Changes in the lymph nodes during the earliest phases of rheumatoid arthritis

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In this project we will perform lymph node tissue analyses in 1) autoantibody-positive individuals who are at risk of developing RA, 2) early arthritis patients who do (RA) or do not (yet) (unclassified arthritis, UA) fulfil 2010 ACR/EULAR...

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

Summary

ID

NL-OMON38509

Source
ToetsingOnline

Brief title
Lymph nodes in the earliest phases of rheumatoid arthritis

Condition

- Autoimmune disorders

Synonym
arthritis, Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Veni grant van NWO

Intervention

Keyword: Immune system, lymph nodes, rheumatoid arthritis

Outcome measures

Primary outcome

1) Differences in phenotype of B-/T-cells/dendritic cells and gene expression

in:

- autoantibody-positive individuals who do/do not develop RA

- autoantibody-positive individuals in comparison to autoantibody-negative

healthy controls

- autoantibody-positive individuals in comparison to early RA/UA patients

Secondary outcome

2) antigen specificity of these involved immune cells.

3) involvement of the stromal microenvironment of the lymph nodes in the

development of RA.

Study description

Background summary

The RA-specific autoantibodies IgM rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can be present 10-14 years before the development of RA. However, only a subset of the individuals who are positive for RF and/or ACPA will develop RA over time. Currently, it is unknown which subset of these autoantibody-positive individuals will make the transition to the development of clinically apparent RA and which subset will not, and why.

The fact that there are no clear signs of synovial inflammation (the synovium is the main target tissue for inflammation in RA) in autoantibody-positive individuals who subsequently develop RA suggests that synovial inflammation develops in a (sub)acute way, which hampers studies of the target tissue during

the transition phase from being autoantibody-positive, and thereby at risk for developing RA, to clinically apparent disease. This underscores the importance of investigating other immune compartments than the synovium as well. As a general principle, the recruitment of activated immune cells to the site of inflammation is initiated after informing a nearby lymph node of a danger signal. Thus, the immune reaction in lymph nodes generally precedes the influx of effector cells into the target tissue. These results support our original idea that we should additionally focus on the lymph nodes to get more insight into the pathogenesis of the earliest phases of RA.
Using flow cytometry analysis we have already observed an increase in activated CD8 positive CD69 positive T cells in early arthritis patients compared to healthy controls. This may be in line with animal models of arthritis showing a decreased CD4/CD8 ratio in lymph nodes before the onset of arthritis. However, since none of the autoantibody-positive individuals in this cohort had as yet developed arthritis, due to a short follow up period, future studies are needed to confirm this. Second, we observed an increase in CD19 positive B cells in early arthritis patients compared to healthy controls and a similar trend for the autoantibody-positive individuals compared to healthy controls. The latter would be in line with findings in animal models of arthritis.

Study objective

In this project we will perform lymph node tissue analyses in 1) autoantibody-positive individuals who are at risk of developing RA, 2) early arthritis patients who do (RA) or do not (yet) (unclassified arthritis, UA) fulfil 2010 ACR/EULAR classification criteria for RA, and 3) autoantibody-negative healthy controls, in order to better understand pathogenetic processes leading to the development of clinically manifest RA.

In this project builds on our earlier findings in about 80 persons and will expand our knowledge.

We will pursue on the initial findings by:
1) further characterization of T-cell/B-cell/DC subsets and identification of antigen-specificity in association with the development of RA, and their antigen specificity.
2) evaluation of B- cell receptor (BCR) and T-cell receptor (TCR) repertoire.
3) identification of molecular processes involved in the earliest phases of RA pathogenesis.

Study design

Observational cohort study with invasive procedure extending earlier findings

Study burden and risks

In total study participants will take part for 2 hours (healthy controls, early RA/UA patients, autoantibody-positive individuals who do not develop RA) or 3 hours (autoantibody-positive individuals who do develop RA) in this study.
If applicable, study participants will have to stop anticoagulant therapy 3 days before until 1 day after the lymph node biopsy procedure. This will be done in agreement with the patient and if necessary with the treating physician.
The lymph node biopsy procedure is generally well tolerated. Only a small hematoma requiring no therapy occurs in most of the cases.

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

Healthy controls: negative for IgM-RF and anti-CCP antibodies
Autoantibody-positive individuals: positive for IgM-RF and/or anti-CCP antibodies + either

arthralgia or a first degree relative with RA.
Early arthritis patients: arthritis < 1 year, disease-modifying antirheumatic drug (DMARD) naive + classified as RA according to the 2010 ACR/EULAR criteria for RA or as unclassified arthritis (UA).

Exclusion criteria

For all individuals:
- Current/previous use of disease modifying anti-rheumatic drugs (DMARDs).
- If applicable: patients in whom anticoagulant therapy cannot be temporarily stopped before the procedure
- Systemic prednisolone use less then 28 days before enrolment
- Present or previous treatment with any cell depleting therapies, including investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
- Presence of any disease for which study subjects need chronic or intermittent immunosuppressive therapy (e.g. prednisolone for COPD).
- History of chronic viral infection
- History of autoimmune diseases
- History of malignancies

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:	Recruitment stopped
Start date (anticipated):	23-10-2013
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	30-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2014
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	NL44446.018.13