Specific Immunotherapy for Allergy in Children

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List of Abbreviations

AAAAI:	American Academy of Allergy, Asthma and Immunology
ACAAI:	American College of Allergy, Asthma& Immunology
AE:	Adverse Event
ARIA:	Allergic Rhinitis and its Impact on Asthma
AD:	Atopic dermatitis
APC:	Antigen presenting cell
CMD:	Cumulative Monthly Dose
DBPC-RCT:	Double-blind, placebo-controlled– randomized clinical trial
DC:	Dendritic cell
DCr:	Protolerogenic regulatory Denteritic Cells
DNA:	Deoxyribonucleic acid
EAACI:	European Academy of Allergy and Clinical Immunology
ECP:	Eosinophil Cationic Protein
EPD:	Enzyme potentiated desensitization
Fab:	Fragment antigen – binding
FcεRI:	High affinity IgE receptor
FDA:	(US) Food and Drug Administration
FEV1:	Forced Expiratory Volume in One Second
FVC:	Forced Vital Capacity
GINA:	Global Initiotice for Asthma
GITR:	Glucocorticoid Induced Tumour necrosis factor Receptor Family Related Gene
GM-CSF:	Granulocyte Macrophage -Colony Stimulating Factor
GP:	General Practitioner
HDM:	House Dust Mite
ICAM-1:	Intercellular Adhesion Molecule-1
ICS:	Inhaled corticosteroids
IDO:	Indoleamine 2,3-dioxygenase
INF:	Interferon
Ig:	Immunoglobulin
ISSAC:	International Study of Asthma& Allergy in

	Childhood
ISS:	ImmunoStimulatory Sequance
IL:	Interleukin
IT:	Immunotherapy
Kd:	Kilo Dalton
LLR:	Large Local Reactions
LR:	Local Reactions
LNIT:	Local Nasal Immunotherapy
MHC:	Major Histocompatibility Complex
mRNA:	Messenger Ribonucleic Acid
NF- kB:	Nuclear Factor Kappa light chain enhancer Enhancer of activated B cells
NIH:	National Institutes of Health
PAT:	Preventive Allergy Treatment (study)
PBMC:	Peripheral blood mononuclear cells
PEF:	Peak Expiratory Flow
PLA_2:	Phospholipase A_2
PPAR:	Peroxisome Proliferator Activated Receptor
PRR:	Pattern Recognition Receptor
RANK:	Receptor activator of nuclear factor
RCT:	Randomized Controlled Trial
SAE:	Serious Adverse Event
SCIT:	Subcutaneous Immunotherapy
sECP:	Serum Eosinophil Cationic Protein
SIT:	Specific Immunotherapy
SLIT:	Sublingual Immunotherapy
SR:	Systemic Reaction
TAT:	Transactivator of Transcription
TCR:	T Cell Receptor
T regs:	Regulatory T Cells
TGF:	Transforming Growth Factor
Th:	T Helper Cells
TLR:	Toll Like Receptor
TNF:	Tumor Necrosis factor
VACM-1:	Vascular Cell Adhesion Molecule-1
WAO:	World Allergy Organization
WHO:	World Health Organization

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Introduction & Aim of the work

Allergic diseases including asthma, allergic rhinitis/ conjunctivitis and eczema affect up to one quarter of the population in western countries at some time in their lives and the prevalence is rising ***(Asher et al., 2006)***. The socioeconomic impact of these diseases on the community is large, including costs of health care and lost work and school hours ***(Masoli et al., 2004)***.

Atopy is defined as the genetic propensity to develop immunoglobulin E antibodies in response to exposure to allergens that can be assessed by skin prick test responses to common allergens ***(Arshad et al., 2001)***. Following initial exposure to allergen in susceptible individuals, IgE antibodies are generated and bind to high affinity IgE Fc receptors (FcεRI) on blood basophiles and skin and mucosal tissue mast cells. On re-exposure to the relevant allergen, biphasic response may be elicited with an immediate hypersensitivity and a delayed inflammatory component ***(Rolland et al., 2009)***.

