Contraindications in Venom Immunotherapy?

Constantinos Pitsios, MD, PhD
“General contra-indications for VIT are the same as for immunotherapy with other allergens.”
Lack of communication/collaboration

- Mentally or physically unable to communicate
- Psychological factors
  - Cooperative
- Adherent to the dates of visit

insufficient and unsafe VIT

Should VIT be continued?

Pregnancy

- Embryologic effect
  - Initiation
  - Up-dosing
  - Maintenance
Uterine contractions

Apis mellifera → Urticaria, Bronchospasm, Nasal congestion
Hypoparathyroidism – under Calcium lactate gluconate

Maintenance dose 100μg
Pretreated 30’: cyclic uterine contractions every 3’
1 month later: same
After Ca++ infusion: no reaction

Immunological effects?


- Premature birth 24th week, 16 days after last wasp venom shot.
- Higher rate of CD8+ /shift from Th2 towards Th1.


- Metzger et al showed retrospectively the safety of SIT in a study in 115 pregnant women, each receiving SIT for allergic rhinitis.
- Abortions were higher in a control group of atopic pregnant.
Pregnancy

- Embryologic effect
  - Initiation
  - Up-dosing
  - Maintenance

BSACI: “the patient should be informed of the risk of anaphylaxis even during maintenance treatment that could potentially affect the foetus.”

AAIITO: “La gravidanza non è generalmente considerata una controindicazione per la IT se la paziente è in fase di mantenimento ben tollerato.”

Drugs

- β-blockers
- ACE-inhibitors
- MAO-inh. antidepressants
- Cocaine - amphetamines
- Immunosuppressive agents
**β-blockers**

Unopposed α-adrenergic effects
Bradycardia, Bronchoconstriction

**β-blockers**

- Increased release of anaphylactic mediators [does it make it more severe - protracted?]
  - Toogood JH. CMAJ 1987; 137:587-8, 90-1.
- Negative effect on therapeutically administered epinephrine [non-selective β-blockers]
- β-blocker in eye-drops can effect too
Are β-blockers a risk factor for anaphylaxis?


Müller UR et al. J.A.C.I. 2005; 115:606. 1,389 VIT
- 4 throughout VIT
- 9 reintroduced at maintenance
- 12 newly started
allergic R: 3/25(β-b) -23/117 (C.V.D.)

β-b not a risk factor

Rüeff F et al. J.A.C.I. 2010; 126:105. VIT Observational study
15 β-b/ 680 β-b not an independent predictor for emergency intervention

Brown SG. J.A.C.I. 2004; 114:371. 1,149 patients with anaphylaxis
Univariate analysis: β-b is risk-factor
Multivariate analysis: β-b is not a risk-factor

β-blockers

- Anaphylaxis is not more frequent under β-b
- Emergency treatment might be ineffective
- When feasible, change to an equally efficacious alternative medication
- When β-b is required, evaluate risk-benefit
ACE - inhibitors

Renin-Aldosterone System is part of a compensatory physiologic response to anaphylaxis
ACE-inh may hamper an effective response during anaphylaxis

- Group A: Patients who well-tolerated VIT [27]
  Levels of ANG I, ANG II, angiotensinogen, renin similar to Control Group

- Group B: Patients with anaphylaxis during VIT [6]
  Reduced levels of ANG I, ANG II, angiotensinogen, renin (p<0.05) vs Control Group

- Control Group: Healthy non-allergic [25]

Dysfunctional Renin-Angiotensin System is a risk factor for anaphylaxis

**ACE-inhibitors and VIT**

- **VIT Observational study**
  - 18 ACE-inh/680 VIT
  - ACE-inh: not an independent risk factor

- **HVA Observational study**
  - 42 ACE-inh/962 HVA
  - 2.3-fold increased risk for severe anaphylaxis

- **Brown SG. J.A.C.I. 2004; 114:371.**
  - 57 ACE-inh/1,149 with anaphylaxis
  - Multivariate analysis: not a risk-factor

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**ACE-inhibitors**

- There is a debate on whether they are a risk factor for anaphylaxis

- When feasible, change to an equally efficacious alternative medication
MonoAminOxidase inhibitors

