

Allergen immunotherapy: a history of the first 100 years

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Purpose of review

To provide a historical perspective on the development of allergen immunotherapy and to describe the progress that has been made in both the clinical application and the scientific understanding of this therapeutic technique in the 100 years since its inception.

Recent findings

Although allergen immunotherapy has been part of allergy practice for a century, it is only in relatively recent years that the cellular and molecular mechanisms which underlie its clinical efficacy have been elucidated. Most recent studies implicate the T-regulatory cell response as central to the development of a tolerogenic state in response to allergen immunotherapy, with both IL-10 and TGF- β playing crucial roles in the development of this cell subset. The clinical application of immunotherapy continues to advance, with promising contemporary studies noting improved safety and efficacy with pretreatment using omalizumab prior to an immunotherapy program as well as the potential for innate immune system modulation with allergen conjugates which can stimulate pattern recognition receptors such as the toll-like receptors.

Summary

After 100 years of clinical application, allergen immunotherapy remains the only treatment modality with the potential for long-term immunologic amelioration of atopic diseases. Future treatment advances in allergen immunotherapy will likely harness the increasing power of molecular and genomic medicine to achieve greater allergen specificity, while improving overall efficacy and minimizing the potential for systemic reactions.

Keywords

allergen-specific immunotherapy, hypersensitivity, subcutaneous immunotherapy

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Introduction

As the 100th anniversary of allergen-specific immunotherapy (SIT) is celebrated, many of the original principles of this innovative therapy as conceived by Noon and Freeman remain valid. However, the understanding of the mechanisms that underpin the efficacy of SIT has increased dramatically over the course of a century of clinical application. Furthermore, as the progress of molecular and genomic technologies continues unabated, it is inevitable that these advances will be incorporated into the future delivery of immunotherapy. The purpose of this review is to provide a historical perspective on the development of SIT, and by doing so, reflect on the pioneering work by dedicated physicians and scientists to create and refine the only technique available to alter the course of atopic disease.

Although Noon and Freeman are justifiably credited with the first successful trial of SIT for the desensitization of grass allergy, Dr Blackley preceded their seminal trial with some of the first investigations into the nature of

pollen allergy and treatment. He described these observations in his 1873 volume *Experimental Researches on the Cause and Nature of Catarrhus Aestivus*. As a sufferer of allergic rhinitis, Dr Blackley experimented upon himself, instilling rye grass pollen into his nostril and observing 'a profuse coryza came on in less than a minute after the application. In 30 min, the nostril was completely occluded, so that it was quite impossible to pass any air through it'. He further extended his experimentation into the realm of treatment by attempting what can be regarded as the first effort at SIT via repeated application of pollen grains to his abraded skin, though he did not note any decrease in his symptoms [1].

At the turn of the 20th century, Dr Dunbar [2] attempted passive immunization with an antipollen antisera which was instilled as an ointment preparation in eyes, nose, and mouth for rhinitis symptoms. In 1911, drawing upon Dunbar's work and the earlier implication by Blackley of pollen as the causative agent of hay fever, Noon and Freeman conducted their seminal trial of SIT with grass pollen extracts [3••]. By doing so, they established several

clinical principles which are still relevant in today's administration of SIT: a protocol of increasing extract dosage, an initial injection interval of 1–2 weeks, and a caution against allergen overdose which might induce anaphylaxis [4]. Although there have been many refinements since this landmark study, these tenets remain fundamentally sound in the delivery of modern SIT. Though Noon died prematurely from tuberculosis at the age of 36, Freeman [5] continued pioneering work in immunotherapy, including the implementation of the first rush protocol for SIT in 1930.

