Leflunomide and Hydroxychloroquine combination therapy for primary Sjögren*s Syndrome

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This study has been transitioned to CTIS with ID 2024-510904-36-00 check the CTIS register for the current data. To assess clinical efficacy and safety of Leflunomide/Hydroxychloroquine in pSS patients in a phase IIb placebo-controlled randomized...

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

Summary

ID

NL-OMON55143

Source
ToetsingOnline

Brief title
RepurpSS-II study

Condition

- Autoimmune disorders

Synonym
Auto-immune exocrinopathy and Sjogren's Syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Primary Sjogren's syndrome

Outcome measures

Primary outcome

Primary endpoint is change in ESSDAI scores from baseline to endpoint at 24 weeks.

Secondary outcome

The secondary endpoint includes changes in unstimulated/stimulated whole saliva output, ESSPRI, ocular dryness and serological and blood inflammatory features at 24 weeks interval. Exploratory endpoints include: ESSDAI and UWS at 48 weeks and other clinical measures at 48 weeks (ESSPRI, etc.), composition of the skin and gut microbiome (as compared to healthy controls) and the validation of possible biomarkers to predict response to therapy.

Study description

Background summary

Primary Sjögren*s Syndrome (pSS) affects 0.5-1% of the general population which makes it the second most prevalent autoimmune rheumatic disorder after rheumatoid arthritis (RA). There is still a large unmet medical need to inhibit morbidity, including severe dryness and invalidating fatigue, and to reduce the risk development of extraglandular manifestations and B cell malignancies. In a recent phase 2a trial, patients with pSS were randomized to leflunomide (LEF)/hydroxychloroquine (HCQ) treatment or placebo, daily for 24 weeks. Twenty-one patients received LEF/HCQ therapy and eight received placebo. Overall, LEF/HCQ appeared to be safe. From 0 to 24 weeks, ESSDAI score was on average 4.35 points lower in the LEF/HCQ group compared to the placebo group (p=0.0078). 11 of 21 LEF/HCQ-treated patients showed a clinical response. Hence, repurposing LEF and HCQ using combination-therapy for the treatment of pSS holds great therapeutic potential. However, the small sample size warrants replication in larger RCTs before its implementation in daily clinical

practice. We hypothesize that the combination of LEF/HCQ significantly and safely inhibits activity of primary Sjögren*s syndrome and molecular fingerprints will allow prediction of therapy response.

Study objective

This study has been transitioned to CTIS with ID 2024-510904-36-00 check the CTIS register for the current data.

To assess clinical efficacy and safety of Leflunomide/Hydroxychloroquine in pSS patients in a phase IIb placebo-controlled randomized clinical trial at 24 weeks, followed by a single-arm crossover and an open extension (total duration of 48 weeks) and to evaluate the capacity of molecular fingerprints in prediction of therapy response.

Study design

Single-center, randomized, double-blind placebo controlled trial, followed by a single arm cross-over open extension

Intervention

For 24 weeks, patients will receive 1 capsule with LEF (20 mg) and 2 capsules with HCQ (2x 200 mg) orally once per day as compared to 1 capsule with LEF-placebo and 2 capsules with HCQ-placebo once per day. For patients with a bodyweight <60 kg the HCQ dosage will be reduced to 200 mg a day. After 24 weeks all patients remain blinded and placebo-patients will receive LEF and HCQ (open label extension).

Study burden and risks

Patients will visit the outpatient clinic 14 times (including screening visit and safety checks) in a period of 48 weeks. At baseline and with 8-week intervals an extensive clinical assessment will be performed, evaluating patient*s symptoms (ESSDAI and EULAR Sjögren's Syndrome Patient Reported Index or ESSPRI), quality of life (Short Form (36) Health Survey or SF-36), EQ-5D -5L, fatigue (Multidimensional Fatigue Inventory or MFI) and oral and ocular dryness (Visual Analogue Scale-scores or VAS-scores). In addition, blood samples will be drawn 9 times. As is common practice in all patients using LEF, physical and laboratory examination will be performed every 2-4 weeks in the first three months, and after that monthly (in total 11 times), in order to preserve their safety. These safety checks (consisting of measurement of blood pressure and laboratory parameters (liver function by ALAT, creatinine ratio, hemoglobulin level, platelets and leucocytes) will be executed by a specialized rheumatology nurse in the UMCU or by the general practitioner of the participating patient. When performed by the general practitioner, the results

will be sent to the research team for interpretation.
Healthy controls will visit the outpatient clinic 7 times in a period of 48 weeks. During these visits gut and skin microbiome will be gathered and people will be asked about nutrition (20-30 min. per 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

In order to be eligible to participate in this study, a subject must meet all of the following criteria.
1. Women and men, aged 18-75 years
2. pSS diagnosed according to the ACR-EULAR 2016 Criteria for pSS
3. ESSDAI >=5
4. Use of a reliable method of contraception

5. Signed written informed consent.

In order to be eligible as healthy control, to compare composition of gut and skin microbiome, a subject must meet the following criteria:
1. family member or friend of participating patient with pSS diagnosis
2. the same sex as participating patient
3. age 18-75 years
4. signed written informed consent to compare composition of gut and skin microbiome

Exclusion criteria

1. Since LEF has teratogenic effects patients who are pregnant or who are wishing to conceive (also men with a female partner of childbearing age) during or within two years after the study are excluded. During the screenings visit, pregnancy will be excluded in all female patients of childbearing age.
2. Patients that breastfeed
3. Patients with therapy resistant hypertension are excluded since this might be aggravated by LEF
4. In case of maculopathy or retinitis pigmentosa the patient will be excluded from participation. Examination by an ophtalmologist will take place on indication.
5. Patients with secondary Sjögren*s Syndrome (Sjögren*s syndrome associated with other connective tissue disease)
6. Patients with hepatic or renal impairment
7. Patients with a severe infection (including hepatitis B,C or HIV)
8. Presence of a malignancy other than mucosa-associated lymphoid tissue lymphoma (MALT lymphoma)
9. Significant cytopenia
10. Concomitant heart- and inflammatory bowel disease
11. Patients suffering from sarcoidosis
12. Usage of HCQ or LEF <6 months prior to inclusion
13. Usage of immunosuppressive drugs, with the exception of a stable dose of non- steroidal inflammatory drugs and a stable, low dose (<=7.5 mg) of oral corticosteroids
14. Inadequate mastery of the Dutch language.

For healthy controls:
1. use of antibiotics in the past 3 months.
2. use of any immunosuppressant drugs in the past 3 months.
3. use of inhalation or nasal spray corticosteroids in the past 3 months.
4. use of mucosal protective agent in the past 3 months.
5. symptoms of flu or stomach flu in te past 4 weeks.
6. Inadequate mastery of the Dutch language.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-10-2021
Enrollment:	104
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Arava
Generic name:	Leflunomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Plaquenil
Generic name:	Hydroxychloroquine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	31-05-2021
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22318
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-510904-36-00
EudraCT	EUCTR2020-001933-11-NL
CCMO	NL73828.041.20