The effects of rituximab and obinutuzumab on lymphocyte subsets in peripheral blood and lymphoid tissues of SLE patients

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This study has been transitioned to CTIS with ID 2024-518965-85-00 check the CTIS register for the current data. The primary objective of this study is to investigate the potential differential effects of RTX and OBI on the composition of lymph…

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON56559

Source
ToetsingOnline

Brief title
Rituximab and obinutuzumab in SLE

Condition

- Autoimmune disorders

Synonym
Systemic Lupus Erythematosus; SLE

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC

Source(s) of monetary or material Support: Roche (Investigator Initiated Study)

Intervention

Keyword: Lymph node, Obinutuzumab, Rituximab, SLE

Outcome measures

Primary outcome

The proportion of patients with depletion of total CD19+ and other B lineage cells in the peripheral blood (quantitative using ImmunoSeq analysis) and lymph nodes, defined as a decrease of >2 points on a 4-point semi-quantitative scale. These will be separate co-primary endpoints. We will statistically test the difference in the proportions of patients with depletion by these criteria in RTX- versus OBI-treated patients.

Secondary outcome

Correlation between CD19+ lymphocyte (and other B lineage cells) depletion in peripheral blood/tissues and clinical response. Depletion (defined as a decrease of >2 points on a 4-point semi-quantitative scale of CD19+ cells in the lymph node) will be related to clinical response (defined as a >4 point improvement in cSLEDAI or any improvement in BILAG-2004 score) in a 2x2 chi-square test for all 20 patients.
Further secondary and exploratory outcomes are changes in B lineage cells and associated (pathogenic) T cell subsets in lymph nodes and skin of SLE patients in comparison to the changes in the peripheral blood compartment, analyses to investigate whether change in B lineage cells and associated (pathogenic) T cell subsets in tissues is associated with clinical outcomes and/or known

serological biomarkers such as antidsDNA and complement components C3 and C4.

Study description

Background summary

Systemic lupus erythematosus (SLE)is an immune-mediated inflammatory disease (IMIDs) of which the cellular and molecular alterations of the immune system driving the diseases still remains largely unknown. Accordingly, it remains difficult to predict the indvidual patient*s response to treatment. Moreover, the patient*s response to treatment remains heterogeneous and difficult to predict, despite the development of a variety of novel and powerful drugs (including the so-called biologicals). Therefore, there is a clear need for the identification and validation of cellular and molecular biomarkers which can provide useful clinical information for diagnosis, classification, prognosis and treatment, as well as the development of new therapeutic strategies. Biomarkers can be found and analyzed in different body compartments, of which the peripheral blood is most easily accessible. However, previous studies in RA and other IMIDs showed that adaptive immune responses in other tissues such as lymph nodes also play an important role. Investigating other immune compartments of the body such as the lymph nodes could result in new insights. To study the early pathogenesis of inflammatory conditions, in 2008 our department initiated core-needle inguinal lymph node biopsy sampling. Since then we performed more than 100 lymph node biopsy procedures. We showed that the procedure is well-tolerated and that, other than a small hematoma which does not require therapy in most of the cases, no complications were reported. In the current study, we aim to investigate the effects of rituximab and obinutuzumab (both anti-CD20 therapy) in SLE by studying the immune alterations taking place in lymph nodes in comparison to peripheral blood. In this way we will be able to compare the effects of rituximab and obinutuzumab and assess potential differential immune alterations in the lymph nodes (secondary lymphoid organ) and the peripheral blood (systemic).

Hypotheses:
• OBI depletes CD20+ cells from the tissues more effectively than RTX
• Clinical treatment results in SLE are related to depletion of CD20+ cells from the tissues
• CD20+ depleting therapy results in significant changes in B lineage cells and associated (pathogenic) T cell subsets in the tissue of SLE patients, which may be different from the changes observed in the peripheral blood

Study objective

This study has been transitioned to CTIS with ID 2024-518965-85-00 check the CTIS register

for the current data.

