IMMUNOTHERAPY IN ALLERGIC RHINITIS

EVIDENCED-BASE OVERVIEW OF THE RULE OF IMMUNOTHERAPY IN ALLERGIC RHINITIS PATIENTS.

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FROM WHERE TO START?

• **Immunotherapy** or hyposensitisation is used when drug treatment fails to control symptoms or produces intolerable side effects.

• **In immunotherapy** .. Allergen is given in *gradually* increasing doses till the maintenance dose is reached.

• **Immunotherapy** .. Down regulate the immune system.
AS WE ALL KNOW ..

- **A. T-helper 1 (Th1) cells** in type 4 delayed reactions, and
- **B. T-helper 2 (Th2) cells** are predominant in type 1 immediate hypersensitivity reactions
  - produce IL-4, IL-5, and IL-13, which direct B lymphocytes to switch to IgE production

  How **APC** will present the antigen on the surface .. **IL4** .. B lymphocytes .. **IgE** .. Mast cells .. Eosinophils
CONTENTS

• History of immunotherapy .
• Mechanism of action .
• The 4 key players .
• Patients selection .
• Contraindications .
• Allergen selection .
• Timing of treatment .
• Efficacy ?
• Cost-effectiveness .
HISTORY OF IMMUNE THERAPY

• The first documented description of clinical application of allergy immunotherapy dates back to the early 20th century. In 1911, Noon and Freeman reported the successful treatment of patients with hay fever using pollen injections.
INTRODUCTION

• **Specific immunotherapy (SIT)**
  • involves a **series** of controlled exposures to escalating doses of allergen, which **alter immune system pathways** and **down-regulate** the allergic response, thereby decreasing the allergic symptoms associated with exposure to environmental allergens.
HOW?

- We will talk about **4 main key players** in the immune system..

1. IL 10
2. IgG Vs IgE
3. Th 1 Vs Th 2
4. T-regulatory cells (T-reg)
MECHANISM:

Unclear..

1. IL-10..

- The first immunologic difference can be detected as early as **7 days** after initiation of immunotherapy, as manifested by a rise in cytokine interleukin (IL)-10. IL-10 has been shown to play a central role in tolerance induction and immunologic **change** with immunotherapy.
Fig. 1. The anti-allergenic properties of IL-10 on different limbs of the allergic immune response. T-reg, T-regulatory cell; EOS, eosinophil. (Reproduced from Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1029; with permission.)
2- IgE Vs IgG

- Shortly after beginning SIT, a slight increase in IgE is noted. Levels of IgE subsequently decrease, and a rise in IgG and IgA levels occurs, particularly IgG4 and IgA2.

- The rise in IgG can be seen at as early as 5 weeks, and is predictive of response to immunotherapy at 1 year.

- “scissors effect”
CONTINUED

3. T- helper 1 Vs t-helper 2 System:

- Th1: type 4 delayed reaction.
- Th2: type 1 immediate reaction.

- **Th2 cells produce** IL-4, IL-5, and IL-13, which direct B lymphocytes to switch to IgE production.

- **Th1 cytokines**, such as interferon gamma, transforming growth factor b, and IL-10, **inhibit** IgE production and are also involved in Th2 regulation.

- atopic conditions ➔ T-cell balance is shifted toward proallergic Th2

- immunotherapy works through restoring the normal Th1/Th2 balance
Fig. 2. Immunotherapy readdressed the balance between Th1/Th2 responses. An increase in IL-10 producing T cells and regulatory T cells is also seen. T-reg, T-regulatory cell; DC, dendritic cell; EOS, eosinophil. (Reproduced from Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1028; with permission.)
4. T regular cells:
• Also plays a key rule in restoring the normal Th1/Th2 balance
• T-reg cells constitute 10% of circulating lymphocytes and have been shown to
• 1- regulate tolerance to both self (internal) and non-self (external) antigens.
• 2- Produces IL10, TGF B.
• 3- affects activation and migration of eosinophils and mast cells to target tissues.
PATIENT SELECTION.

- Can immune therapy be offered to all patients with atopy?
- Things to take in consideration..
  1. Identifiable allergens
  2. The degree of response to prior environmental modulation and maximal pharmacologic treatment, duration and severity of symptoms, and patient compliance must be reviewed.
  3. Alternatively, allergic immunotherapy should be offered to patients who wish to avoid long-term dependence on pharmacologic agents or are seeking a potential cure for their disease.
• According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, indications for immunotherapy in adults and children older than 5 years of age include:

• 1 - Patients with symptoms induced predominantly by allergen exposure.
• 2 - Patients with a prolonged season or with symptoms induced by succeeding pollen season.
• 3 - Patients with rhinitis and symptoms from the lower airways during peak allergen exposure.
• 4 - Patients in whom antihistamines and moderate-dose topical glucocorticoids insufficiently control symptoms.
• 5 - Patients who do not want to be on constant or long-term pharmacotherapy.
• 6 - Patients in whom pharmacotherapy induces undesirable side effects.
HOW TO IDENTIFY ALLERGENS?

- either in vitro testing, such as radioallergosorbent test (RAST) or enzyme-linked immunosorbent assay (ELISA),
- or in vivo testing, such as intradermal, prick, or combined skin testing.

- Alternatively, the testing can be classified as qualitative and quantitative.

