Longitudinal follow-up of the new influenza A/H1N1 virus infection in vivo and in vitro in healthy volunteers

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Ethical review	Approved WMO
Status	Pending
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON34108

Source
ToetsingOnline

Brief title
Influenza-trial

Condition

- Viral infectious disorders

Synonym
flu, influenza A (H1N1)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: B-cells, humoral immune response, New influenza A/H1N1 virus, T-cells

Outcome measures

Primary outcome

A. Frequency of in-vitro responding clones during follow-up of the new

influenza

A/H1N1 virus infection.

B. Functional characterization of individual responding clones.

C. Correlation of T-cell responses with antibody responses.

Secondary outcome

A. antibody titers of 1:40 or more on hemagglutination-inhibition (HI) assay to

quantify the presence of specific antigens.

Study description

Background summary

Influenza is a very common virus that causes considerable morbidity and mortality in the worldwide population on a yearly basis. Moreover, it has a perceived pandemic potential, illustrated recently by the pandemic of the new influenza A/H1N1 virus. (1, 2) Although there is abundant knowledge on the make-up of the influenza virus (3), many facets of the human response against this virus remain unknown. Gaining knowledge on these responses will help us in treating influenza infections and lead to more effective vaccines. Additionally, it might also lead to identification of individuals that have a high risk of morbidity and even mortality during infection.

Up till now, research of influenza responses has mainly focused on antibody responses. This has a practical background, as antibodies can easily be measured in blood, but also as it is thought that antibody responses are the most important mechanism by which the immune system combats influenza viruses. This notion is supported by successful (antibody) protection following vaccination.

Recently, research also turned to the role of T cells in influenza infections as they are the primary responding cells during infection, especially in the absence of protective antibody titers. Moreover, it was stated that T-cell responses have a better predictive value for influenza protection than antibody titers (4). Therefore, T-cells might play a more prominent role than anticipated so far.

However, investigation of T-cell responses, but also of B-cell responses is hampered by limitations. Due to the huge repertoire of T- and B-cell receptors in the human body, it is very difficult to identify (and follow) individual T- and B-cell responses. Recently, a new technique was developed within our department which is able to find and follow individual clonal responses without having any prior knowledge of what these clones look like (5). By combining this technique with recently developed in-vitro stimulation assays, we are for the first time able to identify clones which play a functional role in influenza infections and follow them over time.

This project is embedded in a new research line that has been set-up in the AMC. This research line is a collaboration between the clinical immunology and rheumatology department, the lab of genome analysis and multiple partners in immunology and infectious diseases (e.g. Prof. Dr. R. van Lier/Prof. Dr. I. ten Berge/ Prof.Dr. U. Beuers). We feel this study will not only give us insight in the role of T- and B-cells during viral infection, it can also lead us to a better understanding of the pathology of infectious diseases (such as acute viral infections and auto-immune disease).

Study objective

In this study we will for the first time combine in-vitro stimulation assays and high throughput sequencing to identify, quantify and phenotype the clones that play a functional role in influenza infections and follow them over time. This will lead to the identification and characterization of functional clones.

We want to study otherwise healthy volunteers undergoing new influenza A/H1N1 infection. Since it is very likely that the H1N1 pandemic is returning to the Netherlands in the spring of 2010, we expect to be able to recruit our volunteers through GP practices throughout Amsterdam. They will be seen at the AMC hospital.

Study design

This is a longitudinal study in which we want to investigate the effect of new influenza A/H1N1 virus on the humoral immune system. We will look for individual clonal responses in both the T-cell as well as the B-cell compartment and follow these cell clones over time.

The study will consist of eight visits. In the first visit, the volunteers will be included with confirmed H1N1 infection. This will be confirmed by a routine hospital test (PCR). In all visits we will note relevant clinical parameters and draw blood.

Taken Amount
Purpose Time points
Non-heparinised blood (PAXGene) 2 mL - Full repertoire analysis (T/B cell) Day 0-4

Day 7

Day 14

Day 28

Day 56

Day 84

Day 112

Day 140
Heparinised blood 70-80 mL - Cellular subset analysis (T/B cell) Day 7

- In vitro stimulation assays Day 84
Serum 3 mL - HI assay

Total amount of blood drawn per individual: 70-80ml (2x) + 2ml (8x) = 156*176ml

The following procedures will be performed:
Serum will be separated from whole blood for start of symptoms
PBMC will be isolated from heparinised blood according to standard operating procedures.
* PBMC will be used to look for individual B- and T-cell clones in specific subsets during acute infection and the formation of memory.
* PBMC will be used to study the effects of stimulation with the new influenza A/H1N1 virus on B- and T-cells and the formation of functional clones.

Non-heparinised blood * collected in PAXGene Blood RNA tubes * will be isolated according to standard operating procedures.
* RNA will be used to look for individual B- and T-cell clones in peripheral blood during acute infection and the formation of memory.

Hemagglutination-inhibition (HI) assay will be performed on serum.
* Antibody titers will be determined to quantify the presence of specific antigens.

Study burden and risks

In total, 160-180mL of blood is drawn.

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

- Able and willing to give written informed consent
- Age 18-85 years
- PCR-confirmed new influenza A/H1N1 infection with symptoms present for less than 4 days.

Exclusion criteria

- Therapy within the previous 60 days with:
* any experimental drug
* monoclonal antibodies
* growth factors
* other anti-cytokines
- Therapy within the previous 28 days with:
* anti-viral medication
* parenteral corticoid injections
* oral corticosteroid therapy exceeding a prednisone equivalent of 10 mg daily
- Any clinically significant medical condition
- Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2010
Enrollment:	10
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Amsterdam UMC

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	NL32160.018.10