Leflunomide and Hydroxychloroquine combination therapy for primary Sjögren’s Syndrome

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22318

Source
Nationaal Trial Register

Brief title
RepurpSS-II

Health condition

Primary Sjögren’s Syndrome

Sponsors and support

Primary sponsor: UMC Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

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 (European SS patient reported index), ocular dryness and serological and blood inflammatory features at 24 weeks interval.

Study description

Background summary

Primary Sjögren's Syndrome (pSS) affects 0.5-1% of the general population (female to male ration 9:1) 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 (34). Currently, no therapeutic option is available for this debilitating disease.
Recently, we conducted a randomized, double-blind, placebo-controlled, monocenter, phase 2a trial in patients with pSS. Clinically active (European Sjogren syndrome disease-activity index/ESSDAI≥5) patients were randomized to receive leflunomide (LEF) 20mg and hydroxychloroquine (HCQ) 400mg daily or placebo/placebo (2:1) for 24 weeks. Twenty-one patients received LEF/HCQ therapy and eight received placebo. Overall, LEF/HCQ appeared to be safe and showed a meaningful clinical improvement. From 0 to 24 weeks, ESSDAI scores, the primary clinical endpoint, were on average 4.35 points (95% CI -7.44707 to -1.25178, p=0.0078) lower in the LEF/HCQ group compared to the placebo group (47).
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 as well as identification of pathways that confer lack of response.

Objectives:
1) 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)
2) Identify predictive clinical or molecular measures for response to therapy.
3) Pinpoint underlying molecular pathways associated with lack of clinical response.
Study design: Single-center, randomized, double-blind placebo controlled trial, followed by a single arm cross-over open extension
Study population: In total 52 patients with primary Sjögren's syndrome, 18-75 years, will be treated with either verum (n=26) or placebo (n=26).

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).

Main study parameters/endpoints: Primary endpoint is change in ESSDAI scores from baseline to endpoint at 24 weeks. The secondary endpoint includes changes in unstimulated/stimulated whole saliva output, ESSPRI (European SS patient reported index), 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.) and the validation of possible biomarkers to predict response to therapy.

Study objective

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 as well as identification of pathways that confer lack of response.

Study design

Baseline, week 8, week 16, week 24, week 32, week 40, week 48.

Intervention

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).

Contacts

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Eligibility criteria

Inclusion 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

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

Study design

Design

Study type: Interventional

Intervention model:	Crossover
Allocation:	Non controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2020
Enrollment:	52
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Not applicable

Application type:	Not applicable

Study registrations

Followed up by the following (possibly more current) registration

ID: 55143
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8756

Register	ID
CCMO	NL73828.041.20
OMON	NL-OMON55143

Study results