PRediction Of Flares In Lupus with autoantibodiEs and chemokines (PROFILE)

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

Summary

ID

NL-OMON51008

Source
ToetsingOnline

Brief title
PROFILE

Condition

- Autoimmune disorders

Synonym
lupus, SLE

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: GlaxoSmithKline,GSK

Intervention

Keyword: diagnostics, prediction, systemic lupus eryhtematodes

Outcome measures

Primary outcome

- Profile of autoantibodies and chemokines in visits previous to recorded flares, compared to visits previous to no recorded flares.

- Changes in the profile of autoantibodies and chemokines in patients with lower reported quality of life measured by LupusQoL questionnaire, compared to previous visits of the same patient.

Secondary outcome

Changes in titer levels of autoantibodies before and after start of biological treatment.

Study description

Background summary

Systemic lupus erythematosus (SLE) is a chronic relapsing-remitting autoimmune disease with a wide range of clinical manifestations affecting several organs. Although the management of lupus patients has improved in the last years, accurate models for predicting disease progression are lacking.
In clinical practice, SLE patients can be categorized into three groups:
1. A large group of patients has *quiescent* disease; after diagnosis of SLE and possibly a short induction treatment with corticosteroids, patients remain in a state of remission for years with hydroxychloroquine treatment only.
2. A substantial group of patients has relapsing-and-remitting disease, with mostly cutaneous inflammation but without further organ involvement.
3. A smaller group of patients has severe inflammation with extensive organ involvement, including lupus nephritis and neuropsychiatric SLE (npSLE) as the most threatening complications.
This stratification of patients is reflected by the frequency of hospital visits. Patients with more severe disease activity have a higher frequency of visits to the outpatient clinic and more frequently receive biologicals.(1) In

the UMC Utrecht, patients in group 1. normally visit the outpatient clinic on a yearly basis, patients in group 2. visit 2-4 times a year and patients in group 3. are seen more frequently. However, some patients with quiescent disease for years can still present with an SLE exacerbation, and patients with frequent bouts of inflammation can eventually reach a remission state.
It would be of great value to be able to distinguish these patient categories early after diagnosis. This would aid the clinician in identifying those patients who can safely visit the outpatient clinic only once a year, and conversely, it would be possible to point out which patients should be monitored more closely. Ideally, this early distinction would also correspond with treatment decisions, that is, intensifying treatment when a flare is suspected, or tapering medication when there is a low risk profile. The ultimate goal would be to enable clinicians to identify high risk patients and to treat them with immunomodulating therapy before any inflammatory damage has occurred, for instance with the combination of rituximab and belimumab as is being studied right now.(2,3)
The pathogenesis of SLE is highly complex. Genetic predispositions, proinflammatory and anti-inflammatory cytokines, autoantibodies, lymphocyte subset abnormalities as well as defects in the complement systems all have putative roles in the development of SLE. At present, tools that enable early patient stratification are lacking. Furthermore - except for a possible association of rise in anti-dsDNA-antibodies and the development of lupus nephritis - factors that can predict SLE flares have not been identified.
Active disease has a large impact on the life of SLE patients, since it is known to result in a lower health-related quality of life.(4) Fatigue is an important factor in patient reported quality of life, but interestingly, disease activity is not associated with fatigue.(5) This can lead to a discrepancy, where the clinician assesses the patient*s disease activity to be under control, where the patient is still experiencing a large burden of disease. Due to lack of objective parameters correlating with patient reported outcomes, this discrepancy is difficult to interpret for physicians.
When considering factors that can be relevant for patient risk stratification, the role of (novel) autoantibodies in the pathogenesis of SLE should not be overlooked. Several autoantibodies have been shown to be of diagnostic value for SLE (anti-dsDNA, anti-SmD, anti-Rib-P, anti-PCNA, anti-Chromatin, anti-complement (C1q)) and changes in the level of autoantibodies can reflect disease activity.(6) However, dynamics of antibody levels on their own are insufficient to be used as predictors of lupus activity in individual patients. Moreover, some types of treatment, such as B-cell targeted therapy, are known to influence the dynamics of antibody levels, making them harder to interpret.
Some chemokines and matrix metalloproteases (MMPs) and their inhibitors (TIMPs) have been shown to provide an indication of subclinical injury or inflammation in other inflammatory diseases and in renal inflammation.(7-9) For example, urinary CXCL9 levels were found to be associated with risk of acute rejection of renal transplants and a decline in renal function.(10) In addition, serum levels of CXCL10 have been shown to correlate with lupus activity in patients with SLE.(11) Furthermore, urinary levels of CXCL10 have shown very promising

results in the early detection of allograft rejection in kidney transplants. Currently, an international randomized controlled trial is investigation if early treatment of rejection, detected by urinary CXCL10, will improve outcomes. (12) As of yet, these urinary markers have not been studied in the context of SLE and lupus nephritis. Dynamic levels of these urine markers and the relation to their corresponding serum levels could serve as early indicators of nephritis.

