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Desensitisation - Concurrent Workshop

Saturday, 11 June 2011 Start 4:30pm Duration: 60mins Sigma

Rotorua GP CME 2011
NZMA
General Practice Conference & Medical Exhibition

09-12 June 2011 | Energy Events Centre | Rotorua

Update on desensitisation

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GLORIA Module 4: Allergen Specific Immunotherapy

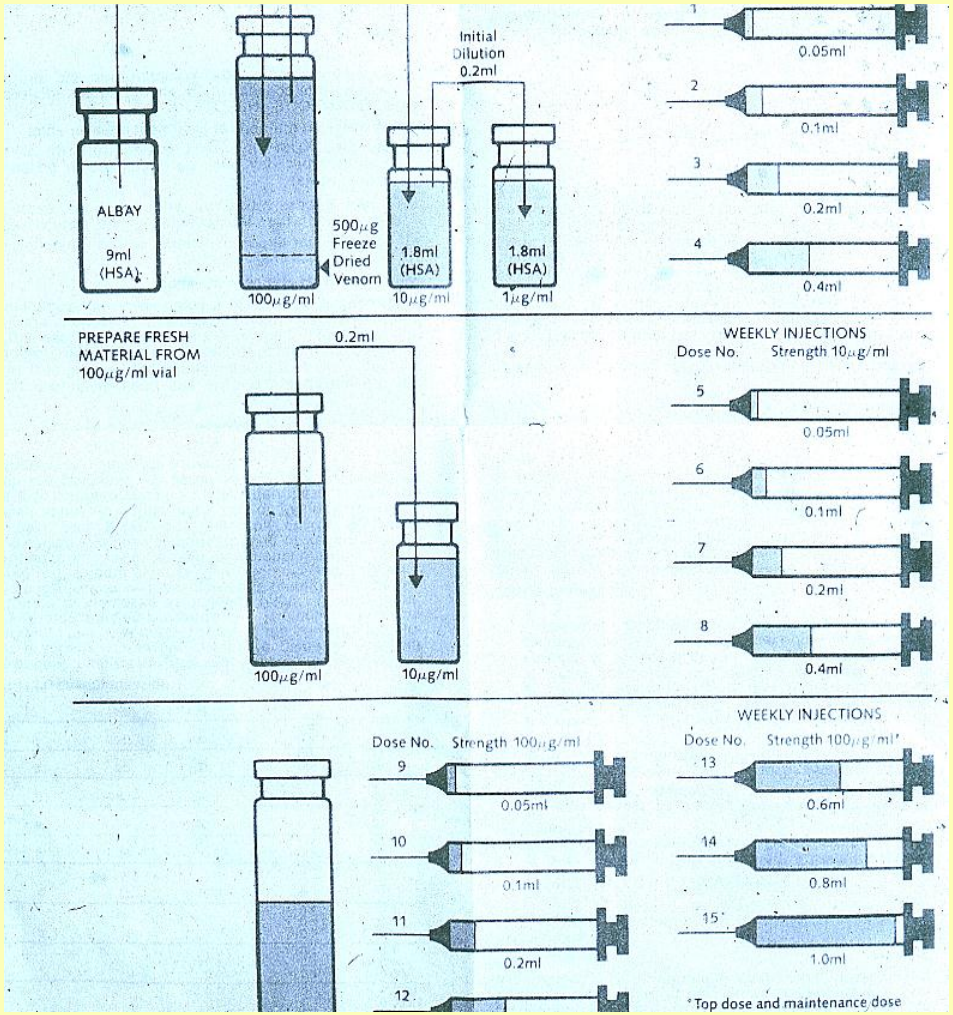
A New Zealand perspective

- **Definition**
- Extracts and standardization
- Efficacy
- Safety
- Long-term benefit
- Practical aspects of immunotherapy
- Mechanisms
- Non injection routes
- Novel approaches
- Summary

Procedure

Allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.

Desensitisation



Allergens

Allergen extracts are a preparation of an allergen obtained by extraction of the active constituents from animal or vegetable substances.

Forms of allergens

For allergen immunotherapy, products may be either unmodified vaccines or vaccines modified chemically and /or by absorption onto different carriers:

- Aqueous vaccines
- Depot and modified vaccines
- Mixtures of allergen vaccines

Standardisation

The quality of the allergen vaccine is critical for both diagnosis and treatment. Where possible, standardized vaccines of known potency and shelf-life should be used.

