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
- FEV_1 > 70% after adequate pharmacological treatment
- Both nasal and bronchial symptoms

Relative Contraindications

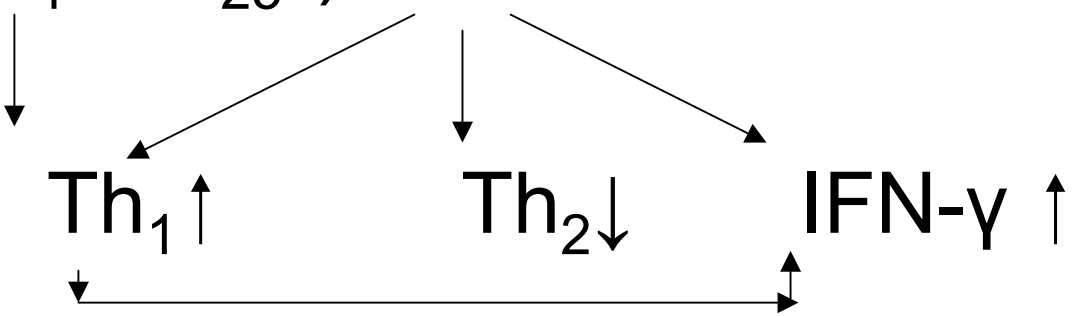
- Severe asthma uncontrolled by pharmacotherapy and/or irreversible obstruction (FEV_1 < 70% after adequate pharmacological treatment)
- Treatment with β-blockers even when administered topically
- Significant cardiovascular disease
- Serious immunodeficiency diseases
- Malignancy
- Psychological illness
- 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



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.
- 2nd 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

	Prick test	**Intradermal**
Sensitivity		better
Specificity	better	
Discomfort		more
Safety	safer	
Reproducibility		better
Testing in infants	can be done	difficult

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

- **<u>Build up:</u>** 0.1 ml of 1:10,000 extract intradermal

  ↓

  Dose advancement 0.5 ml

  ↓

  Concentration increased 1:1,000

  ↓

  Again dose advancement 0.15→0.6ml

  ↓

  Concentration increased every time by 10 i.e. 1:100 (max dose 0.7ml)

- **<u>Maintenance phase:</u>** 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 3rd 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 rhinoconjuctivitis *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-adrenergic 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

Canadian Society of Allergy and Clinical Immunology

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.