A randomized trial to investigate the reset of humoral autoimmunity by combining belimumab with rituximab in severe systemic lupus erythematosus

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

Summary

ID

NL-OMON52462

Source
ToetsingOnline

Brief title
Synergetic B-cell immunomodulation in SLE - 2nd study

Condition

- Autoimmune disorders

Synonym
lupus, systemic lupus erythematosus

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Dutch Kidney Foundation,GlaxoSmithKline

Intervention

Keyword: B cell immunology, belimumab, rituximab, systemic lupus erythematosus

Outcome measures

Primary outcome

The primary clinical efficacy parameter is the treatment failure rate during the 2 years study period.

Secondary outcome

Secondary endpoints are clinical and non-biased immunological effects of the treatment summarized as follows: reduction of disease relevant autoantibodies, in particular anti-dsDNA autoantibody production at 28 weeks, total renal response rate at 28 weeks, regression of immune complex-mediated excessive neutrophil extracellular traps (NET) formation at 28 weeks; sustained, long-term B-cell depletion during 104 weeks; sustained reduction of relevant anti-nuclear autoantibodies, including seroconversion during 104 weeks; and sustained regression of immune complex-mediated excessive neutrophil extracellular traps (NET) formation during 104 weeks. Additionally, the study will perform safety and toxicity monitoring according to Common toxicity Criteria (CTC) developed by the National Cancer Institute (NCI) with the use of Common Terminology Criteria for Adverse Events (CTCAE)and evaluate the reduction of concomitant immunosuppression and the number of moderate and severe flares during study follow-up.

Study description

Background summary

The SynBioSe-1 study is the first study to comprehensively describe the clinical and immunological effects of combining rituximab (RTX) and belimumab (BLM) in patients with systemic lupus erythematosus (SLE). From the pioneering SynBioSe-1 study, we have learned that combining RTX+BLM was safe and well-tolerated with important clinical responses. Immunologically, we unexpectedly observed that long-term B-cell depletion was not achieved due to migration of mature B-cells triggered by depletion of BAFF serum levels. The latter observation was in contrast to the study*s null-hypothesis that combination therapy would lead to long-term B-cell depletion. The contrary was demonstrated, namely the relative early recirculation of mature B-cells. As such, the immunological and clinical lessons from the SynBioSe-1 study in conjunction with accumulating data from several large studies on combination B-cell targeted treatment have led to the postulation that starting treatment with RTX+BLM would result in an improved B-cell targeting strategy, notably on tissue-resident autoreactive B-cells, associated with improved long-term clinical disease amelioration. Therefore, the present SynBioSe-2 study is designed to further investigate the long-term clinical and imunological efficacy of combination B-cell targeting by starting treatment with belimumab followed by rituximab.

Study objective

The primary objective is to assess whether combination treatment BLM+RTX will lead to reduced treatment failure and the improvement of pivotal, SLE-specific autoimmune phenomena compared SLE patients treated with standard of care.

Study design

a multi-center, randomized, controlled, open-label study
Study duration: 104 weeks

Intervention

In addition to standard therapy, SLE patients will receive self-administered, subcutaneous injections of belimumab every week and 2 infusions of rituximab 1000 mg on day 28 (week 4) and day 42 (week 6).

Study burden and risks

There may be a benefit for the subjects participating in this study. The present study will include severe SLE patients who have highly active disease

who need intensive immunosuppressive treatment with mycophenolate according to current conventional treatment guidelines. At present, there is no consensus on the duration of conventional treatment and is continued for many years and sometimes even life-long. Hence, immunosuppressive treatment is associated with (cumulative) toxicity and long- term increased risk for infections or malignancies. Patients randomized to the investigational arm with belimumab plus rituximab will have the opportunity to taper and even stop anti-inflammatory treatment with mycophenolate and steroids. Therefore, the use of belimumab plus rituximab can ameliorate disease activity while potentially reduce infectious complication as compared to conventional intensive immunosuppressive treatment.