Importance of standardisation

Standardization allows definition of the "potency" of allergenic extracts and warrants that the batches of vaccine produced from different lots of raw material are consistent and have comparable activities.

Methods of standardization

Biologically; the potency of the vaccine is compared to the cutaneous response obtained in a reference population;

Immunologically; the potency of the vaccine is based on RAST-inhibition experiments using standard pools of sera.

Units of standardisation

- Protein nitrogen units (PNU- world wide)
- Allergy unit (AU- U.S. FDA)
- Bioequivalent allergy unit (BAU)
- Biologic units (BU- Europe)
- International unit (IU- WHO)
- Index of reactivity (IR- Europe)
- Specific treatment unit (STU)
- Activity Units by RAST (AUR- Europe)

Allergen units

The major allergen(s) content in micrograms per ml is provided for most products.

Standardized allergen extracts should be preferred for allergy diagnosis and therapy.

Indications for immunotherapy

- Hymenoptera venom immunotherapy is the only effective preventive treatment for insect sting-induced anaphylaxis.
- Inhalant allergen immunotherapy reduces symptoms and/or medication needs for patients with allergic asthma and/or rhinoconjunctivitis.
- Others eg drugs are within specialist domain
- Immunotherapy for foods is a research tool currently
- Immunotherapy for eczema is a specialist procedure

Advantages of immunotherapy

- Allergen immunotherapy is the only treatment that can modify the immune response to allergens and alter the course of allergic diseases.

- In some guidelines the indication for allergen immunotherapy for asthma and rhinitis has been separated. This separation is incorrect - respiratory allergy is a unique immunological disorder of the airways. ***However immunotherapy for asthma carries more significant risks***.

Pollens
Cat
House dust mites
Hymenoptera
venoms

(drugs, seminal fluid, others)

Stinging Insects

Apis melifera.

Vespula spp.

Bombus **spp.**

Polistes spp.

Vespa Crabro.

Solenopsis invicta

Long term advantages of immunotherapy

- Symptom improvement and/or reduction of the need for symptomatic drugs in allergic rhinitis and asthma.
- Long-lasting effect once discontinued.
- Prevention of the onset of new skin sensitizations.
- Prevention of the onset of asthma (?).- pre-emptive immunotherapy

Immunotherapy for asthma

- 76 trials with 3,188 patients
- Significant improvement in asthma symptom scores
- Significant reduction of allergen specific bronchial hyperreactivity
- Some reduction also in non-specific bronchial hyperreactivity

Safety of immunotherapy

- Millions of subcutaneous immunotherapy injections are administered annually. The risk of a fatal or near-fatal systemic reaction is small, but significant.

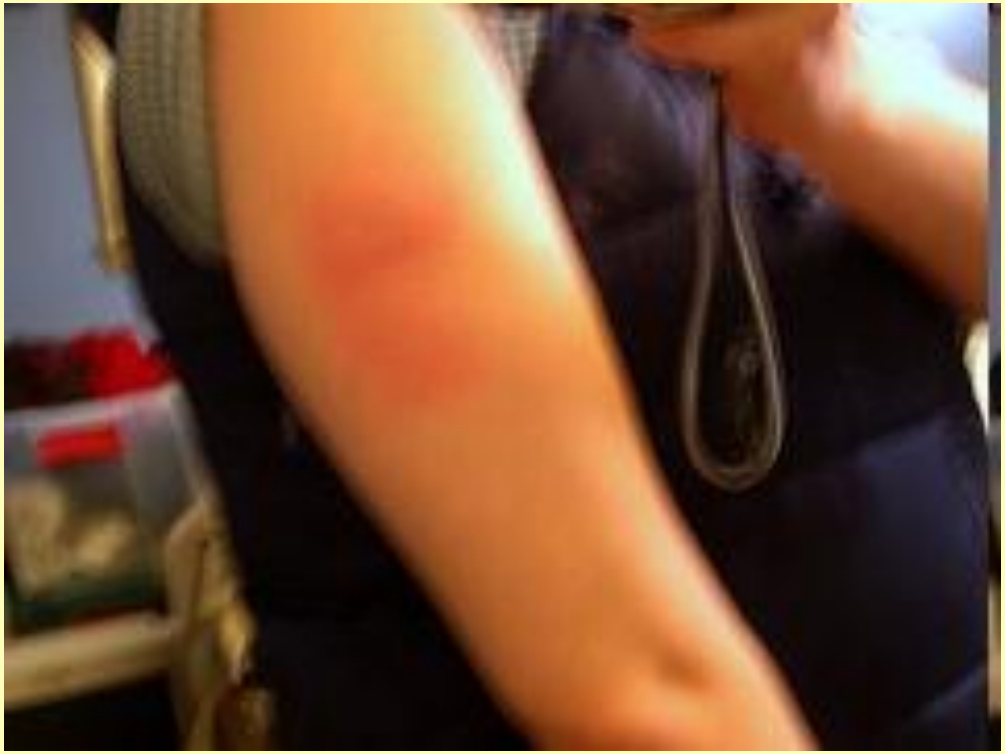
- Physicians prescribing or administering subcutaneous immunotherapy should be aware of these risks and institute appropriate procedures to minimize them.

