Allergen Immunotherapy: Review Article

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Abstract
Background: Allergen specific immunotherapy (AIT) is currently the only known causal effective treatment of IgE mediated allergy. AIT was introduced by Leonard Noon more than 100 years ago and currently is the only disease modifying treatment in allergy. The pioneer clinical trials with the AIT were undertaken by Noon in 1911 and continued by Freeman in Europe in grass pollen seasonal allergic rhinitis. The allergens used in the therapy were water-extracts from grass pollen mixtures. Patients selected for immunotherapy must be identified as having an underlying antigenic trigger through a combination of clinical history taking, skin prick tests, and/or allergen specific IgE blood tests. Since its discovery, specific immunotherapy (SIT) has been commonly performed by the subcutaneous route. It is generally accepted that three to five years are needed to achieve a clinical benefit for either sublingual immunotherapy (SLIT) or SCIT and to maintain it after treatment is stopped. A prominent role in SLIT is played by dendritic cells in the oral mucosa, which are of critical importance in inducing tolerance to antigens. The tolerance patterns - that are promoted by dendritic cells and driven by Treg cells - account for the suppressed or reduced activity of inflammatory cells and for the isotypic switch of antibody synthesis from IgE to IgG, and especially to IgG4. The mechanisms promoted by SLIT.
Keywords: Allergen specific immunotherapy

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Introduction:

Allergen specific immunotherapy (AIT) is currently the only known causal effective treatment of IgE mediated allergy. AIT was introduced by Leonard Noon more than 100 years ago and currently is the only disease modifying treatment in allergy. The pioneer clinical trials with the AIT were undertaken by Noon in 1911 and continued by Freeman in Europe in grass pollen seasonal allergic rhinitis. The allergens used in the therapy were water-extracts from grass pollen mixtures (Jutel *et al.*, 2016).

Allergen immunotherapy was administered as a disease modifying treatment in cases of allergic rhinitis. By giving the patient increasing doses of the allergen at regular intervals (starting with a very small dose) in a carefully controlled way over a period of years, given to the patients by injection or sublingual drops (under the tongue), it is possible to teach the immune system to tolerate the allergen and not 'fight' it. AIT has also been called desensitization or allergy injection therapy **(Nelson, 2014).**

Indication:

Patients selected for immunotherapy must be identified as having an underlying antigenic trigger through a combination of clinical history taking, skin prick tests, and/or allergen specific IgE blood tests **(Hanci *et al.*, 2016).**

The majority of guidelines prove that children with allergic rhinitis that is difficult to manage with conventional treatments are ideal candidates for AIT. However, due to safety concerns, allergic rhinitis must be well controlled with standard pharmacological treatment when the injection is given **(Tsabouri *et al.*, 2017).**

Contraindication:

Absolute contraindications (serious immunologic disease, major cardiovascular disease, cancer, chronic infections, inability to comply, severe psychological disorders) or relative contraindications (pregnancy) are the two types of AIT contraindications **(Pitsios *et al.*, 2015).**

Immunotherapy's mechanism of action:

A key feature of AIT is to change the course of disease by altering the underlying pathology. Currently, two types of AIT are in clinical practice, subcutaneous immunotherapy and sublingual immunotherapy **(Calderon *et al.*, 2013).**

The Pathophysiology of allergic diseases is complex and influenced by many factors, including genetic susceptibility, route of exposure, allergen dose, time of exposure, structural characteristics of the allergen and co-exposure with stimulators of innate immune response such as infections or commensal bacteria. Allergic diseases are characterized by the induction of Th2 cells, together with the production of allergen-specific IgE antibodies and increased eosinophil numbers in the affected tissues and sometimes in peripheral blood **(Akdis, 2012).**

The pivotal action is the anti-inflammatory effect of immunotherapy based on the ability to modify the phenotype of T cells which in allergic subjects is characterized by a prevalence of the Th2 type with production of IL-4, IL-5, IL-13, IL-17 and IL-32 cytokines **(Romagnani, 2006).**

The immunotherapy-induced changes result in a Th1-type response (immune deviation) related to an increased IFN-gamma and IL-2 production or by a Th2 reduced activity, through a mechanism of anergy or tolerance. It is now known that T-cell tolerance is characterized by the generation of allergen-specific T regulatory cells, which produce cytokines such as IL-10 and transforming growth factor (TGF)-beta with immunosuppressant and/or immunoregulatory activity **(Taylor *et al.*, 2006).**

Dendritic cells are professional antigen presenting cells (APCs) that take up antigens and prime T cell responses and therefore likely play an instrumental role in directing these changes in

T cell function. Two major classes of DCs have been identified in the peripheral blood of humans: **(1)** plasmacytoid DCs **(2)** myeloid DCs. Both subtypes regulate allergen-driven Th2 cytokine release by CD4+ T cells underscoring a critical role for these cells in the pathogenesis of allergic disease **(Frischmeyer-Guerrerio *et al.*, 2014)**.

Methods of immunotherapy treatment:

Since its discovery, specific immunotherapy (SIT) has been commonly performed by the subcutaneous route **(Casale and Stokes, 2011)**. However, in early studies subcutaneous immunotherapy (SCIT) was associated with uncommon, but severe or even fatal, systemic reactions **(Roberts *et al.*, 2006)**.

