

Immunotherapy

Chris Doyle
Consultant Nurse
Respiratory & Allergy
Alder Hey Childrens NHS FT

Chris.doyle@alderhey.nhs.uk

October 18th 2014

What exactly is Immunotherapy?

Medical procedure that uses controlled exposure to known allergen to reduce the severity of IgE mediated allergic disease

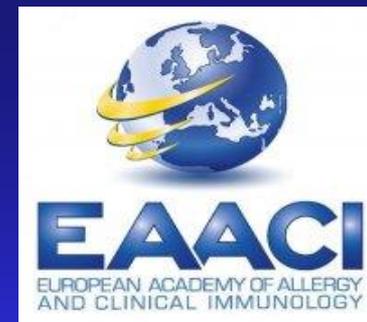
Presently available in 2 forms

Sub cutaneous immunotherapy (SCIT)

Sub lingual immunotherapy (SLIT)

(tablet or drops)

Combating allergy beyond symptoms



Allergen-specific immunotherapy

- 100 years of use
- Traditionally offered to the more severe patients as a 2nd-line treatment

Recently

- Advances in quality and formulation of extracts
- Better delivery systems
- Better understanding of the mechanisms of allergic disease

- There is a call for immunotherapy to come “centre stage”

Why use it ?

Allergies may be;

- Life threatening
- Unavoidable



Benefits of treatment

- Reduced Symptoms
- Reduced need for medications
- Improved Quality of Life



Prevalence of Allergic Rhinitis

Most common allergic disorder seen in clinical practice.

10% of UK population will suffer with AR

Problems with under diagnosis

Incidence increases with age from

< 1% during infancy

10% 6 - 7 year olds ⁽¹⁾

15% 13-14 yrs olds ⁽¹⁾

Incidence stays level in young adulthood

Gradually falls during middle age

Prevalence tripled in last decade in some countries

(1) Isaac Study Phase 3

Allergic Rhinitis

- Current management is based on allergen avoidance
± symptomatic therapy
- Many patients continue to experience symptoms despite symptomatic therapy
- Many aspects of a patient's quality of life are negatively affected by their condition
 - social life
 - school performance
 - work productivity
- Despite this, the condition is sometimes trivialised by patients and healthcare professionals

Quality of Life

- Practical issues
 - Need to rub eyes and nose, blow nose repeatedly, carry tissues and take medication
- Problems at school
 - Hearing impairment and tiredness from poor sleep impairs performance
 - Unable to partake fully in playing on grass, playing with pets, camping trips
- Emotional Disturbances
 - Can't fully integrate with peers and may feel isolated, leading to frustration, sadness and anger

Impact of AR on Adolescents

- Effect on exam performance
 - 50% increased risk of dropping a grade from mocks to formal exam



Juniper EF et al. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol.* 1994 Feb;**93**(2):413-23.

Juniper EF et al. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol.* 1998 Feb;**101**(2 Pt 1):163-70.

Simons FE Learning impairment and allergic rhinitis. *Allergy Asthma Proc.* 1996 Jul-Aug;**17**(4):185-9

Walker S et al. Hayfever has a significant detrimental impact on national exam performance in UK teenagers: case control study. Unpublished data presented at BSACI Annual meeting, 2006.

Grass: The Most Important Allergen

About 95% of allergic rhinitis sufferers in the UK are allergic to grass pollen



Adapted from Allergy: the unmet need. A blueprint for better patient care. RCP June 2003: 35.