Major perennial allergens are from house dust mites (HDM) and domestic pets (cats, dogs) while the main sources of seasonal allergens are grass, tree, and weed pollens. A variety of other substances can be allergenic, including food and occupational materials such as natural rubber latex. In contrast, bee venom or wasp venom allergy occurs equally in atopic and non-atopic individuals ***(Rolland et al., 2009)***.

Mainstay treatment for allergic diseases is allergen avoidance, when feasible, and the use of non-specific pharmacotherapy including antihistamines, beta-2 agonists and corticosteroids for symptomatic relief. In selected patients where there is a clear demonstration of symptoms on exposure to the offending allergen and documentation of allergen-specific IgE, allergen-specific immunotherapy (SIT) to target the underlying disease process may be of great value. This treatment is attractive as it selectively modulates the allergen-specific immune response and is potentially curative ***(Rolland et al., 2009)***.

Immunotherapy was first developed at St Mary's Hospital of London at the end of 19th century ***(Freeman, 1914)***. However, over the years, SIT has evolved in different ways in different centers and in different countries, leading to varied treatment regimens and distinct philosophic approaches to the therapy. In recent years, clinical trials conducted according to modern principles have confirmed the effectiveness of SIT and have validated several of the alternative regimens that have been tried over the years. Most SIT is given by means of injection, but there is increasing interest in performing SIT through the sublingual route ***(Frew, 2010)***.

Immunotherapy has been shown to be effective for venom anaphylaxis and for rhinoconjunctivitis and asthma caused by inhalant allergens ***(Lockey, 2001)***. It is particularly

effective in seasonal pollinosis ***(Varney et al., 1991).*** It confers long-term benefit for at least 3 years after discontinuation ***(Durham et al., 1999b)***. In children, immunotherapy has been shown to prevent onset of new sensitizations ***(Pajno et al., 2001)*** and to reduce progression of rhinitis to physician-diagnosed asthma ***(Möller et al., 2002)***. Immunotherapy is not approved in children before the age of five years ***(O'Hehir et al., 2007).***

Other alternative routes for local administration of allergen immunotherapy including nasal insufflation, bronchial inhalation and sublingual absorption have been explored ***(O'Hehir et al., 2007).*** The most promising of these has been the sublingual route, with several clinical trials demonstrating significant symptomatic improvement ***(Wilson et al., 2005)***.

The aim of this study was to elaborate the subject of immunotherapy, the rationale of its use, its mechanism of action, different regimens, possible complications and outcome. Attention will be paid to include recent data and developments in every aspect of the subject.

Chapter (1)

Allergen Specific Immunotherapy

Allergen immunotherapy (also termed hyposensitization therapy, immunologic desensitization, or allergen-specific immunotherapy) is a form of immunotherapy for allergic disorders in which the patient is vaccinated with increasingly larger doses of an allergen (substances to which they are allergic) with the aim of inducing immunologic tolerance. Allergen specific immunotherapy is the only treatment strategy which treats the underlying cause of the allergic disorder. It is a highly cost-effective treatment strategy which results in an improved quality of life and a reduction in allergic- and allergen-related asthma, as well as a reduction in days off school/work ***(Nasser et al., 2008; Caldrón and Brandt, 2008).*** Allergen-specific immunotherapy is the only known treatment option that is known to modify the allergy disease process (with a possible chance of curing the disease), whereas other therapies merely suppress the symptoms ***(Durham et al., 2006).***

Subcutaneous injection immunotherapy has been shown to be highly efficacious treatment for allergic disease, but due to a rare serious side effect of anaphylaxis, its use is restricted to specialist centers. As a result there has been growing interest in the sublingual therapy which can be safely administered at home ***(Kay, 2007).***

Mechanisms of allergen specific immunotherapy (SIT):

Despite its usage in clinical practice for nearly a century, the underlying immunological mechanisms of allergen-SIT are slowly elucidated. The mechanisms are thought to involve both cellular and humoral immune responses ***(Akdis and Akdis, 2007).***

