Relevant Sensitizing Allergens and Optimizing SIT

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- **Address 5 questions to better optimize AIT:**
  - Is it better to use mono- versus poly-allergen IT in polysensitized patients?
  - Is the quantity of allergen-specific IgE important in clinical responses to AIT?
  - Are recombinant allergens better than “natural” allergens for AIT?
  - Is component-based testing helpful in prescribing AIT?
  - Are there future routes of AIT that could be better?
  - Is it better to use mono- versus poly-allergen IT in polysensitized patients?

- **The Trans-Atlantic Debate:**
  **How Are Polysensitized Patients Best Treated?**
  - **US Approach:** Many allergens simultaneously chosen according to sensitization profile
    - US extracts contain an average of 8 Allergens
    - Advantage in treating as many of the patient’s actual or potential sensitizations/allergies
  - **European approach:** Single allergen chosen according to most clinically problematic allergy
    - Polysensitized patient is not necessarily polyallergic
  - **MYTH:** Patients in the US tend to be more polysensitized so a multi-allergen approach makes more sense.
  - **FACT:** In patients seeking treatment for moderate-to-severe respiratory allergies, polysensitization is more prevalent (50%-80%) than monosensitization in both the US and Europe!

- **Single-allergen SLIT in monosensitized versus polysensitized patients:**
  - In robust, large-scale clinical trials of grass pollen SLIT, polysensitized patients benefited at least as much from AIT as monosensitized patients.

- **Single-allergen SCIT in monosensitized versus polysensitized patients:**
  - No single-allergen SCIT trials have been specifically designed to compare efficacy in monosensitized and polysensitized patients.
- Large-scale, DBPC RCT examining efficacy of single-allergen SCIT featured 77% polysensitized patients and found equivalent efficacy (Frew, JACI 2006).

**Multiallergen AIT In Polysensitized Patients**
- *Very little data*
- **SLIT:** 1 study suggested that coadministration of multiple allergens interfered with effectiveness of timothy grass SLIT (Amar, JACI, 2009).
- **SCIT:** Some data suggest that multiallergen immunotherapy is less effective in polysensitized patients than single-allergen IT in monosensitized patients.

**Summary**
- Single-allergen immunotherapy has proved to be as safe and effective in polysensitized patients as in monosensitized patients.
- Limited data and mostly with grass pollen
- Multiallergen SLIT or SCIT in polysensitized patients needs more supporting data from large clinical trials to validate it as a treatment option.
- Choosing the most relevant allergens for optimizing AIT remains an art- and not science-based practice.

*Is the quantity of allergen-specific IgE important in clinical responses to AIT?*

- Clinical Efficacy Of 300IR 5-grass Pollen Sublingual Tablet In A US Study: The Importance Of Allergen-specific Serum IgE
  - Age 18-65
  - Grass pollen–related ARC for ≥ 2 previous grass pollen seasons
  - Positive skin prick test to timothy grass (wheal ≥ 5 mm and flare >10 mm)
  - Retrospective Rhinocconjunctivitis Total Symptom Score (RTSS; scale, 0-18) ≥ 12 during the previous grass pollen season
  - 300IR SLIT tablets containing equal amts of standardized 5-grass extracts:
    - Orchard grass, Dactylis glomerata
    - Kentucky bluegrass, Poa pratensis
    - Perennial rye grass, Lolium perenne
    - Sweet vernal grass, Anthoxanthum odoratum
    - Timothy grass, Phleum pratense
• Treatment was initiated ~4 months before expected start of grass pollen period and continued for its duration.
  – Clinical Efficacy Of 300IR 5-grass Pollen Sublingual Tablet In A US Study: The Importance Of Allergen-specific Serum IgE showed better results with Higher Grass IgE

Are recombinant allergens better than “natural” allergens for AIT?

