Unraveling Incomplete Lupus - search for prognostic factors for progression to Systemic Lupus Erythematosus

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1) To investigate IFN type I signature as an early biomarker for progression to SLE. 2) To establish effects of increased innate immune system activation on adaptive immune system, in particular on B-cells. 3) To establish IFN type I activation as...

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

Summary

ID

NL-OMON45013

Source
ToetsingOnline

Brief title
Unraveling Incomplete Lupus

Condition

- Autoimmune disorders

Synonym
lupus, SLE

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: Reumafonds

Intervention

Keyword: Incomplete Lupus, Interferon signature, Prognostic factors, Systemische Lupus Erythematosus

Outcome measures

Primary outcome

The main parameter is expression of IFN type I signature

Secondary outcome

- Other parameters of increased innate immune system activation will be measured including levels of MxA in monocytes and serum, TLR protein expression by FACS and TLR mRNA expression by RT-PCR, and serological biomarkers (a.o. TNF alpha, IL-6 and CXCL-10) will be assessed with luminex

- As marker of inflammation and apoptosis, levels of HMGB-1 will be determined.

- Production of different auto-antibodies (IgG, IgA and IgM)will be measured and comprise ANA (titer and pattern), ENA, anti-dsDNA antibodies, anti-phospholipid antibodies and anti-HMGB1 antibodies. Furthermore, levels of BAFF and APRIL will be determined by luminex. Also, the distribution of B cell subsets by FACS analysis with focus on autoreactive effector memory cells will be assessed.

- To investigate the influence of the innate immune system on B cell activation, B cells will be activated in vitro with TLR agonists to investigate ability to produce inflammatory proteins.

- To establish IFN type I activation as biomarker of progression to SLE in skin biopsies. At inclusion, in all ILE patients skin biopsies will be taken of unaffected skin and if present of affected skin. Next to IFN type 1 activation,

markers for apoptosis and TLR expression will be measured, both at protein and mRNA level.

- To investigate the effects of HCQ, all biomarkers mentioned above will be assessed including skin biopsies, before and after 16 weeks of treatment with HCQ, which will be prescribed on clinical grounds.

Study description

Background summary

Systemic lupus erythematosus (SLE) is a complex disease characterized by a broad spectrum of clinical manifestations and a multitude of laboratory abnormalities. However, knowledge is lacking about the earlier phases of the disease, also called Incomplete Lupus Erythematosus (ILE). Also, not all ILE patients will develop SLE. At this moment no biomarkers are known to predict which of these individuals will progress to SLE. We hypothesize that ILE patients who are prone to progress to SLE, will have an increased activation of the innate immune system, characterized by increased type I interferons (IFNs) and Toll Like Receptors (TLRs) expression, leading to increased B cell activation. These changes might be present systemically in the blood as well as in the skin. We postulate that hydroxychloroquine (HCQ) modulates these pathologic differences, as this drug modulates TLR activation.

Study objective

1) To investigate IFN type I signature as an early biomarker for progression to SLE. 2) To establish effects of increased innate immune system activation on adaptive immune system, in particular on B-cells. 3) To establish IFN type I activation as biomarker of progression to SLE in skin biopsies. 4) To investigate the effects of HCQ in a selected group of ILE patients, in whom HCQ is prescribed for clinical reasons.

Study design

This will be a longitudinal follow up study in ILE patients. At baseline clinical data and several markers for innate immune activation and B cell activation will be determined. The same analyses will be done in matched SLE patients and healthy controls. Furthermore, at inclusion in all ILE patients skin biopsies will be taken of unaffected skin and if present of affected skin. All ILE patients will be followed during regularly visits to our out-patient

clinic (every 3-6 months). At each visit blood will be drawn for biochemical and immunological investigation and clinical data will be collected. Progression to SLE will be recorded. In a subgroup of newly diagnosed ILE patients, the effects of HCQ on innate immune system activation and B cell activation will be measured on t = 0 and t = 16 weeks.

Study burden and risks

All patients will receive standard diagnostic workup, treatment and follow up. Procedures that will be solely done for study purposes are: extra blood withdrawal and at entry of the study two or four skin biopsies. When patients participate in the part of the study concerning effects of HCQ, one extra visit to the hospital is required. Healthy controls will be seen by one of the rheumatologists for determining whether they are healthy to serve as controls, and then blood will be drawn during the same visit.

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

Incomplete Lupus patients:
- ANA positivity with a titre of at least 1:80 or higher
- Two other ACR criteria of SLE
- Disease duration of < 5 years
- (Preferable) not yet treated with hydroxychloroquine or corticosteroids
- Being able to give informed consent

Exclusion criteria

- Concomitant chronic diseases that may affect immune system (such as prior or current malignant disease, active infectious disease, other rheumatological disease, kidney disease, active allergy etc.)
- Pregnancy
- < 18 years old

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-03-2016
Enrollment:	143
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL54268.042.15