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REVIEW

Sublingual immunotherapy for the treatment of allergies

N Schellack,[1*] D Engler[1]

[1]*Department of Pharmacy, Faculty of Health Sciences, Sefako Makgatho Health Sciences University*
[*]*Corresponding author, email: natalie.schellack@smu.ac.za*

Abstract

The treatment of allergies often involves pharmacological therapy and recommendations by healthcare workers that the allergen should be avoided. Allergen-specific immunotherapy has emerged as an alternative to effectively decrease the immunoglobulin (Ig) E:IgG4 ratio. Two routes of administration are described, namely subcutaneous immunotherapy, which has always been considered to be the gold standard of treatment, and sublingual immunotherapy, which has recently been shown to have fewer systemic side-effects and improved compliance by patients.

Keywords: AIT, allergic disease, allergen-specific immunotherapy, allergic rhinitis, clinical efficacy, SCIT, SLIT, subcutaneous immunotherapy, sublingual immunotherapy

Introduction

Allergies refer to a hypersensitivity disorder of the immune system, and are the fifth leading chronic disease group globally. The broader name, allergic rhinoconjunctivitis (the involvement of the eyes and nose), is not that well known, and is commonly referred to as allergic rhinitis. Allergic rhinitis presents with the nasal symptoms of congestion and rhinorrhoea, and is commonly associated with ocular symptom complaints.[1–4] Allergic conjunctivitis constitutes an inflammatory response of the conjunctivae to allergens, such as pollen (grass pollen), environmental antigens (dust) and animal dander.[1,3–6]

Allergic conjunctivitis or rhinitis is an acute or chronic illness, and is classified according to the type of allergen and occurrence of symptoms during the course of a year, i.e. seasonal or perennial. The seasonal form usually occurs during the spring and autumn when the level of outdoor allergens, i.e. pollen, is elevated, whereas perennial conjunctivitis or rhinitis is present throughout the year, is more chronic in nature and is caused by indoor allergens, i.e. house dust mites, pets and cockroaches. Recently, this classification was revised by Allergic Rhinitis and its Impact on Asthma (ARIA). The new classification does not involve the type of allergen, but rather involves the duration of symptoms and impact on the patient's quality of life. The classification was revised to differentiate between intermittent (≤ 4 weeks in duration) or persistent (≥ 4 weeks in duration) allergic conjunctivitis or rhinitis.[1,7]

The symptoms that are associated with allergic rhinoconjunctivitis due to an immunoglobulin (Ig) E-mediated inflammatory response include nasal symptoms, such as congestion, nasal itching, sneezing and rhinorrhoea; and ocular symptoms, such as itching, redness, watering, tearing and burning. These symptoms are frequently reported by allergic rhinitis patients, and are more prominent in patients experiencing seasonal allergic rhinitis.[1–6]

Allergic rhinitis symptoms can affect patients' quality of life, including a reduction in sleep quality, the performance of daily activities, cognitive function, work productivity and examination performance in the case of learners. These symptoms also have an impact on patients' psychosocial well-being.[4,7–10]

Atopy in allergy

"Atopy" is derived from the Greek word, *atopia,* meaning "different" or "out of place". The atopic triad refers to three allergic conditions of atopic dermatitis (eczema), allergic rhinitis and asthma. Atopic dermatitis usually presents as the first allergy in this triad, indicative of the start of subsequent allergic diseases. This sequence of progression is referred to as "the atopic march", with some clinical signs becoming more prominent, while others subside.[11] The prevalence of atopic dermatitis was found to be 17% in South Africa, and up to 20% in Kenya in a systematic review performed in 2012. Atopic dermatitis was also found to be on the increase.[12] An estimated 5–20% of children worldwide are affected by it.[13]

Atopic dermatitis is characterised as an inflammatory, relapsing and itchy skin disorder which is not contagious. Dry and scaly patches are present on the skin of the scalp, forehead and face, especially the cheeks, as well as the flexor surfaces of the limbs. The affected areas can be extremely itchy, to such an extent that sleep is affected. The skin can become infected because of scratching, leading to further complications. The disease is debilitating and affects all aspects of patients' quality of life.[13] Atopic dermatitis has an impact on health-related quality of life,

as well as on patients' mental health, and on social and emotional functioning.[14] Patients who are diagnosed with atopic dermatitis are affected, while their families also carry the associated burden, both financially and psychologically.[13,14]