Adverse effects of immunotherapy

- 1. Non-specific reactions (likely non-IgE-mediated), discomfort, nausea, headache, arthralgia.

- 2. Mild systemic reactions; mild rhinitis/asthma (PEFR > 60%), responding to β_2 agonists/ antihistamines. Pre-treatment with antihistamines helps.

Adverse effects of immunotherapy



Moderate/ severe reactions

- 3. Non-life-threatening systemic reactions; urticaria, angioedema, severe asthma (PEFR < 60%). Responding well to treatment.

- 4. Anaphylaxis; itching, urticaria, bronchospasm, with hypotension, requiring intensive care- ***do not continue until specialist opinion sought***

Fatal reactions to immunotherapy

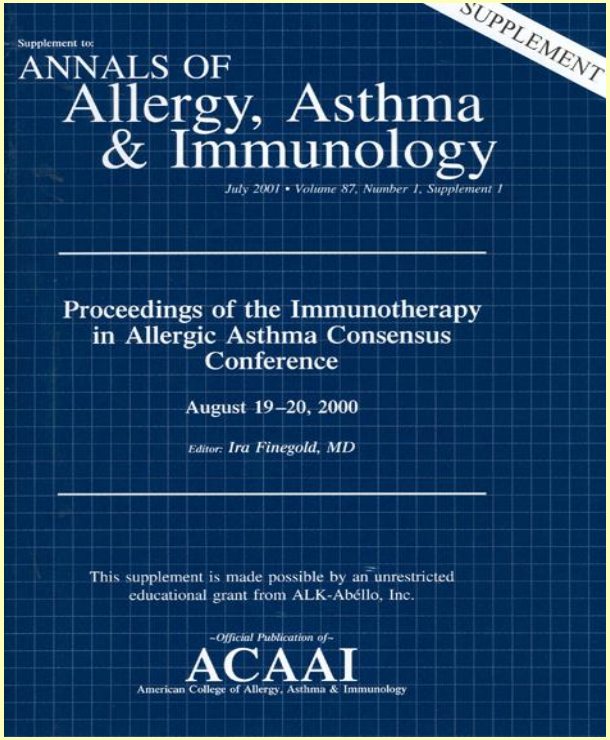
Period 1945-1984

46 Fatalities

Period 1985-1989

17 Fatalities

Estimated risk for fatal reactions less than 1 per 2 million injections



Risk of reactions

- The safety of immunotherapy; a prospective study
- 2,989 patients
- Period 7 months
- Systemic reactions 25/2898 (0.8%)
- No fatalities

Higher risk during induction

	Induction	Maintenance
Patients	1.887	2.691
Visits	38.287	113.550
Reactions	36	62
Rate/pts	1/32	1/47
Rate/visits	1/1063	1/1831

Risk factors for adverse reactions

- Uncontrolled asthma
- Severe asthma
- Use of beta blockers
- Rush immunotherapy
- Pregnancy?
- Build-up phase
- Aqueous preparations
- Use of new vials
- Technical errors

Contraindications to immunotherapy

- Serious immunopathologic diseases and immunodeficiencies.
- Malignancies.
- Severe psychological disorders.
- Treatment with beta blockers, even when administered topically.
- Pregnancy (inhalent induction)

Contraindications to immunotherapy

- Poor compliance.
- Severe asthma, or uncontrolled by pharmacotherapy (FEV1< 70%).
- Significant cardiovascular diseases.
- Children under 5 years (relative contraindication).

