Immunology Meeting

Dr Sarah Sasson
HIV/Immunology Registrar
HIV, Immunology and Infectious Diseases Department, St Vincent's Hospital

Case 1: HPI

• 50M found to have elevated LFT on routine bloods by GP
• Referred to Gastroenterologist who performed a liver screen and Hepatitis serology all normal-no cause found for deranged LFTs

Case 1: PMHx + SHx

• Chronic HIV infection
  ➢ CD4+ 613 (24%) VL UD
  ➢ Lamivudine 300mg, Maravaroc 300mg BD, Raltegravir 400mg BD
• Moderate to severe psoriasis
  ➢ Not responding to topical steroids
• Allergy: Severe rash to amoxycillin

Case 1: Salient features of Examination

• Neurologically patient appears more confused than normal

Case 2: Diagnosis and Management

• The GP performs a diagnostic test which may explain deranged LFTs and physical examination findings
  ➢ What is the test and the diagnosis?
  ➢ A: RPR, Syphilis (likely tertiary)
  ➢ How would you proceed to manage this patient?
  ➢ A: Needs desensitisation and penicillin
Desensitisation to venom and drugs

**Introduction to Immunotherapy**

- Immunotherapy first described by Noon and Freeman in 1911 who increased tolerance to conjunctival grass pollen extract
- It could be argued that these concepts have not changed in over 100 years

**Desensitisation**

- The process by which an allergic response can be overcome by administering gradually increasing doses of the causative allergen to the host inducing tolerance

**Desensitisation**

- May be delivered:
  - Sublingually
  - Subcutaneously
    - usually requires doing up to 3 years
    - Must be done in a setting where cardiopulmonary resuscitation available
    - SCIT for aeroallergens is contraindicated in patients with underlying asthma due to risk of near fatal and fatal anaphylaxis
- Common side effects: flushing, pruritis, erythema and urticaria

**Desensitisation**

- Patient selection in important:
  - Symptoms must be linked to a specific allergen ie not mixed allergens
  - Desensitisation of any kind contraindicated in pregnancy due to rare but real risk of anaphylaxis which may lead to fetal hypoxia

**Desensitisation and β-blockers**

- β-blocker therapy is usually considered an absolute contraindication to desensitisation due to reduced therapeutic efficacy to adrenaline due to underlying beta blockade
  - For some people switching to short acting beta blockers which can be temporarily withheld eg pt requiring VIT with underlying tachyarrhythmias
  - Glucagon should be on hand to partially overcome the effects of β-blockade
**Desensitisation and ACEi**

- ACE inhibitors are a relative but not absolute contraindication

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**Desensitisation to venom**

**Hymenoptera venom Immunotherapy**

- **Hymenoptera**
  - Large order of insects including bees, wasps, ants and sawflies
  - Venom immunotherapy is the only specific treatment to reduce severity and prevent reoccurrence of systemic reactions in patients with a history of life-threatening reactions or anaphylaxis to insect stings
  - Studies in UK/Aus suggest sting allergy is second only to drug allergy as a cause of fatal anaphylaxis
    - Men >40y with concurrent CVD and previous history of sting allergy are at greatest risk of fatal venom anaphylaxis

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Important to obtain good clinical history to ascertain most likely causative species

Investigations:

- SPT 0-100microg/mL
- If SPT negative for intradermal testing
- Demonstration to venom-specific IgE is mandatory prior to proceeding
- Note SPT and serum IgE levels do not correlate clinically with severity of reaction

Choice of venom used depends on history and knowledge of local insect species

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**Hymenoptera venom Immunotherapy**

- Choice of venom used depends on history and knowledge of local insect species
- There is not cross reactivity between honeybee and wasp/hornet species but there is between wasp and hornet species
Patient selection for Venom Immunotherapy

Hymenoptera venom Immunotherapy

Optimal duration of therapy is 3 years
75% of pts still venom IgE+ following this- no benefit to rechecking
Long term follow-up studies in America and Europe have found a cumulative risk of 10-15% for the development of a systemic response 15 years post 3-5 years of venom desensitisation

Venom Immunotherapy: Other considerations

VIT should not be given during an concurrent respiratory tract infection
Contraindicated in “brittle” but not moderate asthma

Systematic review of VIT

Review of 6 RCT and 1 additional trial of 392 patients
Intervention included ant, bee and wasp immunotherapy in children and adults with previous large local or systemic reactions
6 trials used subcutaneous VIT and one sublingual
Systematic review of VIT

Boyle et al. Coch Data Sys Rev 2012

- VIT improves quality of life by decreasing anxiety and limitation of activities

