergen upon re-exposure so preventing the allergen-specific IgE antibodies of the allergic patient to bind to the allergen and thereby reducing or preventing the allergic symptoms. However, with 50 to 80 injections over a prolonged period of time and the constant risk of severe allergic reactions to the injections, immunotherapy is currently only recommended in patients if other treatments fail, in severe cases of allergy or to patients who have life-threatening reactions to insect stings. Although many patients do not complete the arduous treatment regimen, in those that do the success rates at curing the allergy are high.

Furthermore, in the case of some of the most common allergies, such as cat dander allergy, treatment with specific immunotherapy is inadequate because injections of suitably efficacious extract doses induce unacceptably high levels of adverse reactions. For that reason, the cat extract is only administered on rare occasions.

However, there are ways to improve the effectiveness, safety and compliance of allergy immunotherapy to make it a more acceptable option open to all patients with suffering from allergies. Using delivery into the lymphatic system of patients and a proprietary format for the immunotherapy, treatments have the potential to deliver cures to allergies after only three injections and with a greatly lowered incidence of adverse reactions.

ILIT™ – A New Delivery Route for Allergy Immunotherapy

Part of the problem with specific allergen immunotherapy is due to its subcutaneous route of delivery which means that the desensitisation process needs many applications to be completed. The problem of the subcutaneous therapy is that, at the beginning, extremely low doses have to be administered to the allergic patient due to frequently occurring allergic adverse reaction in response to the therapy. Therefore, many applications of increasing dosage are necessary to reach the therapeutically effective concentration of the applied medication.

At **ImVision** we are pioneering an alternative route of delivery: intralymphatic immunotherapy (ILIT™) where the injections are directly in to the lymph nodes. Antigen presenting cells (APCs), which are key to the desensitisation process, are highly concentrated in the lymph system. It is therefore advantageous to deliver the immunotherapeutic directly to the lymph nodes, the place where APCs and other 'key players' of the immune system are present in high density. This new delivery technique has already been clinically validated by Dr Thomas Kündig - clinical advisor of ImVision - and his team at the University Hospital in Zurich, Switzerland, as an effective way to administer allergen immunotherapy. Successful desensitisation can be achieved in a matter of weeks with only three injections using this route of delivery, compared to two to five years of traditional subcutaneous applied immunotherapy. This route of delivery also appears to be safer, generating far fewer allergic responses. These very significant differences should lead to greater compliance and make immunotherapy more attractive as a treatment option.

Clinical proof of concept

ILIT™ was recently demonstrated to be safe and efficacious for the delivery of allergen specific immunotherapy with grass pollen extract in a clinical setting. A group of 54 patients was treated over a three-year period with 54 subcutaneous injections. The comparison group of 58 patients was given three intralymphatic injections over a two-month period. All patients completed the intralymphatic therapy, but only 60% of the subcutaneous

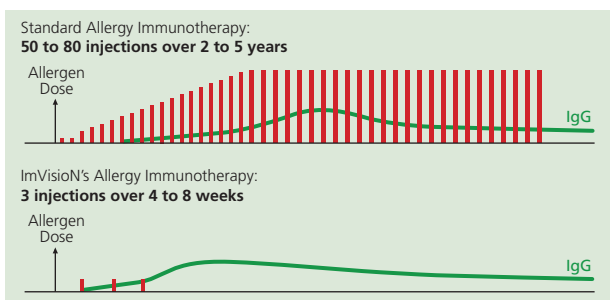


Figure 2 – Rapid therapeutic effect. Cure of allergic disease will be achieved within several weeks as opposed to two to five years with traditional allergen specific immunotherapy.

patients completed the full course of 54 injections over three years. This indicates a higher patient compliance for ILIT™. The patients who received the intralymphatic injections also had significantly fewer adverse events ($p < 0.05$). ILIT™ was subjectively found to be less painful than a venous puncture. Overall, the cure of the allergy was also achieved within three months with ILIT™ as opposed to one year with traditional subcutaneous injections (Figure 2). ILIT™ also worked well with substantially reduced amounts of the allergen (3,000 units as opposed to 4,000,000 units) which has further implications for the safety of this delivery route.