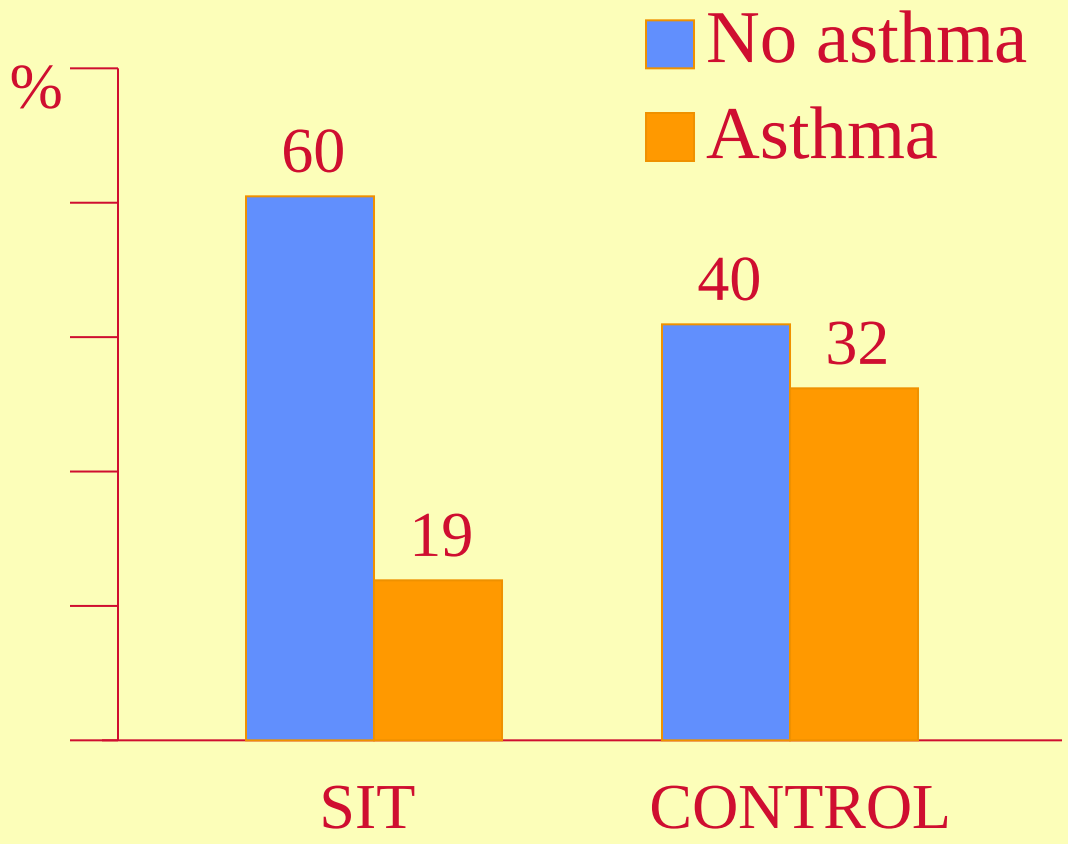
Prevention of new sensitisation

- New sensitizations after 3 years: 55% SIT group vs 100% control group. *Des Roches et al, JACI 1997*

- New sensitizations after 3 years: 25% SIT group vs 67% control group. *Pajno et al, Clin Exp Allergy 2001*

- New sensitizations after 4 years 23% SIT group vs 68% control group. *Purello D'Ambrosio et al, Clin Exp Allergy 2001*

