Novel strategies and future directions in Immunotherapy

Glenis Scadding
RNTNE Hospital, London
Disclosures

• Research funds:
  ALK-Abello, GSK,

• Advisory Boards:
  ALK-Abello, Allergen Therapeutics, GSK, Merck, Uriach, USB

• Speaker/Chair:
  ALK-Abello, GSK, Merck, Uriach
Learning Objectives

• To address how to improve the efficacy and safety of immunotherapy

• To review new therapeutic entities in trial

• To consider the implications of immunotherapy for the allergic march
### Immunotherapy for Allergic Rhinitis

**Subcutaneous Immunotherapy (SCIT)**

Calderon M, 2007

<table>
<thead>
<tr>
<th></th>
<th>SCIT 51*, n = 2,871</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMD (95%CI)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>-0.73 (-0.97, -0.50)</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>-0.57 (-0.82, -0.33)</td>
</tr>
</tbody>
</table>

SMD = Standardised Mean Difference

*Total numbers of studies analyzed

Long-term efficacy of allergen immunotherapy


Problems with SCIT

- Injections
- Time-consuming
- Long term
- Expensive
- Severe adverse events
- Few allergy patients can be treated <5%
Immunotherapy (high dose Ag)

Natural exposure (low dose Ag) + IgE

Th1
IFN-γ
IgG

APC

Th2
IL-4
B cell
IgE

IL-10
TGF-β
IgG4
IgA

Allergy

IL-5
Eosinophil

Novel approaches to immunotherapy

- Adjuvants
- Alternative routes
- Peptides
- Fusion proteins
- Recombinant allergens
Novel approaches to immunotherapy

• Adjuvants
• Alternative routes
• Peptides
• Fusion proteins
• Recombinant allergens
Adjuvants

- Alum
- Lipopolysaccharide (MPL)
- Immunostimulatory sequences (ISS,CpG)
- Anti-IgE
Influence of Aluminium Hydroxide (Alum) on allergen-stimulated cytokine production

IL-5    IL-10    IFNγ
(x10)

Antigen    +       +       +       +       +       +
Alum         -       +        -       +        -       +

Randomised controlled trial with alum-adsorbed grass pollen extract for seasonal allergic rhinoconjunctivitis

UK Immunotherapy Study Group
26 centres, n=410
100,000 SQ, 10,000 SQ and placebo

Reduction in symptom and medication score over placebo – whole season

Rhinoconjunctivitis QoL score

Monophosphoryl Lipid A
Influence of Monophosphoryl lipid A (MPL) on allergen-stimulated cytokine production

Puggioni F, Durham SR, Francis JN Allergy 2005; 60:678-84
Results

- Symptom score eye, lung and nose: reduced in active group p=0.003
- Combined Symptom/Rx score: reduced in active group p=0.013
- Skin test results in active group; reduction in wheal size p=0.04, reduction in sensitivity threshold p=0.03

Drachenberg KJ et al., Allergy 2001; 56: 498-505
ImmunoStimulatory DNA Sequences (ISS)

ISS are oligonucleotides containing unmethylated CG sequences

ISS mimic the innate immune response to microbial DNA

ISS act primarily on antigen-presenting cells to:
  – Enhance antigen uptake and presentation
  – Induce proinflammatory cytokine production
  – Stimulate Th1 and inhibit Th2 T cell development

ISS are recognized by Toll-like receptor 9

ISS 1018

5’-TGACTGTGAACGTTCGAGATGA-3’
AIC - 1018 ISS Linked to Amb a 1

Vaccine: Amb a 1 linked to a mean of 4 molecules of 1018 ISS

Goal: To reduce Th1 and enhance Th2 responses to Amb a 1, the dominant allergen in hayfever due to ragweed

If successful, AIC therapy would replace current 30-60 injection desensitization with a course of 6-7 weekly injections

Kind permission Dr R Coffman
Immunotherapy with a Ragweed–Toll-Like Receptor 9 Agonist Vaccine for Allergic Rhinitis.