There is an increase in the prevalence of food and skin allergies in children aged ≤ 18 years. Furthermore, it has been shown that the occurrence of skin allergy decreases with increasing age, while the incidence of respiratory allergies increases with advancing age.[15]

Approximately 80% of patients diagnosed with atopic dermatitis develop asthma and/or allergic rhinitis as they grow older.[13] Allergic rhinitis may precede the development of asthma, especially if not diagnosed and appropriately treated.[16] Therefore, the development of subsequent atopic disorders might decrease if the disease progression can be altered.[11]

The high prevalence of IgE-mediated hypersensitivity, which places patients at risk of life-threatening conditions such as asthma, has resulted in an increase in the use of sublingual immunotherapy (SLIT) in Europe, with increased interest in countries such as the USA.[17,18] The reasoning behind this movement is that allergen-specific immunotherapy (AIT) treats the symptoms, and also the underlying cause of the disease.[18]

Pathophysiology of atopy

The so-called T helper cell type 1 (Th1)/T helper cell type 2 (Th2) paradigm refers to the balance which exists between the Th1 and Th2 subsets of the T lymphocyte. Both Th1 and Th2 subsets differentiate from CD4+-naïve T lymphocytes, which means that whenever a raised response towards either the Th1 or the Th2 subset occurs, the other will conversely be reduced.[19]

A decrease in Th1 subset production results in decreased levels of interferon-gamma, interleukin (IL)-2 and tumour necrosis factor-beta. A decrease in these cytokines leads to an increase in the Th2 effect owing to a decrease in IgG production, which inhibits Th2 formation.[20]

Infants who are genetically predisposed have an imbalance towards an elevated Th2 cellular response. The Th2 cytokines mediate the release of IL-4, IL-5 and IL-13, as well as IgE production.[21] When IgE binds to an allergen, it gains the ability to bind to the high-affinity IgE receptor (FcεRI) which is expressed on the mast cell surface. When this receptor is stimulated, mast cell degranulation takes place. This degranulation then leads to the release of potent vasodilators, such as histamine, lipid mediators, chemokines and various other cytokines.[22,23] Histamine also has the ability to attract other proinflammatory substances. This cascade, created by the excessive release of histamine, leads to the typical symptoms seen in patients suffering from an atopic disease, such as urticaria, angio-oedema and anaphylaxis.[4]

Platelet-activating factor (PAF) is another endogenous phospholipid mediator of inflammation which is contained within the alveolar macrophages, eosinophils, mast cells, platelets, basophils and neutrophils. PAF is released upon an allergic and inflammatory reaction. The release of PAF is closely associated with increased vascular permeability, bronchoconstriction, eosinophil chemoattraction and airway hyperresponsiveness, all of which are involved in the pathophysiology of allergic rhinitis, asthma and anaphylaxis. PAF levels are often elevated in patients with allergic conditions, compared to those in healthy controls.[5,24,25]

Management using allergen-specific immunotherapy

The first-line management of an atopic disorder is to avoid the causative allergen, if at all possible. The pharmacological management of symptoms includes antihistamines and topical corticosteroids. AIT, which modifies the natural history of atopic disorders, is another option. AIT is effective in patients with allergic rhinitis, and has been shown to alter the underlying cause of the disease.[26] Two options for the delivery of AIT are available, i.e. subcutaneous immunotherapy (SCIT) and SLIT. Although SCIT was viewed as the so-called gold standard for immunotherapy until recently, SLIT is now viewed as a safe and effective alternative.[26,27]

The sublingual route was proposed for AIT in 1987, and SLIT has emerged as the best option for immunotherapy, with comparable efficacy and a better safety profile.[28] Both SCIT and SLIT consistently demonstrated benefit when compared to placebo, and may be more cost-effective per quality-adjusted life-years from the age of six years, when compared to symptomatic treatment.[29]