Pre-emptive immunotherapy



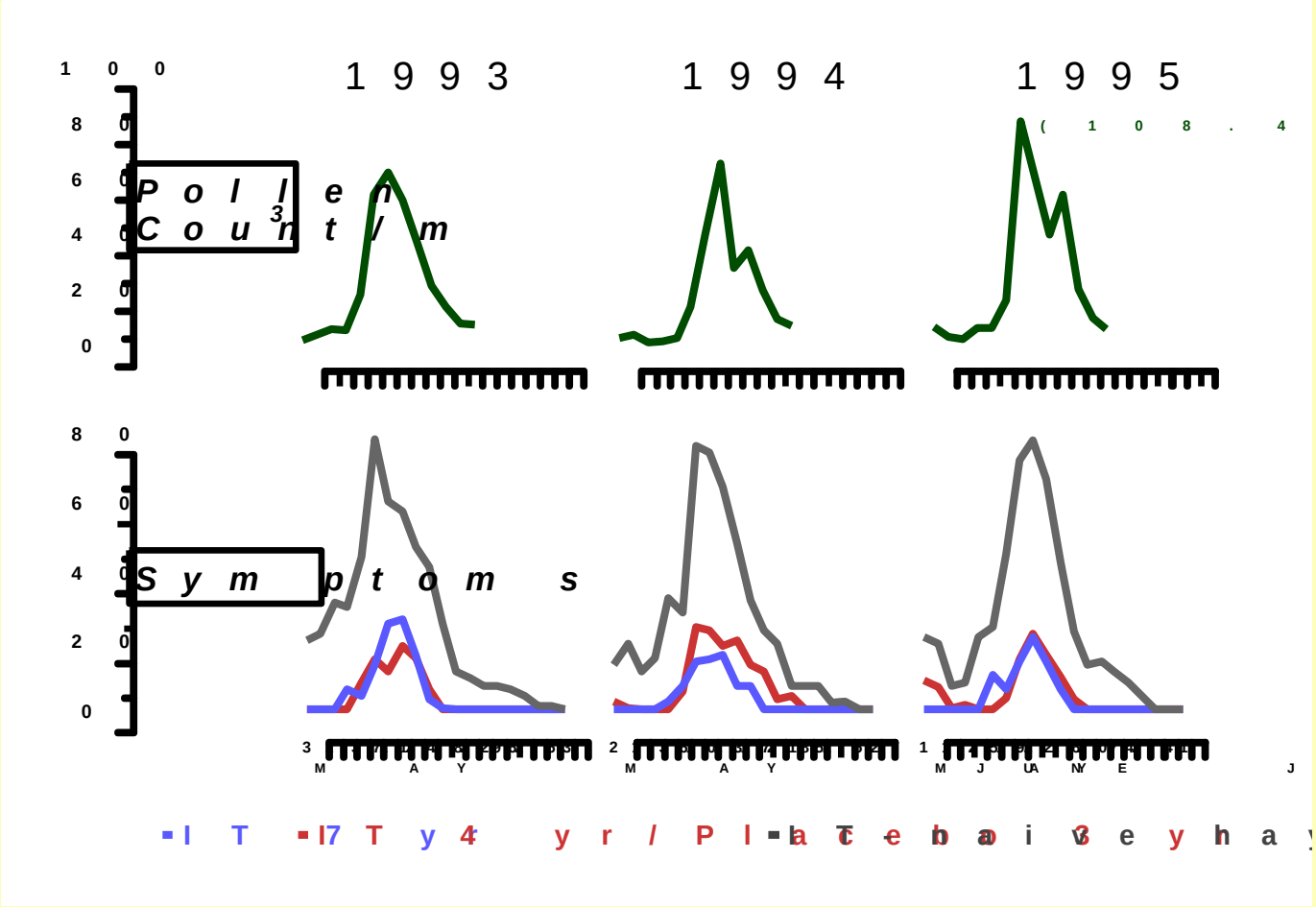
205 children with rhinitis

age: 6-14 yrs

grass or birch allergy

3 yrs immunotherapy

Long-term benefits of immunotherapy



Practical aspect of immunotherapy

- Use upper lateral surface of arm
- Ensure sterile technique
- Use 1ml insulin syringe
- Inject at 45º by deep subcutaneous route
- Record any local/systemic reaction
- Emla patches, ice for children
- Pre-treat with antihistamines

Prescription of IT

- Ideally allergen immunotherapy should be prescribed by a specialist in the field of allergy and immunology.
- IT should be administered by physicians and other health care professionals who are trained to recognize and treat anaphylaxis.
- Patients sensitive to a single allergen versus those who are polysensitized benefit more from immunotherapy.

Selection of patients for IT

- Allergen immunotherapy is more effective in children and young adults.
- Patients with non-allergic triggers may not benefit from IT.
- Allergen immunotherapy preferably should be initiated as early as possible, in the earliest phases of the disease, hopefully to prevent additional sensitization and/or the onset of asthma.
- The ideal patient in GP has allergic rhinitis to 1-2 allergens but no asthma

Selection of patients for IT

- Presence of an IgE-mediated disease (allergic rhinitis) following testing.
- Symptoms are caused by specific allergen(s).
- Exclude other triggers eg salicylate sensitivity.
- Severity and duration of symptoms.
- Response to allergen avoidance and pharmacotherapy.

