Insights into the mechanisms of Immunotherapy

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A Brief History of Allergy & Immunotherapy

- Afflicted Hippias the Athenian, was recognised by Rhazes the Persian, described by John Bostock, the Britain

- The history of allergic rhinitis
  - Aetiology unknown, possibly a disease of social class (19th century)
  - Charles Blackley: pollen caused hay fever (1873)
  - Ingenious research linking pollen load to symptom severity

- Changing prevalence of respiratory allergies:
  - From a rare disease in 1900 to a public health issue today: Prevalence of AR in England and US at the beginning of the 20th century: almost 20 %
  - Today, 1 in 4 people suffer from respiratory allergies
  - 500 million people suffer from AR worldwide
  - Clemens Von Pirquet coined the term ‘allergy’
During last 100 years: Emergence of an effective solution – allergen immunotherapy

The history of allergen immunotherapy

Development in several contrasting periods:
- Promising beginnings
- A fall from grace (1950s-1980s)
- The renewal of AIT with SLIT (1980s)
- Acceleration and recognition in the last 20 years
- A new therapeutic class for severe allergic rhinitis patients
Developments between 1911 and 1950

- The concept of ‘blocking antibodies’
- Robert Cooke – linked allergic rhinitis and asthma (1918)
- Emergence of ‘desensitization’ (1920s)
- Prausnitz and Kustner – Serum transfers transferred sensitivity
- Greater understanding of mechanisms involved
- Clinical testing of subcutaneous formulations
- Vander Veer, Cooke, Black – expanding patient populations in both studies and in general practice, but emergence of anaphylaxis (1930s)
- First controlled study of immunotherapy in allergic rhinitis
- Efficacy testing under controlled conditions – but with substandard preparations (1949)
- Exploration of allergen eradication
- Il-fated initiative to rid New York of ragweed (1946) – focused research towards treatment
Developments between 1930s and 1950s

• Discovery of H1-antihistamine and the development of antihistamines
• H1-antihistamine in 1937 lead to development of first generation of anti-histamines in 1940s – effective but with sedative side effects –
• Development of symptomatic treatments
• research focused towards improving symptomatic treatment
• Development of inhaled steroids
• Cortisol found to be beneficial in asthma – ignites enormous interest in inhaled steroids
Allergen immunotherapy is based on the work of visionaries –
Allergists will recognise elements in Noon’s research that are still present today
• The use of allergen immunotherapy preceded the understanding of the mechanisms – but still widely used in clinical practice and research
• Development of symptomatic treatments between the wars put AIT on the back foot
• Allergen immunotherapy needed to improve in efficacy and safety
The dark ages: 1950s – 1980s

- Subcutaneous immunotherapy haunted by anaphylaxis
- Reports of fatalities discouraged use of AIT – efficacy needs to be balanced against risk
- Researchers looked for safer administration routes and improved
- Allergen immunotherapy is side-lined

- Exploration of extract quality as cause of side effects

- Early placebo controlled study, Frankland and Augustin (1954)
- Efficacy surprisingly high, but negative perception of AIT because greater purification did not resolve side effects

- Golden age for symptomatic, anti-inflammatory drugs
During the 1950s and 1960s

- Targeted immunotherapy to inhaled allergens shown to improve asthma symptoms
  - Johnstone and Crump (1961)
- The research on AIT continued... but on the sidelines
- Efficacy demonstrated in ragweed immunotherapy
  - Lowell and Franklin (1965)
- Efforts to bring a more robust approach to clinical trials in AIT
- *Dermatophagoides pteronyssinus* responsible for house dust mite allergy
  - Voorhorst (1964)

- Advances in the development of *Hymenoptera* venom immunotherapy
  - Loveless (1956)
1980 – 2000: The renewal of AIT

- **Increasing prevalence of allergic rhinitis**
  By 2000 allergy prevalence had risen to 25-30%8

The reasons for the resurgence in interest:
- **Greater recognition of the disease burden**
- Allergic rhinitis no longer regarded as a trivial disease9
- Recognition of consequences on sleep, quality of life, performance
- RQLQ questionnaire (1991)

