Biobanking, identification of biomarkers and the study on immune system in patients with multiple sclerosis

Published: 07-11-2013
Last updated: 26-04-2024

The objectives of this initiative are:1. To establish the disease oriented biobank; processing and storage of blood and CSF specimens and health information of MS patients (which may include health records, family history, lifestyle and genetic...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Observational non invasive

Summary

ID

NL-OMON37545

Source
ToetsingOnline

Brief title
MS biobank

Condition

- Autoimmune disorders
- Demyelinating disorders

Synonym
multiple sclerosis; MS

Research involving
Human

Sponsors and support

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

Intervention

Keyword: biobanking, biomarkers, immune system, multiple sclerosis

Outcome measures

Primary outcome

not applicable

Secondary outcome

not applicable

Study description

Background summary

Biobanking
A biobank is a collection of body fluids (blood, CSF), isolated cells and/or tissue donated by healthy volunteers and/or patients with linked medical information which is made available for further biomolecular and medical research. The Nijmegen MS biobank is a disease-oriented biobank, since the specimens will be collected in the context of medical diagnosis and treatment. Biobanks will provide a resource for researchers to increase their understanding of complex disease such as MS because of its variable course, complexity and heterogeneity. The ability to compare different disease stages and/or forms of treatment at a molecular level is instrumental for finding biomarkers for diagnosis of a disease or prediction of disease progression.

Biomarker discovery
MS is difficult to diagnose at early stages, as the MS signs and symptoms can be similar to those of other diseases and clinical examinations combined with MRI have to be applied. There is an urgent need for minimally invasive, highly sensitive and specific diagnostic and prognostic biomarkers to identify and monitor MS. Biomarkers may aid in diagnosing MS, predicting disease onset, and selecting appropriate therapy. Biomarker discovery will include nucleic acid analysis, proteomics, and the identification of (auto) antibody/autoantigen markers.

Reversion of pathologic autoimmune response
Currently, there is no cure for MS. Instead, available drugs are symptom-reducing immunosuppressing drugs that only delay the inevitable progress of the disease. As these have to be taken for long periods of time to

be effective, the long-term side-effects can be very serious (cancer, infections). The aim of this subproject is to investigate a novel concept to stop the progress of the disease by a therapeutic vaccination. This stops the disease-causing pathologic autoimmune response by inducing tolerance towards specific autoantigens. In this way, the cause of the disease and further progress of the disease can be prevented. To investigate this concept, cells and serum are necessary to determine whether ex-vivo dendritic cells and pathologic autospecific T cells can be stimulated with this therapeutic vaccine such that tolerizing mechanisms are induced and tolerance towards the autoantigen will be induced. This may be the lead towards a curing treatment for MS as well as other autoimmune diseases.

Study objective

The objectives of this initiative are:
1. To establish the disease oriented biobank; processing and storage of blood and CSF specimens and health information of MS patients (which may include health records, family history, lifestyle and genetic information);
2. To develop a diagnostic test for early MS based upon molecular biomarkers (DNA, RNA, proteins, and antibodies) present in sera and CSF;
3. To establish a new therapeutic vaccine approach for MS treatment based on induction of tolerance to autoantigens.

Study design

All patients who come to visit the MS center and satisfy the inclusion/exclusion criteria will be invited to participate in the study. Prior to data assessment and specimen collection, each patient will be given the Patient Information and Consent Form. There will also be an invitation for the MS patients to participate in this initiative and donate blood and/or CSF on the website of Radboud MS Center Nijmegen. Participants will be asked to provide extra blood and/or CSF, if CSF will be taken (see Research protocol; Table 1). Blood and CSF will be taken simultaneously for routine clinical tests and for the studies with only one venipuncture or lumbar puncture. Extra blood and/or CSF specimens will be used for biobanking (Dr. B.A. de Jong), for the study on MS biomarker discovery (Prof. G Pruijn) and for therapeutic vaccine study (Dr. ir.T. Luijkx).