After the publication of Freeman and Noon's trial, SIT gained rapid acceptance as an important component of allergic disease treatment, and there followed significant advances into the clinical aspects of immunotherapy. An important milestone was reached with the publication of Frankland (Fig. 1a) and Augustin's study of grass pollen immunotherapy in 1954, which represents the first double-blind, placebo-controlled trial to demonstrate SIT efficacy [6^{••}]. In 1964, Voorhurst *et al.* [7] identified *Dermatophagoides* sp. as the source of the house dust allergens. Lowell and Franklin [8[•]] demonstrated in 1965 that a single allergen (ragweed) in a multiextract mixture was capable of decreasing seasonal symptoms. Johnstone and Dutton [9[•]] were the first to recognize the concept that SIT could slow the atopic march, showing in a 1968 study that SIT decreased development of asthma in a pediatric population. Ten years later, Norman and Lichtenstein [10[•]] provided important insight into the clinical delivery of SIT, showing in 1978 that the allergen specificity of ragweed sensitivity was due to Amb a 1, the major ragweed allergen. Moreover, they demonstrated that SIT delivered with purified Amb a 1 was equal in clinical efficacy to that using whole-plant extract. The concept of prevention of allergic progression, first

Key points

- Allergen-specific immunotherapy has been successfully used in clinical practice since Noon and Freeman's original study in 1911.
- Subcutaneous immunotherapy has demonstrated clinical efficacy in allergic rhinitis, asthma, and venom hypersensitivity.
- Other routes of immunotherapy, in particular sublingual, have been approved outside the USA for allergic rhinitis.
- An accumulating body of scientific evidence points to the T-regulatory cell response as central in the development of specific immunotherapy (SIT)-mediated tolerance.
- Continued molecular and genomic advances will likely permit increased efficacy of SIT with an improved safety profile.

highlighted by Johnstone and Dutton above, was validated by the 2007 study by Jacobsen *et al.* [11] in which SIT given over a 3-year period to children with allergic rhinitis conferred a two-fold to three-fold risk reduction in the development of asthma.

Venom immunotherapy

Although SIT saw its origins in decreasing the symptoms of troublesome allergic rhinitis, it was expanded with life-saving benefit to patients with allergy to stinging insects. Dr Loveless and Fackler [12] conducted some of the original work in this area, publishing in 1956 a report of uncontrolled experiments in Hymenoptera-sensitive patients treated with either whole-body insect extract or purified venom. In an article published in the *New England Journal of Medicine* in 1978, Lichtenstein, Hunt, and colleagues [13^{••}] (Fig. 1b) validated and extended this work with the first controlled trial of insect hypersensitivity, demonstrating the superiority of purified venom immunotherapy (VIT) versus whole-body extracts. Dr Richard Lockey was among the first to recognize the clinical similarity of various species of ant sting-induced anaphylaxis to that provoked by other Hymenoptera species and also contributed to the identification of fire ant allergens [14,15]. Finally, Lockey *et al.* [16[•]] completed the largest longitudinal study of VIT to date, with enrollment of over 3200 patients from 1979 to 1982. This study was critical to establishing the safety profile of VIT, showing a 12% incidence of treatment-related systemic reactions, none of which proved fatal.

International acceptance of specific immunotherapy

International validation of the accumulating body of evidence regarding the safety and efficacy was achieved

Figure 1 William Frankland and Larry Lichtenstein



(a) Dr William Frankland. (b) Dr Larry Lichtenstein. Courtesy of William Frankland and Larry Lichtenstein.

with the publication in 1998 of the World Health Organization (WHO) position paper on SIT. The international committee concluded that SIT is well tolerated (though noting the risk of anaphylaxis) and is indicated for allergic rhinitis, Hymenoptera hypersensitivity, and allergic asthma. The importance of appropriate patient selection was emphasized (those with inadequate symptom control on standard medications or who were intolerant of the side-effects of these regimens) as was the necessity to have SIT prescribed and administered by a qualified allergist in a clinical setting with the necessary equipment and staff to handle the low but real risk of a systemic reaction [17].

Lasting clinical benefit of specific immunotherapy

The persistence of immunologic tolerance and thus clinical benefit of SIT after cessation of therapy had been a lingering question for both physicians and patients until relatively recently. This question has significant ramifications not only from a pragmatic standpoint (how long to continue a program of SIT once initiated), but also from a disease-prevention perspective (when to initiate therapy in order to reduce new sensitizations and possible progression to asthma). The former has been elegantly answered by Durham *et al.* [18^{••}] in a study published in 1999 in which they observed persistent reduction in symptom scores and lymphocyte skin infiltration following intradermal skin testing for up to 3 years after cessation of a 3–4-year course of SIT; these observations were indistinguishable from those who remained on the SIT program during that time frame. The latter question as to when to initiate therapy with the object of decreasing atopic progression has not been definitively answered, but both the 1998 WHO position paper as well as Jacobsen's 2007 pediatric immunotherapy trial support the early initiation of SIT to decrease the incidence of allergic asthma.