The primary reason for studying the mechanisms of SIT is to seek out the element or elements that are biologically important and hence devise new forms of immunotherapy that might improve efficacy, increase safety margins, shorten treatment courses, or achieve more durable results. Several mechanisms have been proposed (Table I). Whether administered by means of injection or sublingually, SIT induces changes in T cell and antibody responses. The challenge for clinical scientists has been to work out which of the observed changes drive the clinical benefit and which are just epiphenomena ***(Frew, 2010).***

Specific IgE reduction:

Allergen-specific IgE levels increase temporarily during the initial phase of SIT but fall back to pretreatment levels during maintenance therapy ***(Creticos et al., 1984)***. The immediate wheal-and-flare response to skin testing usually

reduces during the initial phases of SIT, but this effect is relatively small compared with the degree of clinical benefit. In contrast, the late-phase response to skin testing is virtually abolished after successful SIT. Similar patterns are observed for late-phase responses in the nose and airways ***(Iliopoulos et al., 1991).***

Induction of IgG4 antibodies:

SIT also induces allergen-specific IgG antibodies, particularly antibodies of the IgG4 subclass. At one time, it was believed that these antibodies might intercept the allergenic particles at the mucosal surface and "block" the allergic response. Current opinion is against this, partly because the increase in IgG levels follows rather than precedes the onset of clinical benefit and partly because many mast cells are on the mucosal surfaces and therefore meet allergen before antibodies can interpose themselves ***(Frew, 2010).***

Moreover, there is a poor correlation between the amount of allergen-specific IgG and clinical protection. In most studies the IgG level correlates better with the dose of allergen that has been given rather than with the degree of protection achieved. That said, there has been a recent resurgence of interest in a possible inhibitory role of specific IgG antibodies in grass pollen immunotherapy ***(Francis et al., 2008).*** In particular, the time course of this effect raises the possibility of specific IgG antibodies interfering with IgE-dependent cytokine secretion

from mast cells or facilitated antigen presentation to T cells. Specific IgA2 levels are also reported to increase with SIT ***(Pilette et al., 2007)*** and secreted specific IgA is suggested to play a protective role at mucosal surfaces following SLIT ***(Bottcher et al., 2002).***

Table (1): Possible mechanisms of immunotherapy.

Reduction in specific IgE levels (long-term)
Induction of IgG (blocking) antibodies
Induction of specific Ig A2
Reduced recruitment of effector cells
Altered T cell cytokine balance (shift to Th1 from Th2)
T-cell anergy
Induction of regulatory T cells
↓ number of mast cells

(*Modified from* ***Frew, 2010).***

T cell responses:

SIT also induces changes in allergen-specific T cell responses. In nasal and skin allergen challenge models, successful SIT is accompanied by a reduction in T cell and eosinophil recruitment in response to allergen. A unifying

mechanism to account for the observed changes in inflammatory cell activity and antibody responses is altered allergen-specific T cell reactivity (Fig. 1). Changes in T cell response to allergen correlate well with clinical improvement, and include decreases in antigen-specific proliferation and production of IL-4, but increased production of IL-10 and TGF-β ***(Jutel et al., 2006).*** Elucidation of the precise mechanisms by which allergen administration during SIT elicits these changes in T cell function will inform refined strategies for SIT specifically targeting the T cell response to allergen ***(Rolland et al., 2009).***

Anergy and apoptosis:

Anergy and/or deletion of allergen-specific T cells during SIT is consistent with the decreased peripheral blood T cell proliferative response to allergen generally observed in SIT-treated patients ***(Rolland & O'Hehir, 1998).*** T cell anergy is defined as antigen induced specific non-responsiveness to subsequent challenge with immunogenic concentrations of antigen ***(Lamb et al., 1983).*** Treatment with high doses of antigen in the form of dominant T cell epitope peptides ***(Higgins et al., 1992)*** or antigen stimulation in the absence of antigen presenting cells (i.e. co-stimulation) ***(Mueller et al., 1989)*** can result in T cell anergy.