Towards prevention of chronic auto-immune disease: dominant B-cell receptor clones predict the onset of rheumatoid arthritis

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Overall aim: Understand the function of BCR clones in the initiation of RASpecific objectives: • Find discriminating surface markers for dominant clones;• Perform single cell transcriptome sequencing to find distinguishing activated inflammatory…

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

Summary

ID

NL-OMON45295

Source
ToetsingOnline

Brief title
BCR clones in preRA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatism, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO,reumafonds

Intervention

Keyword: B-cell receptor, next-generation sequencing, preclinical phase of disease, rheumatoid arthritis

Outcome measures

Primary outcome

The inclusion of approximately 75 individuals who have RA associated

autoantibodies and arthralgia, in whom we successfully collect blood (and

tissue) samples to study dominant clones. Completion of the study period or

development of RA will mean the end of the study.

Secondary outcome

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Study description

Background summary

Rheumatoid arthritis (RA) is a prototypic autoimmune disease affecting approximately 1% of the general population [1]. Inflammation of joint tissue is the hallmark of disease, but the pathogenesis remains to be elucidated. Currently, there is no cure for this disease. Drugs need to be taken on a chronic basis to alleviate pain and prevent joint damage [1]. Interestingly, it might be feasible to prevent RA from occurring.

The rationale lies in the observation that the onset of RA is preceded by a phase of systemic auto-immunity (preclinical phase) [2]. During this phase specific autoantibodies are present in the blood, but there are no signs of inflammation in the joints yet. Individuals with such autoantibodies have a 20-30% to develop RA [3]. This phase truly forms a window of opportunity to intervene with disease development. If we succeed in understanding what causes these at-risk individuals to develop RA, we might be able to prevent the

disease.

In this context, we recently identified a population of B-cell receptor (BCR) clones that is only present in the blood of autoantibody-positive individuals who will proceed to full-blown RA (see preliminary work). Once RA becomes manifest, these clones migrate to the inflamed joint tissue. We hypothesize that these BCR clones are pathogenic and consequently form an attractive target for preventive therapies. The challenge lies in proving that these otherwise poorly characterized cells are pathogenic. To target these clones (demonstrating their pathogenicity) we aim to develop intervention strategies in this project to do so while further characterizing these BCR clones.

As such this project helps to understand if specific BCR-clones contribute to the initiation of RA and focuses on prevention of RA, which is an unmet need in the field. The results will also be of relevance for other diseases in which auto-reactive BCR clones are thought to play a role such as vasculitis, Sjögren*s disease, celiac disease and type 1 diabetes.

Importantly, this research is a follow up on the earlier by METC approved studies conducted in the AMC regarding this subject (MEC 05/107 #05.17.0858 *Pre-synoviomics advanced genomics initiative in pre-clinical arthritis* and MEC 09/048 #09.17.1872 *Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease (PRAIRI)*). The promising results of these studies have been an important incentive to resume research in this field. Of note, in contrast to the aforementioned studies, this is a less invasive study (without repeated biopsies.

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108. Epub 2010/09/28. doi: 10.1016/S0140-6736(10)60826-4. PubMed PMID: 20870100.
2. van Schaardenburg D, Dijkmans BA. Clinical approaches to early inflammatory arthritis. Nature reviews Rheumatology. 2009;5(11):627-33. Epub 2009/09/30. doi: 10.1038/nrrheum.2009.203. PubMed PMID: 19786990.
3. Bos WH, Wolbink GJ, Boers M, Tijhuis GJ, de Vries N, van der Horst-Bruinsma IE, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Annals of the rheumatic diseases. 2010;69(3):490-4. Epub 2009/04/14. doi: 10.1136/ard.2008.105759. PubMed PMID: 19363023.