- intradermal skin end point titration (SET) and modified quantitative testing (MQT) are considered the standard quantitative methods.
CONTRAINDICATIONS

- As stated by Haydon and Gordon. “the only absolute contraindication to immunotherapy is failure to prove that a relevant allergy exists.”
- However, immunotherapy is strongly discouraged in patients whose medical status would preclude them from surviving a systemic adverse reaction or its treatment.
  1. most serious being poorly controlled asthma, because the risk of anaphylaxis is greater in patients with reduced pulmonary function.
  2. Patients on b-blocker drugs are considered high risk because the systemic reaction may be more severe and more resistant to management with adrenergic agents, such as epinephrine.
ALLERGEN SELECTION

- The most commonly used allergens are ..
  1. Dust mites .
  2. Cat and dog dander.
  3. Cockroach.
  4. Molds, and
  5. pollens of trees, grasses, and weeds.
* The allergens are then prepared .
QUESTION !!

• How many allergens to treat?
• All offending allergens?

1- Risk of affecting the efficacy
2- The new theory
TIMING OF ADMINISTRATION.

- Biphasic..
- **1- incremental phase** .. “build up phase”
- **Weekly bases**, escalating doses for 10 – 13 weeks *
- Rush, cluster model.*
- Safety ?**
- **2- maintenance phase** :
  - The frequency of injections is **reduced** from weekly to once or twice monthly during the maintenance phase.
  - For how long ?
  - 3- to 5 years .
  - Stop it if no improvement after 1 year .
EFFICACY IN ADULT

• The 2007 Cochrane meta-analysis that reviewed 51 trials comprising 2871 patients with seasonal AR *
• Among the studies, 15 showed clinical benefits of immunotherapy in patients with seasonal AR, using reduced symptom scores as the primary outcome measure. Furthermore, 13 studies reported reduced medication use scores in patients undergoing immunotherapy.

• Passalacqua and Durham. reviewed recent studies (2000–2006) involving patients with AR treated with immunotherapy. The reduced need for medication and diminished clinical symptoms were confirmed in the patient group receiving immunotherapy.

• Frew and colleagues, for example, followed up 410 patients with grass pollen–induced seasonal rhinitis. In their study, patients treated with immunotherapy had a marked improvement in quality of life compared with a well-matched control group. This finding parallels earlier literature outcomes
• **In summary**, immunotherapy benefits have been thoroughly investigated and confirmed in adult patients with seasonal AR. Data on perennial allergic rhinitis exist in the form of multiple truncated reports.

• A protocol for systematic review of injection immunotherapy in perennial AR was submitted to the Cochrane Library in 2008 and is currently under review.
The data on the efficacy of SIT in children with inhalant allergy remain conflicting.
LONG TERM OUTCOME

• Eng and colleagues presented the longest controlled follow-up studies of grass pollen sensitivity in children treated with immunotherapy. They were able to show that the clinical symptom score and use of medication remained low 6 and 12 years after a 3-year course of specific immunotherapy. In addition, the rates of new sensitization to unrelated antigens remained lower in children treated with immunotherapy compared with controls. This finding suggests that immunotherapy can modulate the natural course of allergy.

• Many other studies... Showed 3-4 years post immunotherapy benefit...
SIDE EFFECTS:

- **Early side** effects manifest within 20 to 30 minutes of injection, and **late side** effects after 30 minutes, most commonly after 6 to 24 hours.

- **Local reactions** present as edema, erythema, tenderness, and pruritus at the site of injection, 1-40%, more with pt with both AR and Asthma.*

- **Systemic side effects** include rhinitis, dyspnea, fever, fatigue, angioedema, urticaria, and anaphylactic shock, less than 2% Within 20 min of the injections, more in the escalating phase.**
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<tr>
<th>Box 1</th>
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<tbody>
<tr>
<td><strong>Factors associated with adverse reactions to SIT</strong></td>
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<tr>
<td>• Early months of treatment (induction course)</td>
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<td>• Dosage errors</td>
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<tr>
<td>• Intravenous injection of dose (inadvertent)</td>
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<tr>
<td>• History of previous systemic reaction</td>
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<tr>
<td>• Extreme sensitivity to allergen</td>
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<tr>
<td>• Vigorous exercise before injection</td>
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<tr>
<td>• Change of vial</td>
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<td>• Febrile illness</td>
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<td>• Uncontrolled asthma</td>
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<td>• Environmental exposure to allergen (e.g., during the pollen season)</td>
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<td>• Administration of β-blocker drugs</td>
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• The economic advantages of allergen immunotherapy over conventional pharmacologic treatment of allergy have been reported by many groups in both American and European health care systems. In both adult and pediatric age group.
• Hankin and colleagues reported that children receiving immunotherapy had lower medical per-patient total health care costs ($3247 vs $4872), outpatient costs not related to immunotherapy ($1107 vs $2626), and pharmacy costs ($1108 vs $1316).
Sublingual Immunotherapy

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KEYWORDS
- Sublingual immunotherapy
- Allergen-specific immunotherapy
- Allergic rhinitis
- Subcutaneous immunotherapy
- Asthma

Key Points: Sublingual Immunotherapy for Allergy

- SLIT has been shown in multiple studies to be efficacious in allergic rhinitis for adults and children.
- SLIT has also been shown to be helpful in asthma and in preventing the development of new sensitivities to allergens.
- Studies have shown immunologic changes in SLIT that are similar to SCIT, suggesting a similar mechanism of action.
- SLIT enjoys a good safety profile, allowing for the convenience of dosing in the home and in individuals unable to tolerate injections, such as young children, although a few cases of anaphylaxis have been reported.
THANKS

THANK YOU

THANK YOU

THANKS

Grazie

Merci

Gracias

Thank You