Mechanisms of action

It has been demonstrated that IT decreases allergen-induced inflammation in allergic rhinitis and allergic asthma.

Pathomechanisms

SIT decreases the migration of eosinophils

Nagayata H, 1996

SIT decreases eosinophil numbers and airways BHR

Van Oosterhat AJ, 1988

SIT decreases the number of mast cells

Durham, S R, 1997

SIT decreases the number and activity of eosinophils

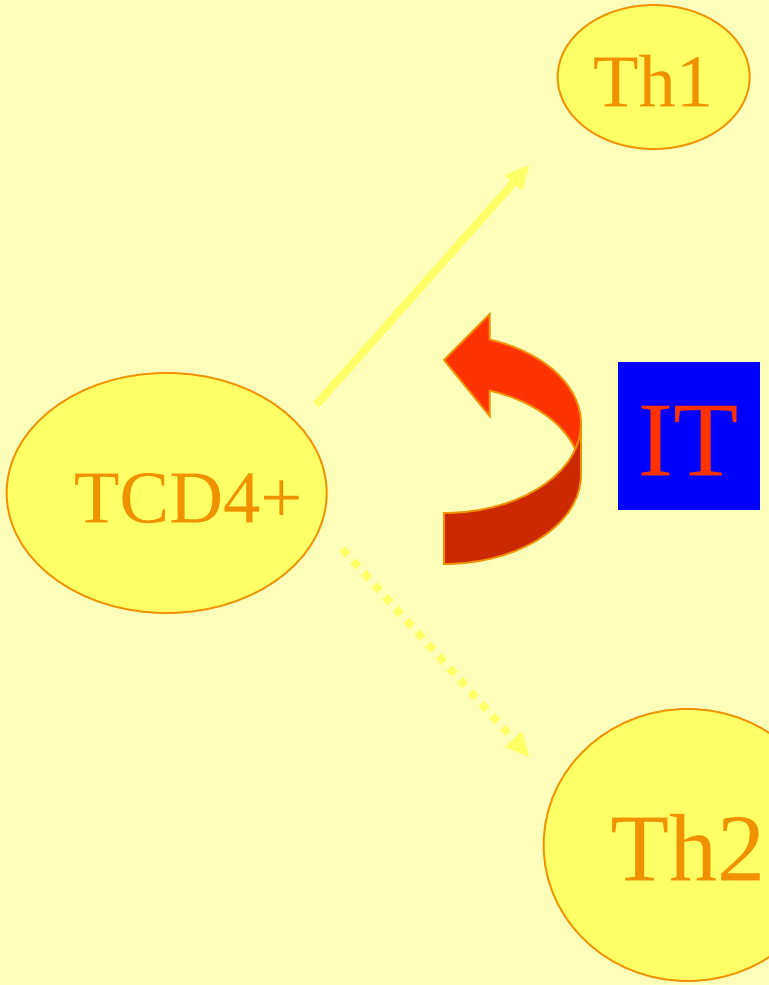
Rak 1988, Durham 1996

Mechanisms of immunotherapy

- Studies have provided insight into the mechanisms of immunotherapy. The efficacy of immunotherapy may be secondary to alteration in the T-cell response to allergen.

- Mechanisms are probably heterogeneous, depending on the nature of allergen, the site of allergic disease and the route, dose and duration of immunotherapy.

Th1/ Th2 paradigm



IL-2
INF-g

IMMUNE DEVIATION?
ANERGY?
BOTH?

IL-4
IL-5
IL-9

Other options for IT

- Oral immunotherapy (OIT): allergen immediately swallowed, as drops, tablets or capsules.

