Sublingual Immunotherapy (SLIT) in Primary Care - The potential.

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What is allergen immunotherapy?

Administration of an allergen in order to achieve immunologic tolerance

Current use for: Allergic rhinitis
Asthma
Venom anaphylaxis
"About the beginning or middle of June in every year .... A sensation of heat and fullness is experienced in the eyes .... To this succeeds irritation of the nose producing sneezing ... To the sneezeings are added a further sensation of tightness of the chest, and a difficulty of breathing"
EXPERIMENTAL RESEARCHES
ON THE
CAUSES AND NATURE
OF
CATAARRHUS AESTIVUS
(HAY-FEVER OR HAY-ASTHMA)
BY
CHARLES H. BLACKLEY, M.R.C.S. ENG.

‘When a small portion of pollen, just enough to tinge the tip of the finger yellow, was applied to the mucous membrane of the nares, some of the symptoms of hay fever were invariably developed, the severity and continuance of which were dependent on the quality and on the number of times it was used.’

LONDON:
BAILLIÈRE, TINDALL & COX,
KING WILLIAM STREET, STRAND.
PARIS: BAILLIÈRE | MADRID: BAILLIÈRE.
1873.
History of immunotherapy

FURTHER OBSERVATIONS ON THE TREATMENT OF HAY FEVER BY HYPODERMIC INOCULATIONS OF POLLEN VACCINE.
J. Freeman

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PROPHYLACTIC INOCULATION AGAINST HAY FEVER
L. Noon B.C. CANTAB., F.R.C.S. ENG., (From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)
Volume 177, Issue 4580, 10 June 1911, Pages 1572-1573

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......described conjunctival provocation of patients with allergic rhino- conjunctivitis and successful treatment using subcutaneous inoculation of extract
Allergens

The most frequent allergens reported were pollen, house dust mite, moulds, dog, cat and other animals (Fig. 2).
Allergens of Proven Efficacy in Double Blind Placebo Controlled Studies

Pollens
Cat
House dust mite
Hymenoptera
WHO position paper: allergen immunotherapy

- High dose, standardised vaccines (5-20mcg major allergen per monthly maintenance injection)
- Mixtures of allergens in polysensitised patients are of no proven value
- Administer in specialist clinics by trained persons with immediate access to adrenaline etc
- Observation period after injections 30min
- Risks of immunotherapy are increased in asthma
- Optimum duration of immunotherapy: 3-5 years

Bousquet J, Lockey RF, Malling HJ et al. Allergy 1998;53:suppl 44:1-42
CSM UPDATE: Desensitising vaccines

BMJ 1986;293:948

- 26 fatalities 1957-1986
- 16/17 in patients with asthma

- Immunotherapy only to be carried out in clinics offering full range of life support.
Birch pollen immunotherapy for hayfever
(2 years, n=46) year 2, 1998

Symptoms

Medication

Grass pollen immunotherapy for seasonal rhinitis/asthma

Walker SM et al., J Allergy Clin immunol 2001;107:87-93
Immunotherapy for rhinitis (43 studies)

Malling HJ. Allergy 1998;53:461-472

- No efficacy (0-29% improvement) - 10 studies
- Low efficacy (30-44% improvement) - 13 studies
- Moderate (45-59% improvement) - 14 studies
- High efficacy (>60% improvement) - 6 studies
Preventative allergy treatment study

Development of asthma at 5 years

N = 142 patients without asthma in season one

Odds-ratio = 2.68 (1.3 – 5.7)

Moller C et al, J Allergy Clin Immunol 2002;109:251-6 (follow up results)
IT: Prevention of New Sensitizations

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*
Immunotherapy in asthma: systematic review (88 randomised controlled trials 1954-2005)

Odds ratios (<1 favours immunotherapy)

Significant improvement in asthma scores  -0.59

NNT to prevent exacerbation  3

NNT to avoid increased medication  4

Significantly reduce specific bronchial hypereactivity

Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2010, Issue 8
Finnish Allergy Programme 2008–2018 – time to act and change the course
Efficacy 1st treatment season: adults
Comparable to sub-cutaneous immunotherapy

Grazax 75,000 SQ-T (median values)
- Symptom score: 34%
- Medication score: 53%

Oralair 300-IR (median values)
- Symptom score: 37%
- Medication use: 46%

Alutard 100,000 SQ-U (median values)
- Symptom score: 34%
- Medication score: 54%

Dahl et al. JACI 2006;118:434-40; Didier et al. JACI 2007;120:1338-45; Frew et al. JACI 2006117:319-25
SCIT preventive effect
Reduced risk of developing asthma