- 2001-55% decrease in peak Nasal Symptom Complex Score (NSCS) (p=0.03)
- 2002 ragweed season 53% reduction in NSCS, p=0.02 with no additional therapy.
- Clinically significant quality of life improvements.
Influence of Immunostimulatory sequences (ISS) on allergen-stimulated cytokine production

Francis JN et al 2006
Influence of adjuvants on allergen-stimulated cytokine production: Summary

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>IL-5</th>
<th>IL-10</th>
<th>IFNγ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alum</td>
<td>↓</td>
<td>⇔</td>
<td>⇔</td>
</tr>
<tr>
<td>MPL</td>
<td>↓</td>
<td>⇔</td>
<td>↑</td>
</tr>
<tr>
<td>ISS</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Anti-IgE and rush Ragweed immunotherapy

Screening

- anti-IgE
- Placebo

1-day RIT

1-day

IT + anti-IgE

Placebo IT + anti-IgE

IT + placebo anti-IgE

Placebo IT + placebo anti-IgE

Specimen Collection

n=39

n=40

n=40

n=40

Week -12

Week 0

Week 12

Week -9

Week -9

Pretreatment

RIT

Maintenance IT + study drug

Follow-up

Pre-anti-IgE, Pre-IT

> 2 weeks anti-IgE

Post-rush, Pre-season

Mid-season

End of study

Follow-up, Pre-season

Ragweed season

Pre-anti-IgE, Pre-IT

> 2 weeks anti-IgE

Post-rush, Pre-season

Mid-season

End of study

Follow-up, Pre-season
Average daily allergy severity scores over the primary ragweed season

Anti-IgE:
- Reduced anaphylaxis x5, p=.026
- Reduced symptoms, P=.044
Adjuvants

- Alum
- Lipopolysaccharide (MPL)
- Immunostimulatory sequences (ISS, CpG)
- Anti-IgE
Novel approaches to immunotherapy

• Adjuvants
• **Alternative routes**
• Peptides
• Fusion proteins
• Recombinant allergens
Meta-Analysis (2007)

Better

-1

-0.73

-0.97

-0.50

SCIT
Calderon 2007

No difference between placebo and treatment

0

-0.0482

-0.69

-0.57

-0.28

-0.15

SLIT
Radulovic 2007

Worse

+1

0.57

0.28

0.15

SLIT
Wilson 2003
Rhinitis, sinusitis, and ocular diseases

Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis

Alain Didier, MD, a Hans-Jörgen Malling, MD, a Margitta Worm, MD, a Friederich Horak, MD, a Siegfried Jäger, PhD, a Armelle Montagut, PhD, a Claude André, MD, a Olivier de Beaumont, MD, a and Michel Malac, MD a Toulouse, Meylan, and Antony, France; Copenhagen, Denmark; Berlin, Germany; and Vienna, Austria.
Sublingual Grass Tablet Immunotherapy

Daily mean symptom scores are plotted as one curve by treatment group with the corresponding scale on the left vertical axis. Daily mean grass pollen counts are plotted as vertical lines and the corresponding scale is on the right vertical axis.

J Allergy Clin Immunol 2007; 120: 1338-45
Original article

Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years

Ronald Dahl, MD, a Alexander Kapp, MD, b Giselda Colombo, MD, c Jan G. R. de Monchy, MD, d Sabina Rak, MD, e Waltraud Emminger, MD, f Bente Riis, PhD, g Pernille M. Grønager, MSc, g and Stephen R. Durham, MD h


GT-08 study design

Grass AIT (Grazax®) Treatment
Placebo Treatment

Follow Up
Follow Up

End of treatment

improvement
One year after grass AIT treatment

Total rhinoconjunctivitis symptom score
(median values)

NB. Both treatment groups had free access to symptomatic medications

medication use
One year after grass AIT treatment

Total rhinoconjunctivitis medication score
(median values)

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Grass AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>Year 2</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>Year 3</td>
<td>60%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Sublingual immunotherapy: the ‘big trials’ in adults

Symptom scores

Medication scores

Median % decrease

Subcutaneous

Sublingual

Sublingual immunotherapy

• SLIT is *effective* compared to placebo

• SLIT is *safe* with only minor local side effects

• Comparative studies, longterm studies and more paediatric studies are needed.
Specific Allergen Immunotherapy
Risk and Benefit

Efficacy ++
Safety +
SCIT

Efficacy +
Safety ++
SLIT
Specific Allergen Immunotherapy
Risk and Benefit

Efficacy ++
Safety +

SCIT

Efficacy ++/-
Safety ++

SLIT

Ask the patient!
Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial.


- Open-label trial
- 165 patients with GP rhinoconjunctivitis
- randomized to 54 s.c. injections with pollen extract over 3 years [cumulative allergen dose 4,031,540 (SQ-U)]
- or 3 intralymphatic injections over 2 months (cumulative allergen dose 3,000 SQ-U).
Results

• ILIT 3 doses increased tolerance to GP nasal provocation within 4 months (P < 0.001).
• equivalent to 3 years SCIT (P = 0.291)
• ILIT decr. hay fever symptoms (P < .001) reduced skin prick test reactivity (P < .001),
• decreased specific serum IgE (P < .001),
• fewer AE than SCIT (P = .001),
• enhanced compliance (P < .001),
• less painful than venepuncture (P = .018)
COMPARISON

**SCIT**
- 3 YEARS
- Special centre
- AE common, can be severe
- Effective

**ILIT**
- 8 WEEKS
- Special centre
- AE less common, none severe
- More quickly effective
Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy.