Postulated mode of action and delivery

SCIT is the most common type of immunotherapy, and was introduced over a century ago in the form of the subcutaneous administration of gradually increasing dosages of a specific allergen. The allergic subjects would then become desensitised to the causative allergen, provided that sufficiently high dosages were administered on a regular basis for at least three consecutive years.[28] The exact mechanism behind immunotherapy is still being investigated. However, it is postulated that contact by the allergen with the oral mucosa (in the case of SLIT) causes a local and systemic immune response. The allergen is "trapped" at the site by the Langerhans-like dendritic cells in the oral cavity. Subsequently, these cells mature and migrate to the proximal lymph nodes where IgG antibodies are produced and suppressor T lymphocytes are induced. Specific molecules are also produced as part of this response, e.g. Fcε-receptor type I, major histocompatibility complex class I and II, and other co-stimulatory molecules. The increase in the antigen IgG antibodies antagonises and blocks the increase in IgE against the antigen. This balance between IgE and IgG is the crucial mechanism behind the success of ASI.[18]

The administration of SLIT to children suffering from allergic asthma, e.g. caused by house mites, has been shown to increase allergen-specific IgG4 levels, thus reducing the incidence of asthmatic attacks.[30] This decrease in IgE:IgG4, brought about by the administration of SLIT, has been confirmed in children with allergic asthma and allergic rhinitis.[30,31]

Immunotherapy, i.e. SCIT and SLIT, is the only treatment with the potential to cure allergic respiratory disease via the modulation of immune system activity.[16]

After receiving an injection, the patient has to remain at the healthcare facility for at least 30 minutes to be monitored for serious side-effects. SCIT requires long-term commitment from the patient, and can result in considerable direct and indirect costs.[32] SLIT is administered as a drop in the majority of instances. Tablets are used occasionally.[18] SLIT can be delivered either via the "sublingual swallow" or the "sublingual spit" method of administration. The agent is kept under the patient's tongue for a short time, i.e. 1–2 minutes, and then spat out (the sublingual spit method). The "sublingual swallow" method, whereby the agent is kept under the tongue for a short period and then swallowed, was utilised in the majority of studies conducted in the past.[33]

Subcutaneous immunotherapy versus sublingual immunotherapy

The choice between SCIT and SLIT therapy is largely determined by the patient, based on factors such as convenience, availability, resources and personal preference. An overview of some of the factors that need to be considered when making a decision is provided in Table 1.[26]

Table 1: Points for consideration when choosing between subcutaneous immunotherapy and sublingual immunotherapy[26]

Parameter	SCIT	SLIT
Indication	Seasonal rhinitis*	Seasonal rhinitis*
	Perennial rhinitis**	Perennial rhinitis*
Remission	Long term**	Long term*
Paediatric experience	More evidence is needed	More evidence is needed
Administration	At a healthcare facility (specialist supervision is preferable)	Self-administered
Side-effects	Local pain and swelling at the site of the injection is well tolerated	Local itching and swelling is well tolerated
Adherence to treatment	Easily monitored	Can be problematic

SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy
* high-quality evidence, **: moderate level of evidence

It has been shown that patients prefer the use of SLIT when given the option, especially because of the convenience of at-home self-administration.[34]

Future advances

A better understanding of oral mucosal immunity, with new proteomic techniques, has led to research into the development of a second-generation sublingual vaccine based on the recombinant allergens.[33,34] These recombinant allergens directly elicit an IgG response and activate the T cells, subsequently reducing allergen-specific IgE, which effectively reduces IgE-specific side-effects, such as mast cell degranulation. Vaccine preparations are also receiving attention in terms of emphasis on allergen presentation, e.g. powder, biofilm or mucoadhesive tablets, which prolong mucosal contact and facilitate capturing the allergen by the immune cells.[34]

Apart from SCIT and SLIT, which use liquid extracts, other methods of delivering immunotherapy are available. These include sublingual immunotherapy tablets, and oral mucosal immunotherapy in which a toothpaste delivery vehicle is utilised.[34]

Conclusion

The use of SLIT is preferred over SCIT as it involves a treatment option which can be self-administered at home, ensuring better compliance by patients. SLIT produces long-term clinical efficacy, and has been shown to reduce allergic rhinitis, asthmatic symptoms and the progression of the atopic march. However, the choice of SLIT versus SCIT therapy is still determined by patient preference. Large head-to-head, randomised, placebo-controlled trials, with known immunotherapies, will assist with prospective treatment decisions. The use of ASI, i.e. SLIT and SCIT, holds future promise in preventing and curing allergic disease.

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