Subject developing asthma at 3, 5, and 10 years
(percent of subjects; n=151)

- Control
- Alutard SQ

* p<0.05

1. Möller et al. JACI 2002;109:251-6
ALK house dust mite AIT
Clinical proof of concept in asthma: MT-02 trial

Randomisation

6 DU* (n=156)
3 DU (n=159)
1 DU (n=146)
Placebo (n=143)

End of trial

3-8 wks 4 wks 40 wks 8 wks 4 wks

Primary efficacy analysis
Comparison of each dose group vs placebo for the reduction in inhaled corticosteroid dose from baseline to end-of-treatment

Baseline Assessment

Efficacy Assessment

*DU = Development Unit (allergen content not disclosed, contains Der p and Der f major allergen)
ALK house dust mite AIT
Median ICS dose reduced by 50% in 6 DU group

Change from baseline of daily ICS dose adjusted for placebo
(µg; mean ±95% CI)

Change from baseline

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median</th>
<th>%</th>
<th>Diff vs placebo</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>143</td>
<td>-100 µg</td>
<td>-25%</td>
<td>-</td>
</tr>
<tr>
<td>6 DU</td>
<td>156</td>
<td>-200 µg</td>
<td>-50%</td>
<td>-100 µg</td>
</tr>
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Confirmatory phase III trial programme being planned

Mosbech et al. Allergy 2009;64 (Suppl. 90):184; Data on file, ALK-Abello
Sub group: ACQ 1-1.5, Max dose bud 800 mcg

Post Hoc analysis: presented EACCI 2011: de Blay, Riis, Canonica

Figure 1: Difference to placebo in reduction of ICS (µg) with 95% confidence intervals; FAS: full analysis set (N=604); Subgroup: daily ICS use of 400-800 µg and ACQ score of 1-1.5 (N=108)
Post Hoc analysis: presented EACCI: de Blay, Riis, Canonica

Subgroup: ACG 1-1.5, dose bud 400-800 mcg
Post Hoc analysis: presented EACCI: de Blay, Riis, Canonica

**Figure 2**: Difference to placebo in overall AQLQ with 95% confidence intervals; FAS: full analysis set (N=604); Subgroup: daily ICS use of 400-800 µg and ACQ score of 1-1.5 (N=108)

P<0.010 v placebo
Long term evidence for sublingual immunotherapy
Immunotherapy:
how do subcutaneous and sublingual compare on evidence

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<thead>
<tr>
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<th>Subcutaneous</th>
<th>Sublingual</th>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Proven&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Proven&lt;sup&gt;7-9&lt;/sup&gt;</td>
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<tr>
<td><strong>Long-term efficacy</strong></td>
<td>Proven&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>Anticipated&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

5. Frew AJ et al. *JACI* 2006
Long term efficacy of immunotherapy

3 years treatment with subcutaneous immunotherapy has been shown to be effective to give at least 6 years benefit after treatment\(^1\)

3 years continuous treatment with Grazax is under evaluation (clinical study GT-08)
Study is in its 3rd year

The World Health Organisation position paper states that many clinicians advise 3-5 years of therapy for patients who have had a good therapeutic response\(^2\)

Could Primary care assist in delivering tolerance induction to allergens?

Se puede atención primaria ayudar a entregar la inducción de tolerancia a los alergenos?

Hypoallergenic foods
Alimentos hipoalergénicos

Aggressive cleaning
Limpieza agresiva

Pet removal
eliminación de animales domésticos
Could Primary care assist in delivering tolerance induction to allergens?

Avoidance is of little benefit

Hypoallergenic foods
Alimentos hipoalergénicos

Pet removal
eliminación de animales domésticos

Aggressive cleaning
Limpieza agresiva

Evitación se demuestra un beneficio limitado
Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

Z. Calamita, H. Saconato, A. B. Pelá, Á. N. Atallah

25 Studies

- NNT to prevent worsening: 3.7
- Standardised mean difference: -0.38
- Allergy Symptoms: SMD -1.18
- Resp function: SMD 1.48
Rhinitis and onset of asthma: a longitudinal population-based study. 2008 Lancet 372:1049-57
Window of Opportunity?
Summary

- Allergic disease is on the increase
- Early multiple sensitisation is a factor in the genesis of asthma
- HDM is an important component of this

Hypothesis:
Identifying those with multiple sensitisations
Administering SLIT for HDM/Grass/Pollen could reduce further Allergic sensitisation and reduce the development of asthma

Unknowns:
Whom?
How Long?
What dose?