Optimizing DMARD therapy for primary Sjogren's Syndrome - Leflunomide and Hydroxychloroquine combination therapy for patients with primary Sjogren's Syndrome

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

Summary

ID

NL-OMON45101

Source
ToetsingOnline

Brief title
LEF/HCQ combination therapy for pSS

Condition

- Autoimmune disorders

Synonym
Keratoconjunctivitis sicca, Sjogren's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Combinationtherapy, Hydroxychloroquine, Leflunomide, Primary Sjogren's Syndrome

Outcome measures

Primary outcome

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

Secondary outcome

Secondary endpoint is stimulated whole saliva output from baseline to endpoint

at 24 weeks.

Study description

Background summary

PSS affects ~1% of the general population, which makes it the second most prevalent autoimmune rheumatic disorder after rheumatoid arthritis. Despite the efforts to treat pSS successfully, advances in pSS treatment remain quite disappointing, and no successful therapy is available. There is a large unmet medical need to inhibit morbidity, including severe dryness and fatigue that these patients experience, and to reduce the risk of extraglandular disease and B cell malignancies. Also, guidelines to assess which patients should be treated with immunosuppressive drugs are lacking. Currently, the implementation of novel biologicals like rituximab is hampered by lack of sufficient clinical efficacy and the high cost/effectiveness ratio. In addition, this latter drug is not easy to administer and safety in pSS patients remains to be demonstrated.
Based on the pivotal role of B cells, T cells and pDCs in pSS and the complementary properties of Leflunomide (LEF) and Hydroxychloroquine (HCQ) to target these, we thus aim to demonstrate that the combination of LEF and HCQ leads to a more efficient inhibition of immune activation compared to these single DMARDs culminating in a higher clinical efficacy in pSS.
The current clinical study exploits advances on a recently discovered

conceptual framework of pSS pathogenesis and implements the beneficial effects of DMARD combination therapy seen in e.g. RA.

Study objective

In a clinical trial it will be investigated to what extent combination therapy with LEF and HCQ will 1) inhibit disease activity, in particular improvement of ESSDAI and dryness and 2) inhibit activity of (autoreactive) B-cells, T-cells and pDCs. In addition, we will study 3) early biomarkers and in vitro bioassays to predict response to therapy

Study design

Double-blind placebo controlled trial

Intervention

For 24 weeks, patients will orally receive 1 capsule with LEF (20 mg) and 2 with HCQ (200 mg), once per day as compared to three capsules with placebo . For patients with a bodyweight <60 kg, HCQ doses will be reduced to 200 mg once a day.

Study burden and risks

Patients participating in the study will be taking medication (3 capsules/day) for 24 weeks. They will visit the outpatient clinic 12 times in a period of 24 weeks. During part of the visits an extensive clinical assessment is performed, evaluating patient*s symptoms (ESSDAI and ESSPRI), quality of life (SF-36), fatigue (MFI), oral and ocular dryness (VAS-scores). In addition, patients will undergo biopsy of the parotid gland twice (before baseline and after 24 weeks of treatment) and blood samples will be drawn four times. During the other visits patients will undergo physical and laboratory examination in order to preserve their safety. At baseline, a chest X-ray and assessment of lungcapacity will be performed, these will be repeated only on indication. At last, patient will undergo MRI of the salivary glands and 18F-FDG PET/CT scan (head to hip) twice.

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

1) Women and men, 18-75 years
2) Primary Sjogren's Syndrome diagnosed according to the American-European Consensus Criteria, revised in 2002
3) Lymphocyte focus score (local lymphocytic infiltrates) *1 in sublablial salivary gland specimen
4) ESSDAI * 5
5) Use of a reliable method of contraception
6) Signed written informed consent

Exclusion criteria

1) Pregnancy or the wish to conceive (also for men) during the study or within 2 years after the study
2) Breastfeeding
3) Therapy resistant hypertension
4) Maculopathy or retinitis pigmentosa
5) Secondary Sjogren*s Syndrome
6) Hepatic or renal impairment
7) Severe infection (including hepatitis B,C or HIV)

8) Malignancy other than mucosa-associated lymphoid tissue lymphoma (MALT lymphoma)
9) Significant cytopenia
10) Concomitant heart- and inflammatory bowel disease
11) Sarcoidosis
12) Usage of HCQ or LEF <6 months year prior to inclusion
13) Usage of immunosuppressive drugs, with the exception of a stable dose of non- steroidal inflammatory drugs (NSAID's) and a stable, low dose (*7.5 mg) of oral corticosteroids
14) Inadequate mastery of the Dutch language;Exclusion criteria for imaging part (MRI and PET/CT)
1. A history of allergy/hypersensitivity to radio-isotopes or gadolinium-containing contrast agents
2. A fasting blood glucose level of >11 mmol/L at screening
3. Standard safety procedures for MRI will be applied, for example patients with metal or internal medical devices within their body will be excluded;Patients that meet any of the exclusion criteria for the imaging part of the study will be excluded only from this part of the study. If that patient does meet criteria for inclusion in the main study, she can still participate to this main part.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-03-2016
Enrollment:	30
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:	26-08-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-06-2017
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003140-12-NL
CCMO	NL49928.041.15