Allergic Rhinitis and its Impact on Asthma (ARIA)



Initiative developed with WHO (1999)

Aims where to;

- update clinicians' knowledge of allergic rhinitis
- highlight the impact of allergic rhinitis on asthma
- provide an evidenced based approach to diagnosis
- provide an evidenced based approach to treatment
- provide a step wise approach to the mgt. of the disease

ARIA 2001

ARIA Classifications

Intermittent

Symptoms < 4 days a week
or Symptoms < 4 weeks

Persistent

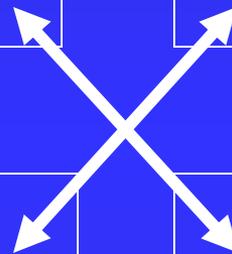
Symptoms > 4 days a week
or Symptoms > 4 weeks

Mild

Normal sleep
No impairment of normal
daily activities,
leisure, school, sport
No troublesome symptoms

Moderate

Abnormal sleep
Impairment of normal daily
Activities, i.e. leisure, sport
Abnormal school & work
Troublesome symptoms



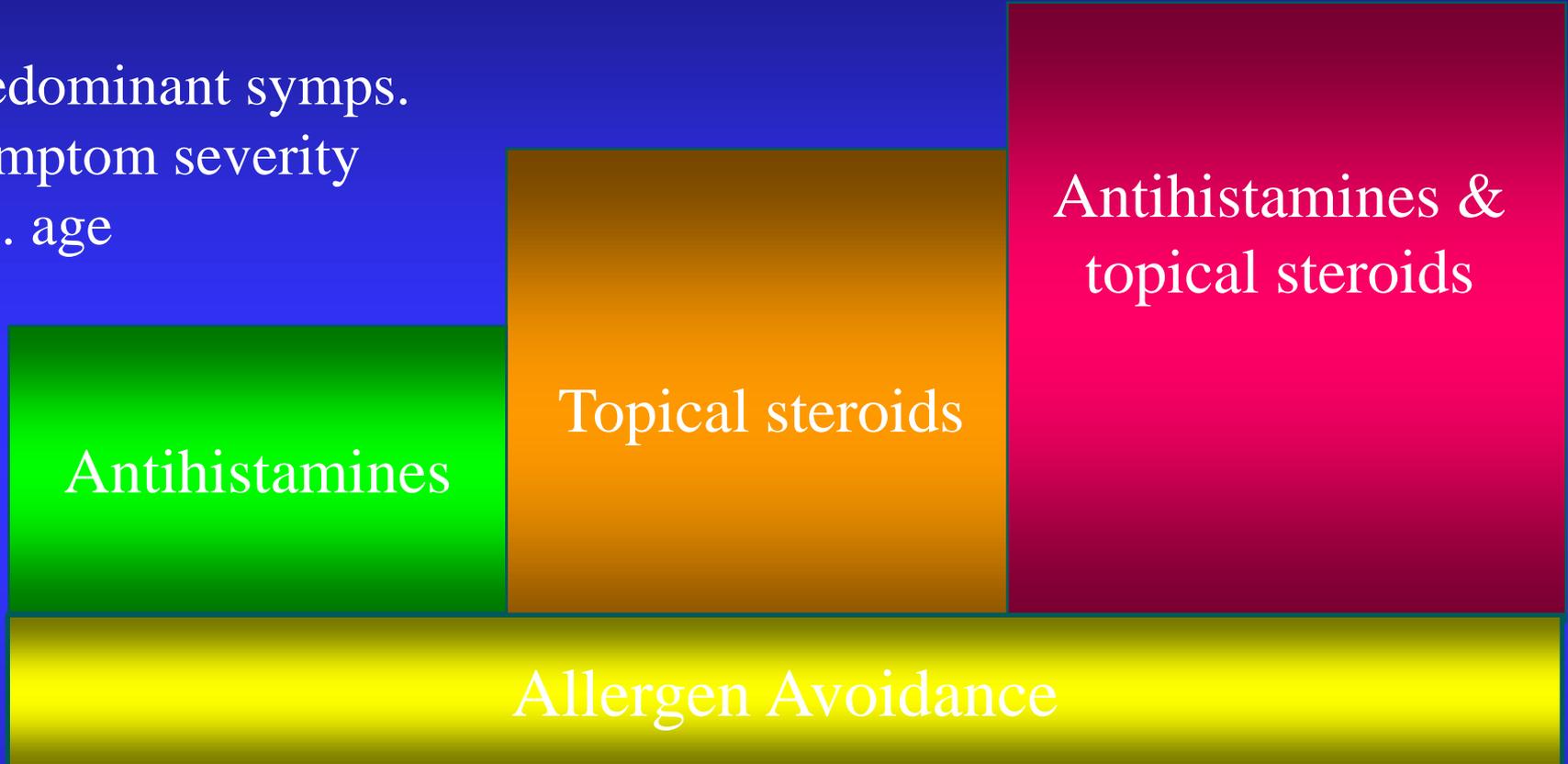
Treatment of Allergic Rhinitis

Treatment considerations

Predominant symps.

Symptom severity

Pts. age



Immunotherapy



Increasing severity

How successful is current management?

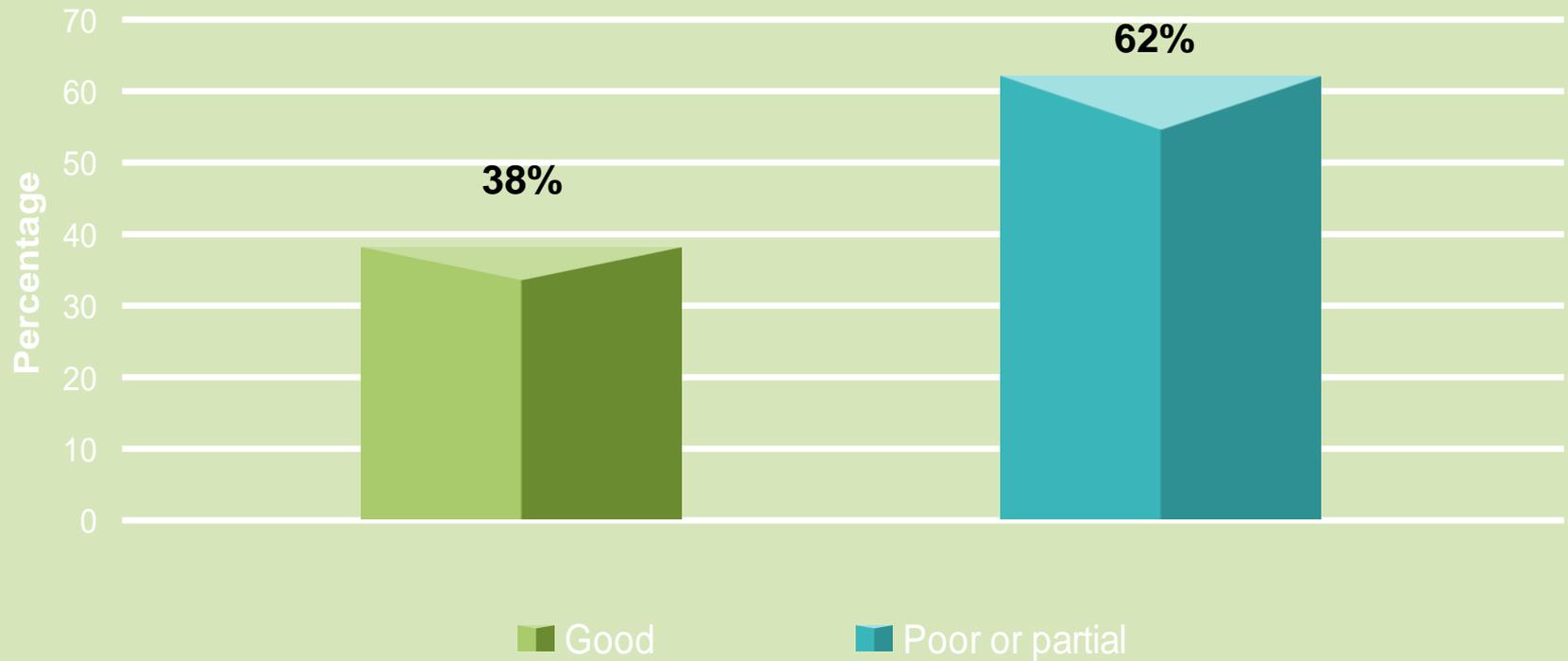
- Avoidance is not always possible or practical
- Most treatment approaches only treat the symptoms of allergic disease
 - antihistamines
 - intranasal corticosteroids
 - chromones
 - decongestants
- 62% of patients receiving optimal standard symptomatic treatment experience poor symptom control