Biobank establishing
Invasive standard procedures such as venipuncture to collect blood specimens and in some cases lumbar puncture to collect CSF will be performed. To get serum samples, 20 ml of blood will be collected into serum gel (brown, 7.5 ml) tubes. To get plasma and blood cell fraction, 10 ml of blood (or 60 ml in case if a patient is involved in the immunological study) will be collected into EDTA tubes. 2 ml of blood will be collected into Paxgene blood DNA tubes for blood collection, stabilization and isolation of genomic DNA. The blood

collection will be performed according to Standard Operating Procedures for the Collection of Blood Samples of the local institution. Patients will be also asked to fill the survey form (attached) to provide health information.
After the specimens has been collected, participant*s name and any identifying features will be replaced with the Subject Identification number (SIN).
The blood and CSF samples will be processed at the place where the collection has occurred or transported to additional sites at the Department of Biomolecular Chemistry (Prof. G Pruijn) and the Department of Medical Immunology (Dr. T. Luijkx), Radboud University (Nijmegen). Blood samples will be processed into following components for long term storage; plasma, serum, and white blood cells. Appropriate aliquoting of specimens will be carried out. Labeled cryovials will be stored in -80°C freezers. Effective tracking systems to track specimens from the site of collection to their arrival in the repository will be installed. Critical components of these systems include unique specimen identifiers, appropriate specimen labels and inventory systems for specimen tracking. Each specimen container will receive a label that tightly adheres under all projected storage conditions.

Biomarker discovery.
Preclinical discovery phase: The identification of exploratory biomarkers (markers in early development) suited for diagnostic use. Several techniques will be used for biomarker development. This step will be performed with a limited number of human serum/CSF samples (n=20 patients per group).
- Nucleic acid and epigenetic analysis: This step will include studies on circulating miRNA and DNA methylation pattern in sera/CSF. Methylated DNA and small RNA library will be generated and validated using high throughput sequencing. Selection of discriminating DNA and RNA molecules by their correlation with different phases of the disease will be performed.
- Proteomics: it will employ analysis of protein composition in blood/CSF over the disease course using mass spectromic approach and identification of possible biomarker candidates. As a first step protein fractionation to deplete highly abundant proteins will be performed. Mass spectrometry will be applied and the list of protein candidates will be generated.
- Identification of MS-associated antibody biomarkers: peptide library screening. Combinatorial libraries of synthetic peptide (antigens) will be used to screen for ligands that bind antibodies abundant in the serum/CSF of MS patients but not healthy controls. Peptide libraries will be screened with pooled immunoglobulins isolated from MS patients.
Preclinical verification:The results from preclinical discovery phase will be tested with sufficient power in a larger defined clinical setting in an independent, prospective cohort of patients (n=35 patients per group). This phase may generate information which may be included into clinical guidelines.

Induction of tolerance to autoantigens
Peripheral blood mononuclear cells (PBMC) will be isolated from blood of MS patients and healthy controls and cultured with auto-antigens under certain conditions. Next, cytokine measurements will be done to assess whether specific

pathogenic T cells can be downregulated or skewed towards a regulatory phenotype (Treg). This would confirm a concept to reverse a pathogenic auto-immune response and induce tolerance to auto-antigens which can be used to develop a curing treatment for MS patients.

Study burden and risks

Risks and burdens: Risk is negligible and the burden is minimal. The most common risks related to drawing blood from patient arm are brief pain and/or bruising. Infection, excess bleeding, clotting or fainting is also possible but unlikely.

Possible benefits: There will not be a direct benefit. However, participation of patients can help researchers to gain knowledge and make discoveries which might help in the future to diagnose or treat patients in a better way.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Reinier Postlaan 4
Nijmegen 6525 GC
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Reinier Postlaan 4
Nijmegen 6525 GC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

-Individuals must be at least 18 years old and able to give informed consent.
-Individuals must have one of the diagnoses: clinically isolated syndrom, relapsing-remitting MS, primary progressive MS, secondary progressive MS, neuromyelitis optica, transverse myelitis, and radiologically isolated syndrome.
-Individuals must be willing and able to provide blood and/or cerebrospinal fluid in addtion to requirement for clinical analysis

Exclusion criteria

-Patients currently diagnosed with an autoimmune disorder other than MS.
-Patients with ongoing bacterial, viral, or fungal infection.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2013
Enrollment:	2000
Type:	Anticipated

Ethics review

Approved WMO

Date:	07-11-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL39513.091.12