Understanding B cell biology in auto-immune diseases.

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

Summary

ID

NL-OMON53019

Source
ToetsingOnline

Brief title
Understanding B cell biology in auto-immune diseases.

Condition

- Autoimmune disorders

Synonym
Autoimmune diseases, Rheumatic diseases

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: NWO Clinical Fellowship grant (to H.U. Scherer);NWO VENI grant (to H.U. Scherer);NWO VIDI grant (to H.U. Scherer),Genmab,Janssen Research & Development LLC,Reumafonds project (to H.U. Scherer);IMI-funded project RTCure (Europeese Unie;to T.W.J. Huizinga)

Intervention

Keyword: auto-immune diseases, B cell biology, Blood, Synovial fluid

Outcome measures

Primary outcome

Various parameters related to the phenotype and function of auto-reactive B

cells

Secondary outcome

Not applicable

Study description

Background summary

Background
This protocol is part of a longstanding research line of our department that investigates the pathophysiology of rheumatic diseases. Our studies on auto-reactive B cells have so far focused on one prototypic rheumatic autoimmune disease: rheumatoid arthritis (RA). The majority of RA patients harbour antibodies against citrullinated protein antigens (ACPA). ACPA are highly disease specific biomarkers that associate with destruction of joints, the pathological hallmark of RA. ACPA presence pre-disease prognosticates RA development, implicating crucial involvement of ACPA in relevant disease-initiating processes. Experimental data support this notion as infusion of ACPA in mice exacerbates arthritis. Moreover, ACPA trigger a variety of inflammatory processes in vitro. Likewise, genetic variants in genes that encode peptidyl arginine deiminases, the enzymes that generate citrullinated antigens, are risk factors for RA. Together, these observations suggest that ACPA and/or the citrullinated antigen-specific B cell response have a central role in RA pathogenesis.

Study objective

Aim of the study
We intend to study in detail the different aspects of B cell biology in the auto-immune diseases outlined above. With the sample material obtained from patients (see below), we will be able to analyze (auto-reactive) B cells and their functional requirements, the interaction with other cells of the immune

system or with stromal cells, the characteristics of the autoantibodies in serum and those produced in culture, as well as functional and molecular aspects of relevant autoantibodies. The studies will include phenotypic analysis of B cells and their interaction partners by flow cytometry and mass cytometry, transcriptomic analyses of isolated B cells, B cell receptor sequencing analyses, single cell cultures and co-culture systems, migration assays, and functional studies including the analysis of secreted autoantibodies by proteomics/glycomics techniques such as mass spectrometry, UPLC and comparable methods. The data obtained need to be analyzed in the light of clinical characteristics such as disease activity, disease duration, treatment and age and sex of the patient. Of note, it is crucial to perform these studies on material from patients, as suitable murine models are not available for the types of auto-reactive B cell responses that we intend to study.

Study design

To achieve our goals, we intend to collect peripheral blood from consecutive patients with clinically suspect arthralgia, rheumatoid arthritis, systemic lupus erythematodes, ANCA-associated vasculitis, and systemic sclerosis. In case patients display arthritis as one of the clinical symptoms and arthrocentesis is performed as part of the clinical diagnostic or therapeutic work-up, also synovial fluid will be studied. Both the cellular and humoral components will be isolated from the material collected. The cellular component will be used to isolate immune cells such as total PBMCs, B cells, T cells and others. Isolated cells will be characterized phenotypically using cell-surface markers (FACS) and functionally in cell type-specific assays (e.g. proliferation, cytokine secretion, in-vitro culture system for autoantibody-producing B cells). The humoral component (serum/plasma/synovial fluid) will be used for measurement of various soluble factors related to the function of B cells, such as (auto-) antibodies, complement factors, coagulation factors, cytokines etc.

Study burden and risks

Potential risks and benefits
Blood sampling will occur at the central blood draw facility *prikpost* of the LUMC (currently located at C2). Therefore, the risks of this study are limited to the collection of peripheral venous blood and includes pain at the place of puncture, hematoma formation and, rarely, short moments of hypotension. These symptoms are usually mild and recover fully. The central blood draw facility is trained and equipped to handle these events appropriately. The aspiration of the synovial fluid will be performed by a rheumatologist but only when he/she decides that this is required for optimal medical care. The participants do not benefit from this study but their participation could lead to improved future therapeutic care.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria patients
- Age 18 years or older (no minors or incapacitated subjects will be included in the study)
- Ability to understand the patient information form and ability to provide written informed consent.
- a definite diagnosis of rheumatoid arthritis, systemic lupus erythematodes, ANCA-associated vasculitis, or systemic sclerosis based on current classification criteria or
- fulfilment of the current classification criteria for *clinically suspect arthralgia* in the concomitant presence of ACPA in serum.
- Written informed consent

Inclusion criteria healthy subjects:
- Age 18 years or older (no minors or incapacitated subjects will be included in the study)
- Ability to understand the patient information form and ability to provide written informed consent.
- a self-reported absence of a definite diagnosis of rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, or systemic sclerosis based on current classification criteria or of complaints compatible with the current classification criteria for *clinically suspect arthralgia*.

Exclusion criteria

Exclusion criteria patients
- Individuals who fail to meet the inclusion criteria
- Individuals for whom the treating physician considers that relevant safety issues apply (such as, for example, severe anemia) that preclude the provision of 50 ml of peripheral blood.
- Individuals who have donated 50 ml of blood (or more) less than two weeks prior to the respective time-point for any reason (such as routine clinical care, participation in another study, blood donations for the blood bank, etc.)

exclusion criteria healthy subjects:
- Individuals who fail to meet the inclusion criteria
- Individuals who have donated 50 ml of blood (or more) less than two weeks prior to the respective time-point for any reason (such as routine clinical care, participation in another study, blood donations for the blood bank, etc.)

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):	05-03-2018

Enrollment:	1095
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	15-01-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-12-2022
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-09-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL62212.058.17