Patient satisfaction with symptomatic therapy

- Postal survey of UK patients prescribed medication for allergic rhinitis by GP
- Results based on answers from 142 people regularly using non-sedative antihistamine + intranasal corticosteroid

Patient satisfaction with symptomatic therapy

Percentage of patients describing their symptom control as "good", "partial" or "poor"



How it is now

Currently, allergies are treated with:

- Short-term symptom relieving drugs
- Long-term anti-inflammatory drugs.

Drawbacks

- The effectiveness of meds in controlling symptoms is suboptimal.
- Symptom relapse occurs when meds are stopped.
- Long-term use of meds increases risk of adverse effects.
- Continuous dependence on drugs is unsustainable.
- Increasing costs of new medications
- Increasing numbers of patients

Role of Immunotherapy in Allergic Rhinitis

- Induces immunological tolerance
- Offers potential for:
 - sustained prevention of all allergic symptoms
 - disease modification to avoid progression
 - disease remission

Immunotherapy in the current guidelines

Immunotherapy “**interferes with the basic mechanisms of the allergy... resulting in immediate symptomatic relief and... a long-lasting and preventive effect**” – ARIA¹

“To make the patient as symptom-free as possible... immunotherapy should be initiated early in the disease process” – ARIA¹

“Trials in immunotherapy show the clinically useful outcomes of decreased symptom scores and medication requirements, as well as improved...airway hyper-responsiveness” – GINA²

1. Bousquet J et al. *J Allergy Clin Immunol* 2001; 108: S147-334
2. GINA Workshop Report (updated 2004). WHO Publications 2004

Subcutaneous Immunotherapy (*SCIT*)

The Gold Standard of Treatment for Hay Fever

Weekly injections of incremental doses of allergen extract until maintenance dose reached

1, 4 or 6 weekly maintenance injections for 2-3 yrs

Monosensitised patients do best

Grass pollen IT commenced pre-seasonally

Motivation essential

SCIT – The Procedure

Injections should always given by staff experienced in immunotherapy

Resuss equipment available

Assess pt. at each visit

- General well being – any febrile illness
- Measure Lung Function
- Antihistamine
- Any adverse reaction at last injection – if so may need to modify next dose or omit

Give injection sub cut outer, upper portion of arm

Subcutaneous Immunotherapy

Contraindications

- <5 yrs >50 yrs
- Medications that interfere with adrenaline
- Severe, uncontrolled asthma
(*mild seasonal asthmatics show particular benefit*)
- Multiple Allergies

Injections can be uncomfortable

Anaphylaxis can occur – rare

Fatalities have occurred (*CSM/BMJ 1986: 293*)

C.S.M. Reports

- In 1986 the C.S.M reported that between 1957-1986 there were 26 fatalities associated with subcutaneous immunotherapy.
- 5 within 18 months preceding the report.
- Asthma was found to be the main predisposing factor.

C.S.M Recommendations 1986

New guidelines were introduced.

- 2 hours observation.
- Full resuscitation equipment available.
- Experienced staff.

1994 BSACI report

- Exclude patients with perennial asthma
- 1 hour wait is adequate

Adverse Reactions

How to avoid.

- Careful patient selection.
- Careful monitoring.
- Staff education.
- Patient education.