Greater patient expectations
- Effective symptomatic treatment had changed patient expectations
- Patients expected effective relief, even a cure

Emergence of sublingual immunotherapy
- Safer and easier administration
1980 – 2000: The renewal of AIT
Emergence of innovative research tools
such as the allergen challenge chamber
Developed by Friedrich Horak in 1985, enabling highly controlled exposures to a defined concentration of air-borne allergen

A favourable environment for AIT
Move towards to recognition
Emergence of guidelines – efficacy of subcutaneous allergen immunotherapy demonstrated in well-designed clinical trials


As knowledge of immune system has grown, so has acceptance of allergen immunotherapy
Scientists began to characterize the cellular aspects of immune tolerance and T lymphocytes in particular
1980 – 2000: Development of SLIT

- Demonstration in a RCT that sublingual formulation is safe and effective
- Patients on SLIT significantly fewer symptoms of rhinitis or conjunctivitis during the pollen season and significant reduction in nasal steroids
- SLIT inexpensive and easy to perform
- Emergence of sublingual immunotherapy
- 58 patients with seasonal pollen rhinitis randomized to placebo or five-grass allergen preparation sublingually for 17 weeks.

- Confirmation of dose response and reduction in medication use with comparable side effects to placebo
- SLIT also lowered incidence of asthma attack
- Leukotriene receptor antagonists introduced
- A new generation of symptomatic treatments arrives
1980 – 2000: SLIT included in guidelines

- EAACI guidelines (1997)
  The use of sublingual immunotherapy justified in clinical practice on the basis of proven efficacy

- Sublingual immunotherapy incorporated in major international treatment guidelines
- WHO guidelines (1998)
  Reviewed the then 8 RCTs of SLIT, concluded “SLIT may be considered as a viable alternative to the injection route in adults”
  On the basis of randomized controlled studies versus placebo sublingual immunotherapy included in allergic rhinitis treatment recommendations
2000 onwards: The recognition of SLIT

ARIA 2001 – major evolution in guidelines
International consensus recommendations:
o Strong place-in-therapy recommendations for subcutaneous and sublingual allergen immunotherapy:
Recognition of SLIT in guidelines, systematic reviews and meta-analyses
– initiating AIT early in the course of allergic rhinitis
– recognizing efficacy
o Insufficient evidence at the time make a distinction between SCIT and SLIT
o Shift towards systemic treatment rather than target organ treatment

As the data accumulates – publication of meta-analyses and systematic reviews
Wilson 2005 meta-analysis (22 RCTs)17 and Cochrane review, updated in 2010 (49 RCTs)18: found that SLIT resulted in significant reductions in symptoms with no reported anaphylaxis
2000 onwards: Regulatory harmonization

Problems with lack of pan-Europe regulation:

Wide variety of unlicensed products
Non-standardized formulations – Lack of credibility
Harmonization of clinical evaluation processes across Europe

German authorities introduced new framework for the production of named patient products (NPPs) followed by other countries like France – and this is when we could start using Immunotherapy in Malaysia, after lengthily discussions with the Ministry of Health etc.

Defined standards of manufacturing practice
Listed allergens – A step towards formulation regulation
2000 onwards: SLIT efficacy confirmed

- Durham study20 (2006)
  - DBPC trial pooling 855 allergic rhinitis patients at various doses with 8 weeks of pre-seasonal and co-seasonal treatment – showed significant improvements in efficacy scores during peak pollen season
  - Efficacy of SLIT tablets proven in well-designed, multinational clinical studies

- Didier study21 (2007)
  - 628 participants randomized to three doses of grass pollen tablet or placebo starting four months before the pollen season – significantly better efficacy scores: Rhinoconjunctivitis Total Symptom Score, medication scores, number of medication-free days