As a consequence, the interest in alternative routes increased, inspiring the search for more effective non-injection routes of administration of allergen specific immunotherapy. Therefore, delivery of allergens through the mucosal route has been proposed, and it has been suggested that the natural mechanisms underlying the induction of oral tolerance at mucosal surfaces may be an effective therapeutic strategy for suppression of ongoing pathological immune responses in allergic diseases **(Passalacqua *et al.*, 2004)**.

Various mucosal routes of administration were proposed and investigated during the last decades, involving local oral, nasal, bronchial and sublingual routes. Controlled trials failed to demonstrate clinical efficacy of oral and bronchial routes. Meanwhile, the efficacy and safety of the sublingual route was documented by numerous controlled trials in children and adults with asthma and rhinitis sensitized to house dust mite (HDM) or pollen **(Wilson *et al.*, 2005)**.

Treatment duration:

It is generally accepted that three to five years are needed to achieve a clinical benefit for either sublingual immunotherapy (SLIT) or SCIT and to maintain it after treatment is stopped **(Tsabouri *et al.*, 2017)**.

The most widely recognized routes of allergen specific immunotherapy are:

I) Subcutaneous immunotherapy
II) Sublingual immunotherapy

I) Subcutaneous Immunotherapy:

Subcutaneous Immunotherapy has been the gold standard, whereas SLIT has emerged as an effective and safe alternative **(Durham and Penagos, 2016)**.

II) Sublingual Immunotherapy:

Sublingual immunotherapy's mechanisms of action

Sublingual immunotherapy involves frequent placement of micrograms to milligrams of allergen under the tongue **(Jones *et al.*, 2014)**. Oral mucosa has a degree of immune privilege and potentially tolerogenic antigen-presenting cells and T-cells. Intraoral environment is protected from inflammatory responses by high levels of secretory IgA, antimicrobial peptides in saliva and commensal bacteria. All factors may be important in facilitating tolerogenic responses to SLIT **(Novak *et al.*, 2008)**.

In the past it was believed that SLIT had different mechanisms of action, but now it has been recognized that the two routes of administration (SLIT, SCIT) share similar abilities **(Incorvaia and Frati, 2009)**.

A prominent role in SLIT is played by dendritic cells in the oral mucosa, which are of critical importance in inducing tolerance to antigens. The tolerance patterns - that are promoted by dendritic cells and driven by Treg cells - account for the suppressed or reduced activity of inflammatory cells and for the isotypic switch of antibody synthesis from IgE to IgG, and especially to IgG4. . Moreover, data obtained from biopsies clearly indicate that the pathophysiology of the oral mucosa plays a pivotal role in inducing tolerance to the sublingually administered allergen, as showed by subjects treated with high-dose SLIT who have a very low number of mast cells and eosinophils - the effector cells of allergic reactivity - both in the epithelium and sub-epithelium layers, and show insignificant changes after SLIT **(Marcucci *et al.*, 2008)**.

The underlying immunological mechanism of SLIT is thought to promote a shift from the T helper cell type 2 -dominant inflammatory environment promoted by many allergic diseases towards T helper cell type 1 immune responses as well as the induction of regulatory T cells and changes in IgG4, IgE and IgA antibody production **(Jay and Nadeau, 2014)**.

Clinical efficacy of sublingual immunotherapy:

The evaluation of clinical efficacy of SLIT relies on the assessment of symptom severity and rescue medication. Most clinical trials used the assessment of traditional symptom scores plus recording of doses of rescue medications **(Đurić-Filipović *et al.*, 2016)**.

Side effects for SCIT and SLIT:

Side effects for SCIT include common local reactions at the site of the injection and more rarely systemic allergic reactions. Systemic allergic reactions can be serious even fatal. To the contrary, SLIT is safer than SCIT. Reactions usually are local and limited to the mouth. Occasionally, system allergic reactions occur however, life-threatening anaphylaxis is extremely rare. For example, 0.1–3.5% of injections result in a systemic allergic reaction for SCIT whereas there is a 0.056% of systemic allergic reactions per SLIT dose. Fatalities have been reported with SCIT but not SLIT. Guidelines, depending on the SLIT product, indicate that the first one or more SLIT doses be administered in a physician-supervised setting and thereafter at home **(Lin *et al.*, 2016)**.

SLIT adverse events were frequently local (75%) and 0.06% of doses administered were classified as severe reactions. The majority of these reactions were gastrointestinal symptoms, rhinoconjunctivitis, urticaria or some combination of these symptoms **(Aissa *et al.*, 2016)**.

1. **Dosing regimen:**

Higher doses were achieved by using a concentrated solution or tablets and by administering the allergen extract more frequently. Many of the recent SLIT studies have used a daily maintenance-dosing regimen. There have been few studies that have compared SLIT dosing frequency regimens in humans. None of the studies compared the same dose administered at different dosing frequencies. All of the dosing-regimen studies compared more than one variable,

which was usually dose and dosing frequency. One four-year study found daily dosing did better than 3 times a week **(Bordignon and Parmiani, 2003).**

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