Careful Patient Selection

- IgE mediated disease, with proven allergy with skin test or sIgE
- Allergic symptoms that are significant to the patient
- Attempts to avoid allergens fail or impractical
- Treatment with medicine is not fully successful or when medication is not well tolerated
- Motivation & compliance with treatment is essential

Careful Monitoring

Only administered under supervision of nursing & medical staff experienced in SCIT

Base line TPR, B/P, O₂ sats, FEV₁

Observed by experienced staff throughout

Repeat observations at 60 mins

IM adrenaline & resuscitation equipment must be available

Patient Education

Patient should be observed for one hour post injection

All forms of sport, exercise, alcohol & hot baths should be avoided for 6-8 hours post injection

Avoid close contact with allergen immediately after injection

Staff Education

Experience, Experience, Experience!
Advanced Life Support Skills

Treating Adverse Reactions.

- Adrenaline
- Antihistamines
- Bronchodilators
- Steroids
- Oxygen
- Fluids
- Resuscitation Equipment

SCIT what is the evidence?

Efficacy	Proven ⁽¹⁾
Long-term efficacy	Proven ⁽¹⁻⁴⁾
Prevention of asthma (children)	Documented ⁽⁵⁾

1. Durham SR *et al.* *N Eng J Med* 1999;341:468-75
2. Jacobsen L *et al.* *Allergy* 1997;52:914-20
3. Hedlin G *et al.* *JACI* 1995;96 (6 Pt 1):879-85
4. Mosbech H *et al.* *Allergy* 1988;43:523-9
5. Möller C *et al.* *JACI* 2002;109:251-6

Alder Hey SCIT Service

Began January 2012

Delivered on day case ward

Children > 6 yrs only

Mod – Severe AR based on ARIA guidelines

Confirmed Allergy to grass by SPT &/or IgE

Inadequate response to conventional therapy

Parental & patient understanding of potential role
of SCIT

Understanding of practicalities of treatment

Written consent/assent

Pollinex Quattro (PQ)

Grass or Tree



Grass - contains 13 common grass allergen extracts

Tree - contains 3 trees (Birch/Alder/Hazel)

Given pre-seasonally

4 injection regimen

Increasing strengths for 3 weeks 300, 800, 2000, then
final 2000 SU/0.5 ml (1- 4 weeks later).

Annually for 3 years

£650 year

Sublingual Immunotherapy (*SLIT*)

Tablets or drops of allergen under tongue
(dose of allergen is greater than SCIT- about 3-300 times higher)

Tablets

- Grazax

Drops

- Staloral or Oralvac
 - HDM
 - Grass
 - Tree
 - Weed

SLIT Drops

Available for

- Mites
- Grass pollens
- Tree pollens
- Weed pollens



Considered in children

- > 2 yrs
- Suffer with Mod to Severe AR (based on ARIA classification)
- Inadequate response to optimal pharmacological therapies
- Parental understanding of potential role of SLIT and the practicalities of treatment

SLIT Drops

Treatment with SLIT involves 2 phases

1) Initiation

Progressive daily increase of doses until maximal tolerated dose is reached

2) Maintenance

Once initiation is completed dose remains unchanged until 3 yr. treatment is complete

Method of Administration

Visit 1 (Day Case Ward)

- Consent
 - Demonstration of how to use
 - No pre-dose antihistamine in order to observe for any s/e
 - Base line observations & QoL scores
 - Keep product under tongue for 2 minutes then swallow
 - Observe 30 minutes
 - Home with initiation & maintenance packs
 - Take treatment once daily every morning for 3 yrs.
- 3 monthly OPD review in Nurse Led Clinic
- Repeat QoL & symptom scores
 - Dispense next 3 months treatment

SLIT Drops

If dose omitted

Less than one day – just take following day

Less than one week – resume usual treatment

More than one week – contact allergy clinic for advice

Treatment may be temporarily interrupted;

During vaccinations/boosters

Infection causing fever $>38^{\circ}\text{C}$

Mouth wounds, extractions

Asthma Exacerbation

SLIT Drops

Storage

Vial in use may be kept at room temperature (bedside cabinet)

Keep remaining vials in pack in fridge and store vertically

If traveling by air, keep vials in cabin, not in the cargo hold

Is SLIT safe?