- Efficacy and safety confirmed in children22,23 (2009)
  - Shown in 278 and 253 children and adolescents with pre- and co-seasonal administration – highly significantly different from placebo in symptom protection, no serious side effects
  - Efficacy confirmed in an allergen challenge chamber from first month of treatment24 (2009)
  - Randomized placebo-controlled study with 89 allergic rhinitis patients taking 300 IR, performed in an allergen challenge chamber – clinically relevant treatment effect from one month and persisted throughout the study
2000 onwards: Greater recognition of SLIT

- ARIA guidelines 2008 update: new recommendations for allergen immunotherapy and SLIT:
  - Allergen immunotherapy recommended for secondary development of asthma
  - Recognition that SLIT is safer than SCIT
  - Stronger recommendations in revised guidelines
  - Greater recognition of SLIT in place-in-therapy
- ARIA guidelines updated in 2010
- SLIT can be used in adults and children with pollen rhinitis
- WAO Position Paper in 2009 on SLIT
  - Emphasized benefits of licensing AIT as a therapeutic class
- EMA guideline published in 2009:
  - Requirements to demonstrate clinically relevant efficacy and safety
  - Covered patient selection, trial design, defined necessary time scales –
  - Towards allergen immunotherapy credibility as ‘proper’ medicine
2000 onwards: AIT comes of age

• Grass pollen sublingual tablets developed
• in accordance with EBM are registered as medicines
• Clinical development programme designed to satisfy the requirements of the EMA
• Registration of sublingual immunotherapy
The new era of AIT is now

- Allergen immunotherapy has a disease modifying effect
- Preventing progression of disease – AIT now impossible to side-line
- Thanks to the tenacity and determination of the visionaries behind it
- The EMA defined appropriate regulations for the
  registration of AIT products
- Allergen immunotherapy tablets are a new class of registered medicines
- Most questions Noon raised have been answered
- But there are still some left: the value of AIT in multiple allergies, the optimal time to initiate therapy in children, place in allergic asthma control?
- The new era of AIT is only just beginning
Immune mechanisms of sublingual immunotherapy

• SLIT is a well-established allergen is a well established allergen specific immunotherapy and a safe and efficient strategy to reorient inappropriate immune responses in allergic patients.
• SLIT takes advantage of the tolerogenic environment of the oral mucosa to promote tolerance to the allergen.

• Several clinical studies have investigated the complex interplay of innate and adaptive immune responses – following the uptake of allergen during SLIT, support the differentiation of T helper cell type 1 (Th1) and the induction of IL-10 – producing regulatory T cells.
Following SLIT, allergic disease promoting T helper type 2 cells (Th2) responses shift to a Th1 inflammatory response, and IL10 and transforming growth factor (TGF) – β production by regulatory T cells and tolerogenic dendritic cells suppress allergen-specific T cell responses.
• These immune changes occur both in the sublingual mucosa and in the periphery of a patient following SLIT.

• SLIT also promotes the synthesis of allergen-specific IgG and IgA antibodies that block allergen specific allergen – IgE complex formation and binding to inflammatory cells, thus encouraging and anti-inflammatory environment.
ALK SQ® HDM SLIT-tablet Development program

ACARIZAX® 12 SQ-HDM
SQ® HDM SLIT-tablet clinical development in 3 continents involving >6000 patients

<table>
<thead>
<tr>
<th>Continent</th>
<th>Year</th>
<th>Sample Size</th>
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<tr>
<td><strong>Europe</strong></td>
<td></td>
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<tr>
<td>MT-01 (Phase I)</td>
<td>2005</td>
<td>n=71</td>
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<tr>
<td>MT-02 (Phase II)</td>
<td>2006</td>
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<tr>
<td>MT-03 (Phase I)</td>
<td>2007</td>
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<tr>
<td>MT-04 (MITRA; Phase III)</td>
<td>2008</td>
<td>n=834</td>
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<tr>
<td>MT-06 (MERIT; Phase III)</td>
<td>2009</td>
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<tr>
<td>P003¹ (Phase II, ECC)</td>
<td>2010</td>
<td>n=124</td>
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<tr>
<td>P008 (Phase I, USA¹)</td>
<td>2011</td>
<td>n=195</td>
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<tr>
<td><strong>Outside Europe</strong></td>
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<td>TO-203-1 (Phase I, JPN²)</td>
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<td>TO-203-3-1 (Phase III, JPN²)</td>
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<td>TO-203-3-2 (Phase III, JPN²)</td>
<td>2014</td>
<td>n=458</td>
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1. Merck holds the product rights in North American region
2. Torii holds the product rights in Japan