– Pros and Cons Of Recombinant Allergens
  ➢ Pros:
    • Ultrapure defined molecules
    • Consistent pharmaceutical quality
    • Dosage in mass units: absolute standardization
    • Dose optimization and formulation
    • Precise monitoring of clinical and laboratory outcomes
  ➢ Cons:
    • Stringent production requirements
    • Selection of isoforms
    • High development costs, limited market potential
    Chapman JACI 2000; Cromwell et al, JACI 2011

• Efficacy Of Recombinant Birch Versus “Natural” Birch Pollen Vaccine For Allergic Rhinoconjunctivitis Study showed equivalent results.
• AIT with recombinant pollen allergens appears safe, well tolerated and effective
  – >30% decrease in symptom-medication scores
  – Optimal maintenance dose 10-15μg allergen
  – Associated with ~2 log incr in Ag-specific IgG
  – Not clear if better clinical outcomes versus “natural” allergens
  – Recombinant products include: Dust mite Cat Grass Ragweed Tree

Is component-based testing (CBT) helpful in prescribing AIT?

• CBT & Patient Selection For Pollen Immunotherapy
  • Many ‘allergens’ are mixtures of various proteins to which individuals are variably sensitized.
  • Advances in molecular biology have led to identification of IgE binding proteins which have been synthesized using recombinant technology
  • The formation of IgE to some of these proteins appears to be associated with a greater risk of developing clinical symptoms.
  • Components and risk assessment

• Component Based Testing
• Significant % of polysensitized patients have IgE against highly cross-reactive panallergens.
• CRD-Based Diagnostics and AIT
• 73% efficacy in patients sensitized to major allergens vs. 16% efficacy in patients sensitized exclusively to minor allergens
• CBT and AIT Conclusions
  ➢ May allow patients’ sensitization profiles to be characterized in greater detail
  ➢ May provide a more precise AIT prescription
  ➢ May assess the clinical risk for reactions (both mild and severe)
  ➢ May help differentiate between symptoms caused by true allergy and symptoms caused by cross-reactivity in:
    ➢ general
    ➢ suspected food allergy patients

Are there future routes of AIT that could be better?
• The Advantages Of ILIT
• Recombinant Intralymphatic Cat IT
  – rFel d 1 fused to the HIV-derived translocation peptide TAT, mediating cytoplasmic uptake
  – To enhance presentation through the MHC class II pathway, a truncated human invariant chain (ii) was also fused to Fel d 1
  – Results in a modular antigen transporter (MAT) vaccine (MAT–Fel d 1)
  – MAT–Fel d 1 in alum was compared with ILIT with placebo (saline in alum) in cat allergic patients
• Recombinant Peptide Principles
  – Identifies and uses T-cell epitopes
  – Binds to MHC class II on APCs to induce TRegs to blunt allergic response
• Less safety issues
  – Lack of B cell epitopes in peptides avoids cross linking of mast cells avoiding need to dose escalate
  – Broadly applicable across range of allergies
  – Allergens already identified
  – Standardized dosing; short course of immunotherapy over 3 months
• Effects Of Cat ToleroMune:
  1 Year Follow-up With No Further Treatment
• ToleroMune /Peptide Summary
  – Peptides manufactured synthetically allowing dose standardization
  – No dose escalation phase
  – Room temperature stable formulation
  – Safety profile looks good
  – Short Course of Immunotherapy over 3 months
    • Clinical Efficacy with 4 administrations
    • Effects lasting 1 year
  – Allergens studied
  – Cat, Ragweed, Mite and Grass in clinical trials
  – Birch epitopes defined
  – Dog and Alternaria in process

• Conclusions:

There are a lot of unknowns in the quest to optimize AIT
  – Is it better to use mono- versus poly-allergen IT in polysensitized patients?
    • Not clear, but data support monotherapy
  – Is the quantity of allergen-specific IgE important in clinical responses to AIT?
    • Probably
  – Are recombinant allergens better than “natural” allergens for AIT?
    • Maybe
  – Is component-based testing helpful in prescribing AIT?
    • Probably
  – Are there future routes of AIT that could be better?
    • Likely