Modular Antigen Transportation

Traditionally, the allergens in immunotherapy are made of extracts from the allergens themselves, which are injected in raw form. The risk of adverse reactions is relatively high, particularly in the early dose escalation stages of allergen-specific immunotherapy. Besides improving the mode of delivery, ImVisioN has also modified the format of the allergen to be injected. The way the antigen is presented is critical in immunotherapy. The effectiveness can be improved by a more directed way of guiding the allergens to the APCs.

In our approach, the allergen is delivered in a modular protein format: Modular Antigen Transportation (MAT) molecules (Cramer *et al.*, 2007) offer the possibility of both, a more directed way of delivery and a safer way which gives better immune resonance (Figure 3). MAT fusion proteins consist of three functional elements:

- A translocation module, which enables the MAT molecule to pass through the cell membrane and to get into antigen-presenting cells (APCs). These cells are the critical cells of the immune system responsible for processing of the allergen and for the stimulation of a specific immune response to such allergen.
- A localisation module directs the allergen protein on its way inside the cells to the place where it is broken up and remodelled for the outside presentation to the T-cells. This improves the presentation of the allergen and its components to the immune system via the MHC class II pathway, thereby inducing an efficient protective immune response (Th1).
- The third module contains the allergen to which the patient is allergic.

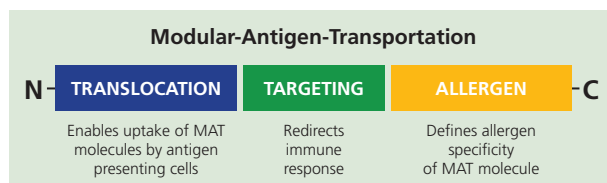


Figure 3 – The modular build-up of the Modular Antigen Transportation/MAT Molecule.

Using ILIT™ and MAT™ to generate a portfolio of allergy treatments

Using both ILIT™ and MAT™ to improve the safety and convenience of allergen-specific immunotherapy, ImVisioN has generated a portfolio of allergy treatments. ImVisioN's lead candidate, IVN201, is about to enter the clinic for treatment of cat dander allergy, two other programmes are addressing birch pollen allergy and house dust mite allergy.

An allergic reaction to cat dander is one of the most common IgE-mediated allergies. Even in dust collected in households where no cats live nor have ever lived, the cat allergens can be found in such a high concentration that allergic persons develop symptoms like asthma or allergic rhinitis. This fact makes allergen avoidance in the case of cat allergy difficult. About 39% of all allergic patients in the US and 30% in Europe are allergic to cat dander.

ImVisioN uses the major cat dander allergen Fel d1 in IVN201. Due to the fact that more than 80% of cat allergy patients have antibodies against this small protein, it is possible to develop a specific immunotherapy with an artificial Fel d1 protein. IVN201 is considered to be a safe and efficacious alternative to treat cat dander allergy using the MAT technology for intralymphatic immunotherapy. In preclinical studies, IVN201 has been shown to be immunogenic in mice and to be effective in a disease relevant animal model. Furthermore, ongoing preclinical safety and toxicology studies indicate that IVN201 is safe and will be well tolerated in humans.

Conclusion

It has been known for some time that specific allergen immunotherapy is the only effective way to cure allergies. But the mode of delivery has ensured that it is too arduous or dangerous for most patients to attempt. ImVisioN has demonstrated that intralymphatic administration (ILIT™) has the potential to cure allergies with fewer injections over a shorter period of time. This route of intralymphatic delivery in conjunction with a novel modular protein format also implies that immunotherapy can be accomplished much more safely than by the conventional subcutaneous application of allergen extracts.

References

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