Allergen standardization

Allergen standardization has been another area where significant progress has been made in the last two decades, though much work remains in this daunting endeavor. In the USA, there are now 19 standardized extracts available, with potency assured by a standardized assay. Standardization in the USA is governed by an initial reference assessment of allergenicity (using highly sensitized individuals) and then a secondary ELISA assay, which assures lot-to-lot bioequivalence [19]. Furthermore, dose recommendations have been validated for these standardized allergens in published practice parameters for SIT. Thus far in Europe, however, there has been no reference allergen standard, and

thus the burden has been placed on the individual manufacturers of extracts to ensure potency and consistency of their products. However, a new initiative to develop international reference allergen standards has been formed in the European Union, dubbed the CRE-ATE project [20].

Mechanisms of specific immunotherapy

The safety profile, clinical efficacy, and practice standards guiding SIT were much investigated in the years following Noon and Freeman's initial observations and are by now fairly well established. However, understanding the mechanisms by which induction of immunologic tolerance to allergen occurs has presented a more daunting challenge and knowledge of these pathways continues to evolve. Prausnitz and Kustner provided the initial observation that passive transfer of hypersensitivity with skin sensitization was possible via what they described as 'reagin' (now known to be allergen-specific IgE) in the eponymous P-K reaction [21]. Years later, the nearly simultaneous discovery of IgE as a fundamental molecule of allergy by Kimishige and Teruka Ishizaka and Johansson and Bennich was a watershed moment in the comprehension of allergic mediators. It continues to be a crucial diagnostic marker (allergen-specific IgE testing for food, pollen, and insect allergies) and therapeutic target (omalizumab) in allergic asthma [22^{••}, 23^{••}]. One of the initial proposals to account for allergen desensitization observed in SIT was the concept of specific IgG 'blocking antibodies'. As early as 1935, Dr Cooke put forth the possibility of the 'development under treatment of a peculiar blocking or inhibiting type of immune body that prevents the action of allergen' after patients had been treated with a ragweed SIT protocol [24]. Twenty years later, Cooke *et al.* [25] confirmed that this serum factor was mostly likely gamma globulin via electrophoretic mobility studies of fractionated serum in ragweed-treated patients. The role of the allergen-specific blocking IgG as a primary mechanism of SIT-induced allergen tolerance has been called into question in more recent years and remains somewhat controversial, though there is evidence that IgG4, in particular, may have such a blocking capacity (via allergen capture prior to reaching mast cell-bound and basophil-bound IgE).

The T-regulatory cell response has been shown to have a central role in the induction of peripheral allergen tolerance. This mechanism was first noted by Rocklin, who identified antigen-specific T-suppressor cells in peripheral blood of patients after SIT-mediated desensitization. This concept was further characterized by Akdis and colleagues, who characterized the crucial role of IL-10 producing T-regulatory cells [26, 27[•]]. TGF- β has also emerged as a central player in allergen

tolerance, as it is responsible for FOXP3-mediated conversion of naïve CD4⁺CD25⁻ T cells into CD4⁺CD25⁺ T-regulatory cells and is required for the expansion and immunosuppressive capability of this cell population [28,29]. Beyond the essential function of the allergen-specific T-regulatory response, the other T-effector cell subsets are suppressed, with a skewing towards Th1 response and away from the Th2 response commonly associated with atopic sensitivity. Although the understanding of the molecular mechanisms that underlie SIT-induced tolerance is far from complete, the ability to manipulate these pathways to induce a beneficial, tolerogenic state in allergic individuals will continue to improve as these mechanisms are elucidated with further precision.