Study objective

Overall aim:
Understand the function of BCR clones in the initiation of RA

Specific objectives:
• Find discriminating surface markers for dominant clones;
• Perform single cell transcriptome sequencing to find distinguishing activated

inflammatory genes/pathways;
• Determine specificity of dominant clones against known and unknown auto-antigens;
• Evaluate whether clones are pro-inflammatory

The results of this study will helpsto understand if specific BCR-clones contribute to the initiation of RA and focuses on prevention of RA, which is an unmet need in the field. The results will also be of relevance for other diseases in which auto-reactive BCR clones are thought to play a role such as vasculitis, Sjögren*s disease, celiac disease and type 1 diabetes.

Study design

This is a prospective study in approximately 75 participants with increased risk of developing RA (arthralgia and high IgMRF and/or anti-CCP) who will accept to participate by signing a written Informed Consent prior to study sampling. The collection of samples of blood and synovial tissue will be used for in vitro cellular assay(s). The total duration of the study is 6 years, consisting of a 36 months inclusion period and up to 36 months for patient participation.

Inclusion visit: This visit takes up to 1 hour. We will get to know the participants and inform them about the study. If they agree to participate, then they will sign the informed consent prior to any study related action. We will take the demographic data, medical history, medication use and perform a global physical and joint examination resulting in a DAS-28 score for each participant. 2,5ml blood for PAXgene, 4 ml for EDTA, 4ml of IgMRF and anti-CCP and 8,5ml for ESR and CRP will be drawn to conclude this visit. The total blood drawn in this visit is 19ml. This blood can then be used to identify the participants with dominant B cell receptor clones in the blood. Participants without dominant BCR clones will form the control group for those with dominant BCR clones.

Visits 1-6: There will be 6 fixed study visits every half year and 1 variable study visit, spread out over 3 years. The visits will take up to 30 minutes each. During these visits we take the medication use, the current complaints, if infections have arisen and perform joint examination. In visit 6 or when arthritis develops, inflammatory parameters (ESR, CRP 8,5ml) will be determined, in addition to 2,5ml PAXgene and 70ml heparin for PBMC isolation that we will draw in each of these visits. This blood can be used for FACS, cell sorting and sequencing experiments.

The study ends for participants in case they develop arthritis or if they complete the trial period. In participants that develop arthritis, we draw blood once more as in visit 6. Furthermore, in these patients, a mini-arthroscopy will be planned to obtain tissue samples. Afterwards, the patients will directly be enrolled in regular clinical care and will be

treated. Beneficial to the participants is that they will remain under clinical supervision every 6 months, will have immediate access to care when they develop arthritis and will be treated very soon after disease manifestation.

Study burden and risks

This is a study without any interventions, except for blood withdrawal and synovial tissue biopsies during mini-arthroscopy in patients who develop arthritis. We do not expect any serious adverse events (SAE) from venepuncture. There are very small chances of bleeding after the mini-arthroscopy. If a SAE occurs, this will immediately be reported to the METC.

The participants will be invited several times to come to the hospital during the research period.

Inclusion visit: One visit of approximately 60 minutes. We do not expect any difficulties regarding the joint examination and blood withdrawal.

Other visits: Participants will visit every 6 months for a total period of 36 months. These visits take up to 30 minutes each. We do not expect any difficulties regarding the joint examination and blood withdrawal. When an arthritis develops during the research period, we can react quickly. The patients will undergo a mini-arthroscopy to gather synovial biopsy. Clinically this technique is performed frequently and is safe. The risk of a serious adverse events is low (1%). Furthermore, the mini-arthroscopy might aleviate pain.

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

Male and female patients of more than 18 years old diagnosed with arthralgia and anti-citrullinated peptide antibodies and/ or rheumatoid factor.
- Having given written informed consent prior to undertaking any study-related procedures.
- Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

Exclusion criteria

- Under any administrative or legal supervision.
- Conditions/situations such as:
• Patients with conditions/concomitant diseases making them non evaluable for the primary endpoint
• Impossibility to meet specific protocol requirements (e.g. blood sampling)
• Patient is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol
• Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-06-2017
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO

Date:	01-03-2017
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	NL59944.018.16