Study objective

The primary objective of this study will be to prospectively evaluate the predictive value of a combination of chemokines, MMPs/TIMPs, and autoantibody levels for predicting flares in patients with SLE. This approach allows identification of the markers with the best predictive value.
As a secondary objective, this study will investigate whether dynamic changes in autoantibody- and chemokine levels differ between patients treated with or without anti-B-cell therapy (for instance, with rituximab or belimumab). In patients treated with anti-B-cell therapy lower autoantibody levels are observed, which could influence the combination of markers being studied. Until now, it is unclear whether the degree of lowering autoantibody levels after treatment is correlated with treatment efficacy and whether changes in autoantibody levels in SLE patients treated with anti-B-cell therapy can be indicative of lupus flares. This study will give insight into this relationship.
We will also assess the relationship of these biomarkers with patient reported quality of life and fatigue. These markers might provide the physicians extra tools on how to interpret the discrepancy between objective measurements by the physician and patient reported outcomes.

Study design

This is a prospective, observational single centre cohort study, conducted at the department of Rheumatology and Clinical Immunology of the UMC Utrecht. Included patients will be followed for 2 years. First measurements will be performed at baseline, follow-up measurements will be performed every 3 months. Data from baseline measurement will be used to investigate a cross-sectional research question (RQ4). As this is an observational study, treatment decisions will be left to the discretion of the treating physician.
At the first visit, informed consent will be collected from the patient. At the first visit, the patients* medical history and medication history will be collected. If not performed historically in the last 12 months, laboratory assessments for antinuclear antibodies (ANA) will be performed, as well as specification of found ANA*s by lineblot assay, as well as screening for antiphospholipid antibodies (aPL). The acquired damage in patients with SLE is scored with the SLICC-ACR Damage Index, which will be repeated at the last visit of the patient.

At each visit, the disease activity of the patient will be assessed by the study physician, using the SLEDAI-2K, PGA and SLE Flare Index (SFI). Blood and urine samples will be collected at every visit, to examine for presence of autoantibodies and chemokines. Patients will be requested to fill out two questionnaires, the LupusQoL and the Fatigue severity scale. Utilization of health care services and changes in medication will be evaluated at every visit. Weight and blood pressure are measured every visit, as well as routine lab evaluation. Cardiovascular risk screening is performed annually. An overview of all study procedures is presented in table 1. All collected data will be used to answer RQ1-RQ3.
The data from the measurements from the D1 visit will be used to answer RQ4. Patients will be stratified in three risk groups based on a combination of number of outpatient clinic visits, hospital admittances and intensity of immunosuppressant therapy (dose of prednisone, use of DMARDs, biologics, cyclophosphamide) in the year before inclusion. The risk groups are the low-risk (quiescent) group, the intermediate (relapsing-remitting) risk group, and the high-risk (severe inflammation) group. Newly diagnosed patients (diagnosis <1 year), for whom insufficient information is available to accurately stratify at the beginning of the observational period, will also be included as a separate fourth group.
This allocation is based on 4 variables: outpatient clinic visits, hospitalizations, medication use and amount of prednisolone used. Hydroxychloroquine (HCQ) is the basis of treatment for all patients with SLE. If treatment with HCQ is not sufficient, (low dose) prednisolone and/or other immunnosuppressants are used. A small number of patients experience severe flares despite immunosuppressant therapy and are subsequently treated with biologicals, such as belimumab or rituximab.
Patients will be stratified in the highest group corresponding to the allocation criteria. For specific analyses, patients in group 3 will be split into two subgroups, patients receiving anti-B-cell therapy (3a) and patients who do not receive anti-B-cell therapy (3b).

Study burden and risks

N/A

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Have a diagnosis of SLE according to EULAR/ACR criteria
• Age >= 18 years

Exclusion criteria

• Subjects participating in another study in which the subject receives immunosuppressant medication

Study design

Design

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

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-09-2021
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	16-07-2021
Application type:	First submission
Review commission:	METC NedMec

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	NL75276.041.21