Clinical application of gene expression analysis in patients with insect venom allergy

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Primary objective: Is there a gene expression profile which may predict the long term effect of venom immunotherapy?Secondary objective: Which genes are differentially expressed after venom immunotherapy?

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Observational invasive

Summary

ID

NL-OMON33607

Source
ToetsingOnline

Brief title
Gene expression analysis in insect venom allergy

Condition

- Allergic conditions

Synonym
Hymenoptera allergy, insect venom allergy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: gene expression, immunotherapy, insect venom allergy

Outcome measures

Primary outcome

The main parameter of the study is the gene expression profile which may

predict the long term effect of venom immunotherapy.

Secondary outcome

1. The secondary parameter is the gene expression profile which will be

specific for patients with the highest risk at a systemic reaction at a resting

* before insect venom immunotherapy?

2. The tertiary parameter is the gene expression profile specific for patients

with the lowest risk of the systemic reaction to insect sting at the end of

maintenance phase of VIT?

Study description

Background summary

Insect venom allergy (defined as at least one life systemic IgE mediated reaction in lifetime after an insect sting) is present in approximately 1-3% of population [1].
The treatment of choice in insect venom allergy (IVA) patients is venom immunotherapy (VIT) with bee, wasp or Polistes venom. VIT has two phases: (1) a built-up phase where increasing amounts are administered until the maintenance dose of allergen has been reached and (2) a maintenance phase where the maintenance dose is administered every 4 to 6 weeks. The built-up phase lasts from 1 day to 7 weeks depending on the protocol. In the UMCG patients start at the day care reaching 1/10th of the maintenance dose, and continue in the outpatient clinic with weekly one injection with increasing amount of venom during about 6 weeks. At this time the risk at a systemic reaction to a subsequent sting is reduced from 70% (before the start of VIT) to 3% after reaching maintenance dose [5]. To reach long-term protection the maintenance

phase has to be continued during at least 3 years (in patients with mild systemic reaction, grade I-III Mueller) to 5 years (in patients with anaphylaxis (grade IV Mueller), enabling the lifelong prevention of anaphylactic reactions even after stopping VIT in most patients.
After stopping VIT the risk at a re-systemic reaction increases in some patients, in most patients it remains low. Unfortunately it is not possible to predict inefficacy in the individual patient. Some parameters are of influence. Firstly, the duration of treatment influences the risk at a re-systemic reaction: after 2 years of VIT the risk is higher than in patients where VIT has been stopped after 3- 5 years maintenance course (30% vs 3%) [1,5]. Secondly it is known that patients with side effects during treatment are more prone for inefficacy; prolongation of VIT is able to reduce the risk at a re-systemic reaction [1,5]. Thirdly, the amount of allergen might be not enough. It has been shown that continuation of VIT with an increasing dose (eg 200 ug) is able to reduce the risk in these patients [9]. Fourthly, it is known that it depends on the culprit insect: in wasp venom allergic patients: the long-term effectiveness of therapy is assessed as 85-95%, but in patients allergic to bee venom it is about 75-85% [1]. Fifthly, the severity of the sting reaction: the less severe, the better the protection. Overall it is known that 10-20% of subjects remain vulnerable to insect venom in spite of completion the treatment [2]. Unfortunately it is not possible to predict inefficacy of treatment so far [3,4,5,6,7].
The immunological mechanism(s) responsible for long-term protection achieved in VIT are mainly unknown [7]. It is hypothesized that it is related to mast-cell inactivation [7], a shift from Th2 to Th1 cytokine induction [8], lymphocyte Treg up regulation and T cell tolerance induction [8], monocytes activation [3] and/or suppressed antigen presentation by dendritic cells [8]. It seems quite likely that more than one pathway and more than one cell type are involved and responsible for the effect of VIT. Thus gene expression will be studied in peripheral blood using mRNA from all cell types without cell separation. Additionally the protocol of RNA isolation and gene expression analysis used in the protocol are standardized methods which avoid human laboratory errors and might by adapted to clinical practice in the future. Differences in gene expression will be studied in different patient groups: in group 1 (the long term protection after VIT was achieved * finished VIT, re stung without reaction) and 2 (the immunological mechanism responsible for protection was not effective* finished VIT, re stung with anaphylaxis) will be related to the gene expression in group 3 and 4 (resp. highest (before VIT) and lowest (3 to 5 years of VIT) -risk of systemic reaction after resting). The gene expression profile achieved after 3-5 years of VIT might be similar to the gene expression profile in patients who do not react after re-sting, whereas gene expression profile of those who react in spite of treatment might be comparable with untreated patients.
Better understanding of molecular differences in patients with venom allergy after completion of VIT may elucidate molecular modifications in pathways that predict ineffective treatment. This will enable to predict the necessity of modification of treatment in individual patients. The treatment may be modified