*Note: Sample sizes are approximate and may vary.*
Trials in both AR and AA patients (Europe)

- MT-02: AA and AR – phase II
  - MT-02 AR subgroup
    Responder analysis
  - MT-02 AA subgroup
    Responder analysis
- MERIT (MT-06): AR – phase III
- P003: AR and AA – phase II
  Environmental Exposure Chamber
- MITRA (MT-04): AA – phase III
SQ® HDM SLIT-tablet – a highly standardised product

Dermatophagoides pteronyssinus

Group 1

Group 2

Dermatophagoides farinae

P003 – clear dose-response with early onset of effect within 8 weeks

Total rhinitis symptoms score

- Placebo (n=41)
- 6 SQ-HDM (n=41)
- 12 SQ-HDM (n=42)

Baseline 8 weeks 16 weeks 24 weeks

-1.37 (20%) p=0.007
-1.23 (18%) p=0.032
-2.08 (30%) p<0.001
-1.98 (27%) p=0.003
-3.62 (49%) p<0.001

P003 – clear dose-response with early onset of effect within 8 weeks

MERIT (MT-06) – Year around treatment effect with early onset of effect at 14 weeks.

Total combined rhinitis score

Placebo 6 SQ-HDM 12 SQ-HDM

Weeks

~ 9 months

* Statistically significantly different to Placebo

MERIT (MT-06) – Clinical relevance in HDM allergic rhinitis

- Reduced burden of symptoms as well as medication use all year around
- Probability for having an AR-exacerbation-day* is halved

➢ Extrapolated to full year: 40 days with allergic rhinitis exacerbations is reduced to 19 days

* defined as fulfilling the inclusion criteria of MT-06 of burdensome disease with moderate-severe symptoms despite using pharmacotherapy
MERIT (MT-06) – All individual symptom scores significantly reduced for 12 SQ-HDM


* Statistically significantly different to Placebo
Significant effects on individual RQLQ domains with 12 SQ-HDM

Most frequent adverse events are local reactions in mouth and throat

MITRA (MT-04)¹

- Oral pruritus
- Throat irritation
- Oedema mouth
- Tongue pruritus
- Parasthesia oral
- Ear pruritus
- Nausea
- Lip oedema
- Lip swelling
- Lip pruritus

Percentage of subjects

Placebo 6 SQ-HDM 12 SQ-HDM

MERIT (MT-06)²

- Oral pruritus
- Throat irritation
- Oedema mouth
- Parasthesia oral
- Tongue pruritus
- Ear pruritus
- Oral discomfort
- Glossodynia
- Tongue oedema
- Pharyngeal...
- Lip swelling
- Lip oedema
- Eye pruritus

Percentage of subjects

Placebo 6 SQ-HDM 12 SQ-HDM

Dose related induction of sIgG$_4$ antibodies

MITRA (MT-04) (N=829)

Conclusions

• The SQ® HDM SLIT-tablet was **efficacious in both HDM AR and AA**, also when both manifestations were present simultaneously
  – Primary endpoints met in both the AR and AA trials that can be translated to significant clinical benefits for patients with moderate to severe disease, and who are not controlled by pharmacotherapy

• **Onset of effect** was found after **8-14 weeks and sustained** throughout the year of treatment

• Treatment was **well-tolerated** within the listed safety precautions supporting at home administration (once first dose is tolerated under physician supervision)
Bibliography

4. ARIA. *Allergy* 2008: 63 (suppl.86) 8-160
Thank you
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