Immunotyping lymph nodes in immune-mediated inflammatory diseases (IMIDs): lymph node cellular and molecular biomarkers in IMIDs

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

Summary

ID

NL-OMON55414

Source
ToetsingOnline

Brief title
Immunotyping lymph nodes in immune-mediated inflammatory diseases (IMIDs)

Condition

- Autoimmune disorders
- Joint disorders

Synonym
chronic inflammatory diseases, IMID

Research involving
Human

Sponsors and support

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

Intervention

Keyword: biomarker, IMID, lymph node, pathogenesis

Outcome measures

Primary outcome

Differences in lymph node cellular composition and functional aspects in patients with established IMIDs, pre-clinical patients eventually developing IMIDs compared to pre-clinical patients that do not develop IMIDs, and of lymph nodes of first degree relatives compared to patients with IMIDs, all compared to lymph node tissue of healthy controls. Additionally, differences in cellular composition and functional aspects between lymph nodes and synovium/MRI in patients with established IMIDs or pre-clinical patients at risk of developing IMIDs (optional).

Secondary outcome

not applicable

Study description

Background summary

Immune-mediated inflammatory diseases (IMIDs) refers to inflammatory arthritic and systemic inflammatory diseases. Examples of these diseases are rheumatoid arthritis (RA), spondyloarthritis (SpA), osteoarthritis (OA) and gout, systemic lupus erythematosus (SLE), Sjogren*s Syndrome (SS), systemic sclerosis (SSc), IgG4-mediated disease and various forms of vasculitis. The cellular and molecular alterations of the immune system (the immunotype) driving these diseases still remain largely unknown. Accordingly, it remains difficult to

correctly diagnose and classify these diseases at an early stage and to predict the evolution of the disease in an individual patient. Moreover, despite the development of a variety of novel and powerful drugs (including the so-called biologicals), the patient*s response to treatment remains heterogeneous and difficult to predict, and no curative therapies exist. Therefore, there is a clear need for the identification and validation of cellular and molecular biomarkers which reflect directly the immunotype of a given disease and can provide useful clinical information for diagnosis, classification, prognosis and treatment, as well as the development of new therapeutic strategies. Biomarkers of the immunotype can be found and analyzed in different body compartments, of which the peripheral blood and the intra-articular synovial fluid or tissue are most easily accessible. However, previous studies in RA and other IMIDs showed that adaptive immune responses take place before clinical signs of arthritis or inflammation in other tissues are present. Investigating other immune compartments of the body such as the lymph nodes could reveal early driving pathogenic mechanisms, because the immune response in lymph nodes generally precedes the influx of effector immune cells into the target tissue. To study the early pathogenesis of inflammatory arthritic conditions, in 2008 our department initiated core-needle inguinal lymph node biopsy sampling. Since then we performed more than 80 lymph node biopsy procedures. We showed that the procedure is generally well tolerated and that, other than a small hematoma which does not require therapy in most of the cases, no complications were reported. In the current study, we aim to extend our analyses by investigating and comparing the pathogenesis of different IMIDs by studying the immune alterations taking place in lymph nodes during early and pre-clinical disease in comparison to peripheral blood ánd immune alterations taking place in the endorgan, e.g. the joint (knee or ankle) by taking synovial biopsies during a mini-arthroscopy. This procedure has been performed frequently in our department over the last 15 years and we have ample expertise. Recently, new MRI techniques have become available that are able to quantify joint inflammation more accurately (hitherto only tested in children). Therefore, we want to perform an MRI of the joint that will be biopsied later. In this way we will be able to asses and compare immune alterations in the lymph nodes (secondary lymphoid organ), peripheral blood (systemic) and the joint (end organ for the disease).

Study objective

The primary goal of this study is to identify immunological alterations in lymphoid tissue of patients with various forms of inflammatory arthritis and systemic inflammatory diseases, and to correlate these alterations with diagnosis, disease stage, prognosis, and treatment response. We aim to identify and validate novel biomarkers that can be used for personalized medicine in IMIDs.

The specific types of immunological alterations that we will study include: TCR and BCR repertoire, phenotype and function of (auto-reactive) T and B cells,

cytokine production by innate immune cells and stromal cells, genetic, epigenetic and transcriptional alterations of immune cells and stromal cells, signalling events in immune cells and stromal cells, antigen presentation and immunomodulation by stromal cells

All these parameters will be compared between lymph nodes, blood and joint (synoviumbiopsies and MRI, optional) in different diseases, between different patients within one disease, and between different phases of the disease to determine their potential value as disease biomarker.
To interpret our findings, inclusion of autoantibody-negative healthy controls and (autoantibody positive) patients at risk of developing IMIDs, as well as first degree relatives of certain patient groups is crucial.

Study design

Patients with IMIDs will be recruited from the outpatient clinics of the Amsterdam Rheumatology and immunology Center (AMC, VUmc and Reade) and referred to the AMC for participation in this study. Any patient with arthritis or inflammatory systemic disease from known (e.g. RA, SpA, OA, UA, crystal arthropathies, SLE, SS, SSc, vasculitis) or unknown origin can be included in the study. Demographic data and clinical data regarding classification of diagnosis, medication use and disease activity will be collected. In total 600 patients will be included starting march 2018 with an inclusion period of 3 years. In addition, we will include patients who are at risk of developing IMIDs, first degree relatives of patients with IMIDs 18-40 years old, autoantibody-negative healthy controls, in order to better understand pathogenetic processes leading to the development of clinically manifest RA, SpA and other IMIDs. Lymph node and blood samples will be obtained in all individuals. From patients with an IMIDs or an increased risk of developing an IMID, mini-arthroscopy for synovial biopsies and/or MRI will be performed if patients are willing (optional).

Study burden and risks

The risk of developing a hematoma after the biopsy is approximately 3%. This will heal spontaneously. Mini-arthroscopy gives a small (<0,3%) risk on a hematoma, bleeding or infection. MR imaging does not give any additional risk, besides a possible allergic reaction to the contrast agent. The contrast agent used is however the same as used in standard clinical practice.
The patient will visit our outpatient clinic several times. Total duration: 5 hours.
For the healthy controls the total study duration will be 1,5 hours.

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

IMID patients
patients at risk of developing IMID
first degree relatives of IMID patients
healthy controls

Exclusion criteria

patients unable to give informed consent

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-05-2018
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	17-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2021
Application type:	Amendment

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	NL52469.018.15