- The most common adverse events (AE's) are throat irritation and oral pruritis
- All AE's were mild or moderate in severity
 - there were no serious events
- No systemic AEs were reported
- No patient required adrenaline

Is SLIT effective in children ?

Meta-analysis of SLIT vs. placebo for AR in patients
3-18 years of age

10 RCT studies included 484 children
(*245 SLIT and 239 placebo*)

Allergens used

Mites	n=4
Grasses mix	n=3
Parietaria	n=1
Olive	n=1
Pollen mix	n=1

9 studies used drops

1 study used tablets

Mean duration of study was 21 months

Is SLIT effective in children ?

SLIT induced a significant reduction in nasal symptoms

SLIT group had a significant reduction in medication

SLIT course less than 18 months less effective

More effective in Monosensitised patients

SLIT effective with pollens not so with mites

Immunotherapy's: how they compare in practice

	<u>Subcutaneous</u>
Induction phase	1- 4 Weeks
Route	Injection
Post-dose observation	60 minutes
Close clinical monitoring	Mandatory
Compliance	Controlled by the physician/patient

Immunotherapy's: how they compare in practice

	<u>Subcutaneous</u>	<u>Sublingual</u>
Induction phase	1-4 weeks	1-12 days
Route	Injection	Sublingual
Post-dose observation	60 minutes	Not needed*
Close clinical monitoring	Mandatory	Standard – new drug
Compliance	Controlled by the physician/patient	Home administration

* Observation required for 20 mins following first dose only

Immunotherapy's: how they compare on evidence

	<u>Subcutaneous</u>
Efficacy	Proven ¹⁻⁵
Long-term efficacy	Proven ¹⁻⁴
Prevention of asthma (children)	Documented ⁶

1. Durham SR *et al. N Engl J Med* 1999; 341: 468-75

2. Jacobsen L *et al. Allergy* 1997; 52: 914-20

3. Hedlin G *et al. J Allergy Clin Immunol* 1995; 96(6 Pt 1): 879-85

4. Mosbech H *et al. Allergy* 1988; 43: 523-9

5. Frew AJ *et al. J Allergy Clin Immunol* 2006; 117: 319-25

6. Möller C *et al. Allergy Clin Immunol* 2002; 109: 251-6

Immunotherapy's: how they compare on evidence

	<u>Subcutaneous</u>	<u>Sublingual</u>
Efficacy	Proven ¹⁻⁵	Proven ⁷⁻⁹
Long-term efficacy	Proven ¹⁻⁴	Proven ^{7, 10}
Prevention of asthma (children)	Documented ⁶	Documented ⁸

1. Durham SR *et al. N Engl J Med* 1999; 341: 468-75

2. Jacobsen L *et al. Allergy* 1997; 52: 914-20

3. Hedlin G *et al. J Allergy Clin Immunol* 1995; 96(6 Pt 1): 879-85

4. Mosbech H *et al. Allergy* 1988; 43: 523-9

5. Frew AJ *et al. J Allergy Clin Immunol* 2006; 117: 319-25

6. Möller C *et al. Allergy Clin Immunol* 2002; 109: 251-6

7. Di Rienzo V *et al. Clin Exp Allergy* 2003; 33: 206-10

8. Novembre E *et al. J Allergy Clin Immunol* 2004; 114: 851-7

9. Dahl *et al. Allergy* 2006; 61: 185-90

10. S Radulovic *et al. Allergy* 2011;66:740-752

Immunotherapy Checklist

- Is the patient sensitised?
- Is the allergen clinically relevant?
- Are avoidance measures practical?
- Are high-quality, standardised treatment products available?
- Can the patient be treated safely?
- Will the patient be compliant and motivated?

“OK, where’s that nurse that works in the allergy clinic”?



Any Questions?