Drug desensitisation

- Drug hypersensitivity accounts for 15% of adverse drug reactions
  - May be immediate/IgE mediated e.g. penicillin
  - Delayed (non-IgE mediated) e.g. aspirin/NSAIDS
- Note: a hypersensitivity type reaction that occurs at the time of first exposure to a drug must be non-IgE mediated and may result from direct release of mediators from mast cells and basophils e.g. Red Man Syndrome and Vancomycin

Drug desensitisation

- Desensitisation to IgE-mediated reactions have been employed for:
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Insulin
  - Platin
d- As well as to non-IgE reactions to:
  - Aspirin (pseudo-allergy)
  - NSAIDS (pseudo-allergy)
  - Radiolotope contrast
  - Vancomycin

Desensitisation to drugs

- Involves a closely supervised graded administration of a drug to a patient with a history of a hypersensitivity response
- Administered over hours-days until the total cumulative therapeutic dose is tolerated
- There are no clinical trials to validate dosage regimes
Drug desensitisation: Clinical scenarios

- In what clinical scenarios may drug desensitisation be indicated?

**Indications:**
- The drug is irreplaceable
- The drug is more effective than its alternatives

**Contraindications:**
- Uncontrolled asthma FEV1<70%
- Haemodynamic instability or unstable CVD
- TEN/SJS

Drug desensitisation: Penicillins

- Skin testing is suggested where available for risk-stratifying patients prior to desensitisation
  - SPT to major and minor determinants have a high negative predictive value
  - Patients with negative SPT do not require desensitisation
  - Patients with positive SPT suggested to avoid penicillins and cephalosporins and undergo desensitisation to these agents if required

Drug desensitisation: Algorithm

Example 3. Indications or common clinical scenarios for drug desensitisation
- Life-threatening or serious infections where no alternative antibiotic is available
- Neumoplastra
- Infants in pregnancy
- Infective endocarditis
- Tuberculosis
- Multiple antibiotic allergies in cystic fibrosis
- Cancer chemotherapy
- Asymptomatic AAA, hypertension to:
  - Aspirin induced asthma
  - Aspirin induced nasal polyposis
  - Cardiac stent using dual antiplatelet prophylaxis
- Anti- phosphorylcholine antibodies
- Non-controllable anti-inflammatory drugs (NSAIDS): patients requiring pain control as an arthritis and pain management
- Patients with a positive history of aspirin allergy to aspirin and/or NSAID
- Penicillin hypersensitivity in a patient needing cardiac surgery

**Desensitisation:**
- Avoid medication

Drug desensitisation: Penicillins

Example 5. A protocol for oral penicillin desensitisation [15]

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**Cumulative dose in units**

- **Immediate reaction suggesting type I HIE:**
- **Desensitisation:**
- **Avoid medication**

Krishna and Huissoon Clin Exp Immunol 2010

Liu et al Clin Exp Allergy 2011
Drug desensitisation: Carboplatin

- Cornerstone of chemotherapy for ovarian cancer
- 27% of patients develop Type I hypersensitivity after 7 or more cycles; 90% of these have cutaneous manifestations and 77% cardiovascular compromise
- SPT to platin prior to the 8th dose has a high NPV (98.5%)
- Once a patient has a Type I hypersensitivity reaction to a platin (or +SPT) physicians are forced with the dilemma of
  - Re-administer same agent
  - Change to a different platinum drug
    - 1 reported fatality
  - Perform desensitisation

Drug desensitisation: mAb

- Rate of Type I hypersensitivity are:
  - Rituximab 5-10%
  - Infliximab 2-3%
  - Trastuzumab 0.6-5%

Drug desensitisation

- Tolerance induced by drug desensitisation is lost within a few days of taking the drug
- My be carried out orally or intravenously
  - Initial dose <1:1000th of final drug dose
- Allergic reaction should be treated with antihistamines, adrenaline and steroids
- Dose reduction and re-escalation can be re-attempted to induce tolerance
  - In some patients this reduction/re-escalation needs to be repeated several times

Desensitisation: Conclusions

- Desensitisation is a process by which a host may be tolerised to allergens through administration of gradually increasing doses
- It is thought this process results in stabilisation of allergen: IgE complexes on the mast cell membrane which prevents degranulisation
- The process may take hours to years to complete

Desensitisation: Future Directions

- Efforts should be made to standardise desensitisation protocols across centres
- Further clinical trials in this areas would improve the evidence base for this practice

Desensitisation: Conclusions

- There is good evidence for the use of Hymenoptera venom immunotherapy for prevention of severe systemic response, large local reactions and improvement in quality of life
- Drug desensitisation is indicated in patients with a history of type 1 hypersensitivity reactions to drugs:
  - which are essential to their medical care
  - Which are superior to other choices
  - When the benefits of desensitisation outweighs the risk
Thank You