Alternative specific immunotherapy delivery modalities

Thus far, this historical perspective has focused on SIT as first delivered by Noon and Freeman, that is, subcutaneously. Although generally well tolerated, there remains a small but real risk of a systemic reaction (including life-threatening anaphylaxis) with subcutaneous immunotherapy (SCIT) as documented in the nearly simultaneously reports by Lockey *et al.* and the British Committee on Safety of Medicines [30,31]. Borne partly from a desire to enhance patient safety and partly to improve compliance, there has been increasing interest in alternative modes of SIT delivery. Most prominently among these has been the increasing clinical acceptance of sublingual immunotherapy (SLIT) as part of standard allergy practice, particularly in Europe. Scadding and Brostoff [32] published the first controlled trial of SLIT in 1986, in which they reported symptom improvement and increase in peak morning nasal inspiratory flow in a small cohort of dust mite allergic patients. Passalacqua *et al.* [33] validated and extended these findings mechanistically, noting diminished conjunctival inflammatory cell infiltrate and intercellular adhesion molecule 1 expression in addition to decreased symptom scores in patients treated with dust mite SLIT. In 2009, a World Allergy Organization position paper confirmed the safety and clinical efficacy of SLIT, after review of over 60 controlled trials, most of which used monomeric therapy to grass pollen or dust mites [34]. The international committee concluded that there is substantial evidence in both adults and children for the routine use of SLIT to treat allergic rhinitis and suggestive, though not definitive evidence, for efficacy in treatment of allergic asthma. Currently, the U.S. regulatory approval by the Food and Drug Administration (FDA) is still pending and SLIT is not part of routine allergy practice in the USA. The use of SLIT for other indications such as atopic dermatitis or food allergy should be considered

investigational at this point, though there is a growing body of evidence that SLIT may be efficacious in peanut allergy [35].

Investigational forms of specific immunotherapy

There are numerous experimental approaches under active investigation to enhance the efficacy of SIT as well as decrease the small but persistent risk of anaphylaxis during its delivery. One such approach is the use of omalizumab, an anti-IgE monoclonal antibody, during the initiation phase of immunotherapy. This method has been shown to decrease systemic reactions requiring epinephrine, and further appears to increase efficacy as assessed by rhinitis symptom scores [36]. A similar study design in moderate persistent asthma also resulted in decreased systemic reactions when patients were treated with a 12-week omalizumab course prior to a 4-week, cluster SCIT protocol, and further, a significantly increased percentage of the omalizumab group were able to reach the target immunotherapy maintenance dose [37]. Thus, initial trials of anti-IgE therapy as a pretreatment regimen prior to initiation of SCIT show promise by both improving safety and increasing ultimate therapeutic efficacy.

Another strategy has been to attempt to modulate the innate immune system in concert with the adaptive changes mediated by traditional SCIT by the chemical addition of Toll-like receptor (TLR) agonists. The Pollinex Quattro vaccine (Allergy Therapeutics, Worthing, UK) is one such effort which has been licensed in the UK, with pollen extracts linked to a TLR4 agonist. Preseasonal administration of four injections shows significantly reduced skin test reactivity, decreased allergen-specific IgE seasonal rise, and decreased symptom scores in both adults and children [38]. Trials were initiated in the USA with this product, but subsequently suspended because of an adverse event. In a similar vein, TLR9 immunostimulatory elements such as CpG nucleotide sequences have been conjugated to Amb a 1 in an effort to reduce allergenicity and improve immunogenicity and have been shown *in vitro* to reverse the Th2 skewing that typically occurs on allergen stimulation to a more favorable Th1 cytokine profile [39]. However, difficulties with study design led to inconclusive data with an investigational Amb a 1/CpG conjugate, TOLAMBA (Dynavax Technologies, Berkeley, California, USA), and its development has been discontinued [40]. Finally, alternative routes of allergen administration have been explored beyond the traditional SCIT and the evolving SLIT. Perhaps the most innovative of these techniques is intralymphatic allergen injection, which in one limited trial offered comparable symptom improvement in grass-allergic

patients with three intranodal injections over 2 months versus 3 years of conventional SCIT [41].

Conclusion

For the last 100 years, the pioneering technique of subcutaneous allergen desensitization first developed by Noon and Freeman has proven quite resilient and, in fact, central to the practice of clinical allergy. It remains the only therapeutic modality by which long-term immune modification can be achieved and has afforded not only symptomatic relief to untold numbers of allergic patients, but also life-saving benefit in the case of venom hypersensitivity. So while we are indebted to generations of scientists and physicians for their outstanding contributions to the understanding of the mechanisms and clinical application of immunotherapy, we embrace the many new technological approaches that hold promise for the treatment of allergic patients and that perhaps one day may give rise to a cure for atopic diseases.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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