by (1) prolongation the treatment period or (2) increasing the dose of drug to improve the protection against anaphylaxis. The results of the project may also allow for creating new diagnostic methods of insect venom allergy.
If we find clear cut differences in the patient group we will seek to confirm this result in a larger group of patients in cooperation with the insect venom allergy interest group of European Academy of Allergy and Clinical Immunology.

Study objective

Primary objective:

Is there a gene expression profile which may predict the long term effect of venom immunotherapy?

Secondary objective:

Which genes are differentially expressed after venom immunotherapy?

Study design

Description This is an observational case-control study with a retrospective analysis of the follow up of the patients treated with VIT to evaluate to the long-term protection in patients who experienced a re-sting, comparing
1- those without a reaction at a re-sting after stopping VIT
2- to those who did experience a re-systemic reaction at a re-sting after stopping VIT
and subsequently compare the gene expression profile of these patients.
Patients will be recruited from the insect venom allergy database of Department of Allergology. .The patients will be asked if they are willing to visit the outpatient department and take part in the study.
In addition, two groups of patients will be studied to relate the results to the changes in gene expression during VIT:
3 - patients who routinely start VIT at the day care of allergology of UMCG
4- patients who routinely visit the outpatient department of allergology of UMCG after 3-5 years of VIT
The differences in gene expression profiles will be studied. Those subjects who react to a re-sting in spite of treatment with VIT probably have lost protection or never had protection induced by immunotherapy. In patients before VIT the risk at a systemic reaction when restung is about 70%, whereas in patients who completed VIT this risk is reduced to about 3% [1,5]. Thus the results in groups 3 and 4 are essential to understand the importance and findings in groups 1 and 2.

Duration of the study: 2008-2009

Procedures

Patients of group 1 and 2 will be asked to visit the outpatient clinic in order to collect blood samples (see above).
The samples in the group 3 will be taken just before the start of VIT in the hospital at the daycare. In the group 4 blood samples will be collected when routinely visiting the outpatient clinic after 3 to 5 years of VIT.

Study burden and risks

The proposed study has no risks for the health of investigated individuals.
The burden for patients in group 1 and 2 is related to the unscheduled visit in the outpatient department; therefore travel cost compensation is planned.
The burden for patients in group 3 and 4 is minimal because the blood samples will be taken as a routine procedure.
The benefit for patients is different with respect to the different patient groups. Subjects with a reaction after re-sting may prolong the immunotherapy or increase the dose of allergen used to gain better protection from systemic reactions after resting.
Remaining subjects will be informed about the results of the gene expression profile.
The results of the study might be important for the assessment of the risk of insect sting anaphylaxis and to advice on preventive methods to the individual patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria are the diagnosis of insect venom allergy based on medical history (grade IV according to Mueller before VIT), positive skin tests or sIgE and exclusion of mastocytosis

Exclusion criteria

Exclusion criteria are lack of consent, pregnancy, severe chronic or/and malignant disease, mastocytosis

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-01-2009
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL26199.042.08