INVESTIGATIONS & PROCEDURES IN PULMONOLOGY

Immunotherapy in Asthma

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Definition

Involves

• Administration of gradually increasing quantities of specific allergens to patients with IgE-mediated conditions till a dose is reached which is effective in reducing disease severity from natural exposure
Objectives

• To reduce responses to allergic triggers that precipitate symptoms in the short term
• Decrease inflammatory response
• Prevent development of persistent disease in long term
IT in Other diseases

Efficacy demonstrated in
• Stinging-insect hypersensitivity
• Allergic rhinitis or conjunctivitis
• Allergic asthma.

Not effective
• Atopic dermatitis
• Urticaria
• Potentially dangerous if used for food or antibiotic allergies
Indications in asthma

- Demonstration that disease is due to IgE mediated allergy
- Insufficient response to environmental control or pharmacotherapy
- Environmental control not feasible
- Significant side effects of pharmacotherapy
- Poor compliance to therapy
- FEV₁ > 70% after adequate pharmacological treatment
- Both nasal and bronchial symptoms
Relative Contraindications

• Severe asthma uncontrolled by pharmacotherapy and/or irreversible obstruction (FEV$_1$ < 70% after adequate pharmacological treatment)
• Treatment with β-blockers even when administered topically
• Significant cardiovascular disease
• Serious immunodeficiency diseases
• Malignancy
• Psychological illness
• Pregnancy: should not be started
Role of Immunotherapy

- Allergen avoidance & IT have the potential to modify the natural course of disease
- Prevents sensitization to new allergens in monosensitized patients
- Prevents progression of rhinoconjunctivitis to asthma
- Effects of IT for grass, tree or ragweed pollen allergy last several years after discontinuation
- If relapse occurs the immunologic memory persists & there may be good response to new IT regimen
Mechanism of immunotherapy

- Allergen → Th$_2$ stimulation → IgE
- Later exposure → immediate mediator release → eosinophilic & basophilic inflammation
- IT Allergens → T regulatory cells (CD$_4^+$CD$_{25}^+$) → IL-10
  
  \[ \text{Th}_1 \uparrow \quad \text{Th}_2 \downarrow \quad \text{IFN-}\gamma \uparrow \]
Blocking Antibody

Natural allergen exposure after IT

↓

IgG4 instead of IgE

↓

blocks Ag

↓Immediate mediators
Less mast cells

↓ late phase
altered TH1/TH2 ratio
Preparation of Allergen Vaccines

- **Allergenic extract**: preparation of allergen from extraction of active component of animal/vegetable substances
- **Allergenic product**: biologic product including allergenic extract administered to pts for diagnosis or treatment
- Standardization is based on detection of IgE Ab to allergen
Recombinant Antigens

- Newer method is by production of human recombinant proteins
- Cloning of cross-reactive major allergenic proteins reduces the panel of extracts required for diagnosis/therapy
- With this allergen vaccine can be characterized in terms of content (ng or mcg)
- Fel d 1, Lol p 1, Amb a 1, & Bet v 1
Allergen vaccines

- **Aqueous vaccines**: heterogeneous mixtures of allergenic & non-allergenic materials. Used for venom & inhalant immunotherapy
- **Depot & modified vaccine**: To make IT more effective & to reduce side effects by reducing the capacity to induce IgE mediated reactions.

Types of modification:
- **Physical**: adsorption, Al, Calcium phosphate, Tyrosine, Liposomes
- **Chemical**: formaldehyde, glutaraldehyde & alginate modified vaccine
- **Combination**: tyrosine adsorbed, glutaraldehyde modified vaccine & aluminium hydroxide adsorbed formaldehyde vaccine
Skin testing

- Detailed history is required to select correct Ag
- In prick method a drop of glycerinated Ag is put on the surface of skin & then a prick is made.
- 2\textsuperscript{nd} method: intradermal injections
- Results are read after 20 minutes
Precautions before skin tests

• Avoid antihistamines & cromolyn sodium 48 hrs prior
• Sympathetic amines which depress immediate reaction to be stopped at 10 pm previous day
• Corticosteroids to be tapered and preferably withheld 48 hrs prior
## Prick vs intradermal

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<thead>
<tr>
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<th>Prick test</th>
<th>Intradermal</th>
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<tbody>
<tr>
<td>Sensitivity</td>
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<td>better</td>
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<tr>
<td>Specificity</td>
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<td>Discomfort</td>
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<td>Safety</td>
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<td>Reproducibility</td>
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<td>Testing in infants</td>
<td>can be done</td>
<td>difficult</td>
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Monitoring response

- Improvement in lung function: spirometry or peak flow measurements
- Sequential monitoring of symptoms
- Medication score
- Bronchial responsiveness to allergen or to stimuli such as histamine or methacholine
Routes of Immunotherapy

- Subcutaneous
- Oral
- Sublingual
- Nasal
- Bronchial
Method of SCIT

- **Build up:** 0.1 ml of 1:10,000 extract intradermal
  - Dose advancement 0.5 ml
  - Concentration increased 1:1,000
  - Again dose advancement 0.15 → 0.6 ml
  - Concentration increased every time by 10 i.e. 1:100 (max dose 0.7 ml)

- **Maintenance phase:** Final guide of dose is symptom relief or maximum tolerated dose
Method of SCIT

• NBHLI recommends once patient achieves maintenance level monthly injections should be given
• Therapy should be extended for 3-5 years
• If there is no response following two allergy seasons after reaching maintenance (or 1 year) → discontinue
What to do after 5 years?