MAO inhibitors prevent the breakdown of sympathomimetic drugs. Epinephrine + MAO inhibitors = hypertension and tachycardia. Non used, due to interaction with foods (tyrosine).
Cardiovascular diseases

Elder ages

- Hypertension (90.8%)
- Coronary disease (12.7%)
- Arrhythmia (5.6%)


particularly elderly patients with pre-existing cardiovascular disease die from HVA
Lower age limit

Asthma

VIT is contraindicated in patients with brittle asthma or chronic severe asthma, although may be cautiously initiated in patients with moderately severe asthma, after establishing good control.
Immune disorders

Immunodeficiency

Immunosuppression

Acquired Immunodeficiency

Autoimmune diseases

Human Immunodeficiency Virus – Structure

Symptoms of systemic lupus erythematosus may vary widely with the individual

Butterfly rash

Raynaud’s phenomenon

Pleural effusions

Heart problems

Lupus nephritis

Arthritis
### HIV DISEASE

<table>
<thead>
<tr>
<th>CD4 Cell Count Categories</th>
<th>Clinical Categories</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
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<tr>
<td></td>
<td>Asymptomatic, Acute HIV, or PGL</td>
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<td>(1) ≥2500 cells/μL</td>
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<tr>
<td>(2) 200-499 cells/μL</td>
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<tr>
<td>(3) &lt;200 cells/μL</td>
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### AUTOIMMUNE DISEASES

AUTOIMMUNE DISEASES


- Number of tender-swollen joints
- Duration of morning stiffness
- Level of daily functional abilities
- Complete Blood Count
- ESR
- RF
Does AIT protect?

- 18,841 AIT
- 428,484 Conventional treatment

Cox regression (survival analysis)

AIT vs Conventional treatment

✓ Lower mortality [Hazard ratios, 0.71; 95% CI, 0.62-0.81]
✓ Acute infarction [HR, 0.70; 95% CI, 0.62-0.81]
✓ Autoimmune disease [HR, 0.88; 95% CI, 0.74-0.99]


Immune disorders

Although concern about the safety of allergen immunotherapy in patients with autoimmune disorders has been raised in the past, there is no substantive evidence that such treatment is harmful in patients with these diseases. Therefore the benefits and risks of allergen immunotherapy in patients with HIV infection, other immunodeficiencies, or autoimmune disorders must be assessed on an individual basis.

Cox L, et al, JACI, 2011; 127; S1-S55
NEOPLASIAS

- Breast cancer (Stage I)
  - 3 months maintenance ➔ local tumor relapse (3b)
  - Surgery + Radiation + Chemo ➔ 5yrs VIT

- Cutaneous-Systemic Mastocytosis
  - Maintenance ➔ melanoma (no metastasis)
  - Surgery ➔ 5yrs VIT

- Melanoma during maintenance
  - Surgery ➔ no remission after 4 yrs

- Lung Adenocarcinoma (1a stage)
  - Started VIT 5th year of adc ➔ 5yrs no remission

Cancer and VIT

23 HVA patients (/1,099)
- 7 during VIT
- 10 before VIT
¬ 1 newly diagnosed
¬ 1 metastatic progression
6 completed VIT

11 HVA with cancer (/985)
- 7 started VIT
¬ 1 new tumor
2 completed VIT

Is VIT a risk factor?

Follow up of HVA patients
- 341 on VIT → 8 developed cancer (1-4 yrs after)
  - 4 stopped for chemo or surgery
- 312 under conventional treatment → 7 cancer
VIT can be introduced to a patient with cancer when severe Hymenoptera allergy occurs, but discontinuation may be considered if therapeutic priorities (such as chemotherapy or surgery) have changed.

Concluding suggestions

- Lack of communication
- Insufficient adherence
- Start during pregnancy
- β-blockers
- ACE-inhibitors
- MAO inhibitors
- Cardiovascular disease
- Infants
- Elder age
- Uncontrolled asthma
- Immunodeficiency
- Immunosuppression
- HIV
- Autoimmunity
- Malignancy