The primary objective of this study is to investigate the potential differential effects of RTX and OBI on the composition of lymph nodes and other target organs (i.e. skin and/or kidney) as well as (subsets of) immune cells in the peripheral blood. Furthermore, we aim to identify immunological alterations in lymphoid tissue and inflamed skin and/or kidney tissues of SLE patients and to correlate these alterations with disease stage/phenotype, prognosis, and treatment response. We thereby aim to identify and validate novel biomarkers that can be used for personalized medicine in SLE.

Study design

Patients will receive either RTX 2x1000mg + 100mg methylprednisolone or OBI 2x1000mg + 100mg methylprednisolone (two-week interval) in a non-blinded clinical trial. Researchers in the lab handling patient samples and performing analyses will be blinded for the treatment.

Intervention

RTX 2x1000mg vs. OBI 2x1000mg + 100mg methylprednisolone (two-week interval)

Study burden and risks

The patient will receive an infusion of RTX or OBI twice (with an interval of 2 weeks). In addition, a needle biopsy will be taken from an inguinal lymph node twice and in total blood will be taken 4 times (max 94ml). If there is also SLE activity in the skin or kidney, we want to examine these tissues as well. However, these last 2 tissues are optional and the kidney biopsy is only done if clinically indicated (once). The research will increase the insight into the pathogenetic processes that play a role in the onset and persistence of SLE and the effect of anti-CD20 therapy on this. This insight may lead to the identification and validation of new biomarkers that bring "personalized medicine" in SLE a step closer. In addition, new insights into the pathogenesis can lead to the development of new therapies or therapeutic strategies. In this study, obinutuzumab and rituximab are compared to see if either provides better B cell depletion in the tissues. In view of the relatively small risk of complications, we consider this study justified.

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

SLE patients who:
1. fulfill ACR 1997 and/or SLICC and/or ACR/ EULAR 2019 criteria,
2. have a SLEDAI-2K score >=6.
3. are aged between 18-75
4. are clinically determined to have severity of disease and refractoriness that supports the off-label use of anti-CD20 therapy

Exclusion criteria

- Patients who are not able to give informed consent. - Pregnancy - Severe renal impairment (eGFR <30ml/min/1.73m2 according to CKD-EPI formula) - Present or previous treatment with any cell depleting therapies, including anti-B-cell therapy, belimumab or other investigational agents (e.g., abetimus sodium, anti CD40L antibody, BG9588/ IDEC 131) in the last 3 years. Investigational agent applies to any drug not approved for sale in the country in which it is being used. - Intravenous cyclophosphamide 90 days prior to anti-CD20 therapy - Any non-biologic investigational agent (investigational agent applies to any drug

not approved for sale in the country in which it is being used) 30 Days Prior to anti-CD20 therapy (or 5 half-lives, whichever is greater) - Live vaccines within 30 days prior to baseline or concurrently with anti-CD20 therapy - Presence of any other disease for which study subjects need chronic or intermittent immunosuppressive therapy (e.g. prednisolon for COPD). - History of infection: • Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) • Hospitalization for treatment of infection within 60 days of Day 0. • Use of parenteral (IV or IM) antibiotics (anti-bacterial, antiviral, anti-fungal, or anti-parasitic agents) within 60 days of Day 0 - History of malignancies neoplasm within the last 5 years except basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and with no evidence of metastatic disease for 3 years - Have any intercurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study, including evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, poses a significant suicide risk - Have a history of a primary immunodeficiency, including significant IgG deficiency (IgG level < 400 mg/dL) or IgA deficiency (IgA level < 10 mg/dL) - Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 365 days prior to Day 0 - Have a historically positive HIV test or test positive at screening for HIV - Hepatitis status: • Serologic evidence of current or past Hepatitis B (HB) infection based on the results of testing for HBsAg and HBcAb as follows: patients positive for HBsAg or HBcAb are excluded • Positive test for Hepatitis C antibody - Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies - Have any other clinically significant abnormal laboratory value in the opinion of the investigator

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2023
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyva
Generic name:	Obinutuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-03-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	22-02-2024
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
EU-CTR	CTIS2024-518965-85-00
EudraCT	EUCTR2022-004335-12-NL
CCMO	NL83820.018.23