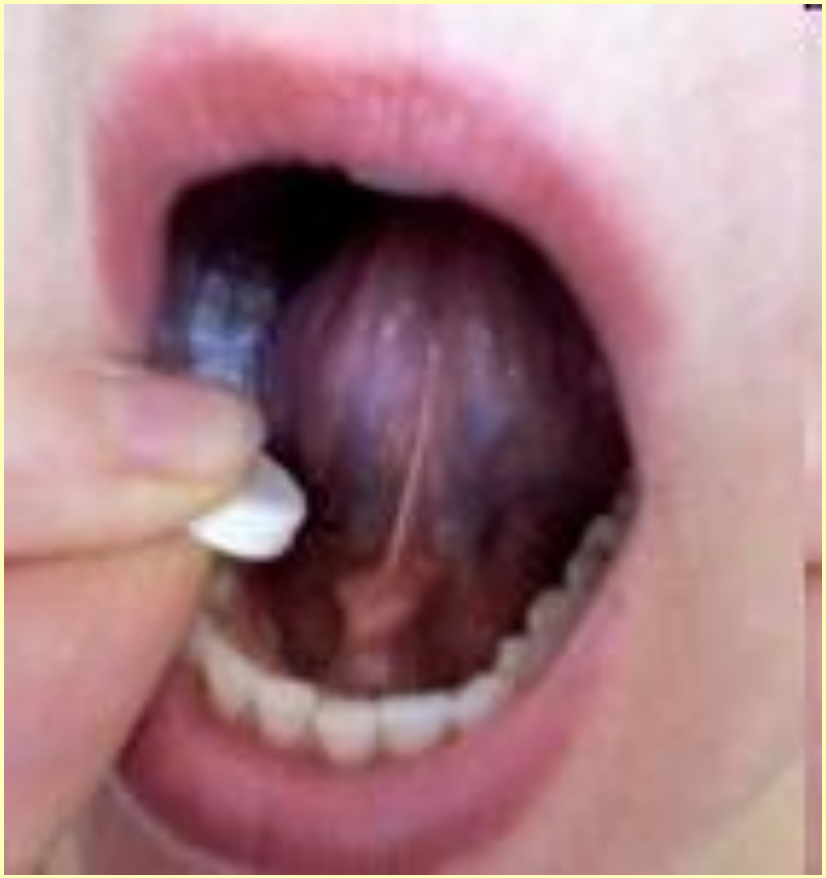
- Sublingual immunotherapy (SLIT): allergen kept under the tongue for 1-2 minutes, then swallowed (the sublingual- spit mode is no longer in use).

Sublingual immunotherapy

- A meta-analysis of 22 DBPC trials has shown that SLIT is effective in rhinitis caused by pollens and mites.
- There are few studies showing additional efficacy on asthma symptoms.
- More studies about efficacy in children are required
- Probably less effective than subcut IT.

Sublingual immunotherapy

Sublingual immunotherapy



Benefits of sublingual IT.

The long-lasting effect has been demonstrated in children with mite-induced asthma.

Di Rienzo et al Clin Exp Allergy 2003

The preventive effect on new skin sensitizations has been demonstrated.

Marogna et al Allergy 2004

Adverse effects

- In post-marketing studies, the overall rate of side effects (all grades) ranges between 3% and 8% of patients.
- The most frequently reported side effects are local (gastrointestinal); oral itching/swelling, nausea, stomach-ache.
- The side effects are usually mild and treatment discontinuation is rarely required.

Adverse effects of SLIT

- Gastrointestinal side effects are dose-dependent.
- Low risk of life-threatening side effects. Anaphylaxis has been described rarely
- The occurrence of systemic effects in controlled trials does not differ from the placebo treated patients.

Indications for SLIT

May be indicated in pollen and mite induced rhinitis and asthma in adults and children, using maintenance dosages 5 -100 times higher then injection IT.

Issues to consider with SLIT

- Very few direct comparisons with SCIT
- In New Zealand much more expensive
- May be indicated in very young children
- Or where there have been adverse effects from SCIT.

IT products in New Zealand

- Alustal (Stallergenes, EBOS)
- Phostal (Stallergenes, EBOS)
- Pangramin (ALK, NZMS)
- Alutard (NZMS)

Issues to consider

- Only Alustal is registered by MEDSAFE
- Others imported under section 29
- Issue of ACC coverage
- Consent

The future of IT

- New immunological treatment modalities for allergic diseases are presently under investigation:
- Liposome vaccines
- Adjuvants
- Anti-IgE antibodies combined with IT
- Peptide vaccination
- Recombinant allergens
- cDNA vaccines

allergen avoidance
indicated when possible

pharmacotherapy
safety
effectiveness
easy to be administered

patient

immunotherapy
effectiveness
specialist prescription
may alter the natural course of the disease

patient's education
always indicated