The risks related to study participation lies predominantly in the side effect profile of the biologicals used, as extensively described in §6.4. Minor risk is involved with the placement of an intravenous access needle for truxima infusions (twice) and the subcutaneous injection of belimumab. At study entry a renal biopsy is required to diagnose lupus nephritis in those cases where renal involvement is suspected. The renal biopsy will already be performed as part of routine clinical evaluation of an patient with the suspicion of lupus nephritis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Subjects enrolled in the study must meet the following inclusion criteria:
1) Adults with the age of 18 years and above,
2) Have a clinical diagnosis of SLE according to the SLICC criteria 2012 (see appendix 1)
3) Severe, active SLE disease (see also section 5.3.3.2.), defined as a situation in which 1 or more of the following criteria are met:
a. SLEDAI (SLE Disease Activity Index) with 12 or more points
b. New or worse SLE-related activity of major organs, i.e.: CNS-SLE (includes NPSLE), vasculitis, nephritis, pericarditis and/or myocarditis, myositis, thrombocytopenia<60, hemolytic anemia< 4.4mmol/L
c. high disease activity that requires or warrants induction treatment by switching to or increasing dosage of oral mycophenolate
4) Persisting or progressive disease activity despite the use of conventional maintenance immunosuppressive treatment (e.g. mycophenolate or azathioprine)
5) Positive for relevant SLE-specific autoantibodies defined as a situation in which 1 or more of the
following criteria are met:
a. ANA seropositivity, as defined by a positive ANA-titer >= 1:80, before and at screening :
- Positive test results from 2 independent time points within the study screening period; OR
- One positive historical test result and 1 positive result during the screening period. Historical
documentation of a positive test of ANA (eg, ANA by HEp-2 titer, ANA by ELISA) must
include the date of the test.
b. Anti-DNA seropositivity, as defined by a positive anti-dsDNA serum antibody >= 30 IU/mL,
before and at screening:
- Positive test results from 2 independent time points within the study screening period.
- One positive historical test result and 1 positive result during the screening period. Historical
documentation of a positive test of anti-dsDNA (eg, anti-dsDNA by Farr assay or ELISA)
must include the date of the test.
6) Female subjects are eligible to enter the study if she is:
- Not pregnant or nursing

- Of non-child-bearing potential (i.e. after hyseterectomy, postmenopausal, bilateral ovariectomy or documented bilateral tubal ligation or other permanent female sterilization procedure)
- Use of effective contraception:
• Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject.
Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception; OR
• Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
o Oral contraceptive, either combined or progestogen alone
o Injectable progestogen
o Implants of levonorgestrel or etonogestrel
o Estrogenic vaginal ring
o Percutaneous contraceptive patches
o Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
o Male partner sterilisation (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, *documented* refers to the outcome of the investigator's/designee*s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject*s medical records.
o Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)
• These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.
• Female subjects using mycophenolate mofetil (MMF) should be made aware that MMF affects the metabolism of oral contraceptives and may reduce their

effectiveness. As such, women
receiving MMF who are using oral contraceptives for birth control
should employ an additional
method (e.g., barrier method).

Exclusion criteria

Subjects will be excluded from participation if they meet any of the following exclusion criteria:
1) Active pregnancy, as proven by a positive urine beta-HCG test or a positive serum beta-HCG
2) Significant hypogammaglobulinemia (IgG < 4.0 g/L) or an IgA deficiency (IgA < 0.1 g/L)
3) Immunization with a live vaccine 1 month before screening
4) Active infection at time of screening, as follows:
- Hospitalization for treatment of infection within previous 60 days of
day 0 of the study
- Use of parenteral (intravenous of intramuscular) antibiotics (
including anti-bacterials, anti-virals,
anti-fungals or anti-parasitic agents) within previous 60 days of day
0 of the study
- Serological evidence of uncontrolled, active viral hepatitis defined
as: patients positive for HbsAg
test or HBcAb or a positive hepatitis C antibody not treated with
antiviral medication
5) Have a historically positive HIV test or test positive at screening for HIV
6) Have a history of a primary immunodeficiency
7) Have a neutrophil count of < 1.5x10E9/L
8) Have a significant infection history that in the opinion of the investigator would make the
candidate unsuitable for the study
9) Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or
murine proteins or monoclonal antibodies
10) Have any other clinically significant abnormal laboratory value in the opinion of the investigator
11) Have current drugs or alcohol abuse or dependence within 365 days prior to Day 0 of the study
12) Have an active malignant neoplasm or one in the history of 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
13) Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months or who, in the investigator*s opinion, poses a significant suicide risk

14) Have any other clinically significant abnormal laboratory value, any intercurrent significant medical or psychiatric illness that in the opinion of the investigator would make the candidate unsuitable for the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-10-2018
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	benlysta
Generic name:	belimumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	truxima
Generic name:	rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-09-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	25-09-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	12-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-12-2022
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
EudraCT	EUCTR2018-001392-21-NL
CCMO	NL65720.058.18