- RDBPCT 37 patients GP +ve
- Patches- allergen (21) or placebo (16) before & in GP season
- Primary outcome= nasal provocation-improved in both groups yr 1(p<.001;<.03) allergen only yr 2( p<.003)
- Eczema at site in active group
Novel approaches to immunotherapy

- Adjuvants
- Alternative routes
- Peptides
- Fusion proteins
- Recombinant allergens
Fel d 1: multiple peptides “prototype vaccine”

Fel d 1 Chain 1
EICPAVKRDVLFLTGTPDEYEQVAQYKALPVVLENARILKNCVDAKMTEDKENALSSLDDKITYSPLC
EICPAVKRDVLFLTGLTLGTPDEYEQVAQY
EQVAQYKALPVVLENA
KALPVVLENARILKNCV
RILKNCVDAKMTEDKE
KMTEEDKENALSSLDDK
KENALSSLDDKITYSPL

Fel d 1 Chain 2
VKMAETCPFYDYFVFAVANGNELLKSLTKVNATEPERTAMKKIQDCYVENGLISRVLDGLVMTTISSSKDCMGAEAVQNTVEDLKLNLTLGR
VKMAETFYDFVFFA
CPFYDYFVFAVANGNEL
GNELLKLSTLTKVNAT
LTKVNATEPERTAMKK
TAMKKIQDCYVENGLISRVLDGLVMTTISSSKDCMGAEAVQNTVEDLKLNLTLGR

Poorly soluble

Kaiser et al., J. Biol. Chem 2003
PIT reduces the cutaneous late phase reaction to Fel d1

Oldfield WLG, Larché M, Kay AB. Lancet 2002
Improved ability to tolerate exposure to cats following peptide immunotherapy

Oldfield WLG, Larché M, Kay AB. Lancet 2002
Novel approaches to immunotherapy

• Adjuvants
• Alternative routes
• Peptides
• Fusion proteins
• Recombinant allergens
A novel human immunoglobulin Fcγ–Fcε bifunctional fusion protein inhibits FcεRI-mediated degranulation
Daocheng Zhu, Christopher L. Kepley, Min Zhang, Ke Zhang and Andrew Saxon

Inhibition of basophil histamine release

Fcγ-RRIIb

FcεRI

Fcγ-Fcε construct (GE2)
Novel approaches to immunotherapy

- Adjuvants
- Alternative routes
- Peptides
- Fusion proteins
- Recombinant allergens
Rhinitis, sinusitis, and ocular diseases

Allergen-specific immunotherapy with recombinant grass pollen allergens

Marek Jutel, MD,a Lothar Jaeger, MD,b Roland Suck, PhD,c Hanns Meyer, Dipl Math,c Helmut Fiebig, PhD,c and Oliver Cromwell, PhD e Wroclaw, Poland, and Jena and Reinbek, Germany

Vaccine

• Alum-adsorbed recombinant allergen mixture (endotoxin free)
  – Phl p2 5 mcg
  – Phl p5a 10 mcg
  – Phl p5b 10 mcg
  – Phl p6 5 mcg
  – Phl p1 10 mcg

• Alum-adsorbed histamine (0.125 mg/ml)
Combined symptom/medication scores
Results (mean data, per protocol set) n=57

- Symptoms
  - 36.5% reduction, p=0.015

- Rescue medication
  - 36.5% reduction, p=0.66

Combined Sx/Rx score

- 38.9% reduction, p=0.44
- 38.5% for ITT population, (p=0.051)
Allergen-specific antibodies

- IgE
- IgG1
- IgG4
A recombinant grass allergen mixture can be an effective and safe treatment to ameliorate symptoms of allergic rhinitis.

Associated increases in Allergen specific IgG antibodies with a reduction in IgE antibodies.
Summary

Allergen immunotherapy
• reduces symptoms and Rx needs
• has long-lasting benefits
• with potential to modify the natural history of allergic disease.

Novel approaches with documented clinical benefit include:
• sublingual, lymph node and epicutaneous routes
• the use of adjuvants
• use of recombinant allergens
• and of anti-IgE.