Continuation beyond 5 yrs if:
• Marked improvement but with persisting symptoms
• Continued need for periodic medical therapy

Patients who need to resume IT after discontinuation will have to go back to weekly schedule
Rush IT

- Disadvantage of classic method: Time
- Rush IT can provide hypo-sensitization in short time
- 3-4 injections are given every 3\textsuperscript{rd} day to build the dose faster. More chances of anaphylaxis used for pre-seasonal & co-seasonal IT
SLIT

- SL swallow: Soluble tablets or drops to kept under tongue then swallowed
- SL spit: 70% of dose retained in mucosa
- Amount of allergen required is more than required in subcutaneous method (X 3-375)
- Build up phase then maintenance phase
- Accelerated build up phase easier to achieve
Advantage of SLIT

• Minimal adverse effects; near fatal events rare
• Ultra-rush protocols may be used
• Avoidance of injections
• Visits reduced
• Though cost of extract is more but overall cost of SLIT is less as compared to SCIT
• Compliance: 96% adherence rate
Efficacy

Three meta-analyses:

• Immunotherapy in asthma: an updated systemic review. 62 RCTs
  
  *Abramson et al. Allergy 1999*

• Meta-Analysis of Prospective, Randomized, Double-Blind, Placebo-Controlled Studies: 24 studies 962 patients with asthma.
  
  *Ross et al. Clin Ther 2000*

• Allergen immunotherapy for asthma
  
  *The Cochrane Database of Systematic Reviews 2003*
Allergen immunotherapy for asthma

75 trials included (52 of 54 previously included trials and 23 new trials).
3,506 participants (3,188 with asthma)

**TRIALS**

- House mite allergy 36
- Pollen allergy trials 20
- Animal dander allergy 10
- *Cladosporium* mould allergy 2
- Latex 1
- Multiple allergens 6

*The Cochrane Database of Systematic Reviews 2003*
Allergen immunotherapy for asthma

- Significant reduction in asthma symptoms and medication: standardized mean difference -0.72, (95% CI -0.99 to -0.33)
- To avoid one deterioration in asthma symptoms NNT 4 (95% CI 3 to 5)
- To avoid one requiring increased medication NNT 5 (95% CI 4 to 6).
- Reduced allergen specific bronchial hyper-reactivity
- No consistent effect on lung function.

The Cochrane Database of Systematic Reviews 2003
Efficacy of SLIT

- Well documented in allergic rhinitis
- In asthma: no meta-analysis
- Studies have demonstrated that benefits are similar to SCIT
- Equal efficacy in adults and children
- Prevents development of asthma in children with rhinoconjunctivitis
  
  *J Allergy Clin Immunol.* 2004 Oct

- There are only 2 studies comparing SLIT with SCIT: equal efficacy (N= 58;20)

  *Allergy 2004. Clin Exp Allergy 1996*
IT or Inhaled Steroids?

• Only one study available
• Open, parallel, comparative trial: 51 young patients administered either immunotherapy or budesonide for 1 year
• Budesonide: faster improvement during the first few months
• Cessation of budesonide: More rapid decline in benefits
• Immunotherapy resulted in slow but steady improvement which did not decline as rapidly as budesonide on cessation

W.A. Shaikh. Clinical & Experimental Allergy 1997
Safety of immunotherapy

• Systemic allergic reactions associated with the injection of allergen vaccines usually begin within 20 minutes. May also begin later
• Most reactions are mild
• Severe and fatal reactions have been reported
• With multiple reactions or in severe asthma, consideration should be given to discontinuing injections
Deaths associated with IT

- USA: 1945-85: 46 deaths
- UK: 1985-89: 17 deaths
  1992-93: 6 deaths
- AAAI: 1985-89: 17
  Severe asthma: 76%
  High sensitivity by skin test or RAST: 71%
  Prior systemic reactions: 36%
- VPCI: 2 cases of anaphylaxis over 20 year period
Risk factors associated with anaphylaxis

• Errors in dosage
• Failure to reduce the dosage after a longer than scheduled interval
• Administration of the wrong extract
• Inadvertent intravenous administration
• Failure to postpone injection because of infection or asthma exacerbation
• Failure to observe patients for appropriate length of time
• Use of beta-adenrenergic blocking agents
• Uses of mixtures of allergens
• Immunotherapy during the active allergy season
Precautions

• %age of subjects experiencing systemic reactions↑ in accelerated & high dose regimens
• Premedication with antihistamines, steroids reduces side effects
• Waiting period of 20 minutes is recommended by AAAI (30 minutes by EAACI)
• **Longer waiting period** recommended for high risk patients:
  Rush IT
  High degree of hypersensitivity
  Beta blockers; cardiovascular disease
Summary of recommendations

Guidelines
Allergen immunotherapy is effective in patients with an allergy to insect stings or allergic rhinoconjunctivitis,

In some patients with asthma

• who have definite history corroborated by positive results of skin tests

• for whom avoidance of the allergen and drug therapy are not sufficiently effective
Asthma guidelines
CMAJ Nov 1999

- IT is generally not recommended in treatment of asthma (level IV)
- IT should not be used in place of avoidance of allergens (level III)
- IT with clinically relevant allergens may be considered if disease activity is inadequately controlled by avoidance of allergens & pharmacotherapy (level I)
- IT should be avoided when asthma is poorly controlled (level III)
BTS Asthma Guidelines

Thorax 2003

• At present immunotherapy cannot be recommended for primary prevention.
• For pollen immunotherapy in children with allergic rhinitis there is a lower rate of onset of asthma
• Immunotherapy may reduce asthma symptoms and use of asthma medications, but the size of benefit compared with other therapies is not known.
BTS Asthma Guidelines

*Thorax 2003*

- No properly controlled studies making direct comparisons between conventional asthma pharmacotherapy and allergen immunotherapy.
- The preparation of materials for immunotherapy, dose frequency and duration of therapy has not been optimized.
- The risk benefits compared with pharmacotherapy require careful consideration.