Randomized, double-blind, placebo-controlled phase III study (ASAP III study) to assess the efficacy and safety of Abatacept treatment in patients with primary Sjögren*s syndrome (ASAP III study = Abatacept Sjögren Active Patients phase III study)

Published: 20-03-2014
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Primary: to assess efficacy of weekly subcutaneous (SC) administration of Abatacept vs. placebo on disease activity assessed with ESSDAI at in patients with pSS. Secondary: to assess efficacy of Abatacept on clinical, functional, subjective, and...

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

Summary

ID

NL-OMON44430

Source
ToetsingOnline

Brief title
ASAPIII

Condition

- Autoimmune disorders

Synonym
primary Sjögren's syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: Abatacept, Efficacy, Safety, Sjögren's Syndrome

Outcome measures

Primary outcome

The primary endpoint is the difference in ESSDAI score between the Abatacept

and the placebo group at 24 weeks.

Secondary outcome

Secondary endpoints are clinical, laboratory, functional, subjective, and

histological parameters and the occurence of adverse events, treatment

discontinuation and laboratory abnormalities.

Study description

Background summary

Primary Sjögren*s syndrome (pSS) is a chronic inflammatory and lymphoproliferative disease with autoimmune features. pSS is characterised by a progressive lymphocytic infiltration of the exocrine glands, notably the lacrimal and salivary glands (1). The main clinical features are a progressive dryness of the eyes, mouth, vagina and skin. Furthermore, various extraglandular manifestations may develop of which restricting fatigue is the most common. Patients may be restricted in their activities and their participation in society, resulting in a reduced health-related quality of life (HR-QOL) and an impaired socioeconomic status (2). The latter results in lower employment rates and more disability as compared to the general population. The estimated prevalence of pSS in the general population is between 0.5-2%, which makes pSS, after rheumatoid arthritis (RA), the most common systemic autoimmune

disease (1,3). Most of the traditional anti-rheumatic drugs used in RA and systemic lupus erythematosus (SLE) have been tried in pSS with limited results. Currently, biological agents have been introduced in various systemic autoimmune diseases. These biological agents enhance or replace conventional immunosuppressive therapy. In contrast to RA and SLE, no biological agent has yet been approved for the treatment of pSS. Abatacept is a fully human soluble co-stimulation modulator that selectively targets the CD80/CD86:CD28 co-stimulatory signal required for full T-cell activation, and T cell dependent activation of B-cells. We have recently shown in a phase II open label study that abatacept treatment of pSS patients has promising efficacy results, as reflected by a significant decrease in disease activity indices such as the EULAR Sjögren*s Syndrome Disease Activity Index and Patient Reported Index (ESSDAI and ESSPRI) (4). Importantly, we also have shown that abatacept is safe and side effects are very limited in pSS patients. For these reasons a larger and randomized controlled trial (RCT) with abatacept is warranted. Furthermore, we want to take into account possible factors that may influence the effectiveness of abatacept treatment. As has been shown in other studies, the gut microbiome may play an important role in the effectiveness of immunotherapy and can possibly be used as a biomarker for personalized medicine.

Study objective

Primary: to assess efficacy of weekly subcutaneous (SC) administration of Abatacept vs. placebo on disease activity assessed with ESSDAI at in patients with pSS. Secondary: to assess efficacy of Abatacept on clinical, functional, subjective, and histological parameters over 48 weeks in patients with pSS. To evaluate the safety of abatacept, by monitoring serious adverse events (SAE), adverse events (AE) related SAE and AE, treatment discontinuation related to SAE and AE, and lab abnormalities over 48 weeks in patients with pSS. Exploratory: to assess the efficacy on laboratory parameters over 48 weeks in patients with pSS. To investigate whether the effectiveness of abatacept treatment on symptoms in pSS patients is influenced by the gut microbiome.

Study design

The first stage is a 24-week randomized, double-blind, placebo-controlled phase III study to assess the efficacy and safety of Abatacept (weekly SC administration of 125 mg Abatacept or placebo) in patients with pSS. The primary endpoint (ESSDAI) will be evaluated at 24 weeks. The second stage is composed of a 24-week open-label period in which both Abatacept and placebo treated patients will receive Abatacept for 24 weeks. The total study duration will be 48 weeks where after the study will be opened.

Intervention

Weekly subcutaneous administration of 125 mg Abatacept up to 48 weeks (see

study design for details).

Study burden and risks

Weekly subcutaneous injections of abatacept or placebo will be administrated by patients themselves or by their home physician, home care organization or informal caregiver (e.g. their partner) during 48 weeks. For screening purposes, patients will undergo venapunction, electrocardiogram (ECG), chest X-ray, pregnancy test and screening for human immunodeficiency virus (HIV) latent tuberculosis (TB) and viral hepatitis. A parotid gland biopsy will be done in patients who have never had a salivary gland biopsy, to confirm the diagnosis of pSS. At week 0, patients will visit the nurse practitioner for the first abatacept injection, and to learn how to administrate subcutaneous injections. Patients will be seen by their rheumatologist or nurse practitioner prior to the study, at baseline and 8 times during treatment. During these visits, venapunction and physical examination is performed and patients will be asked to fill in questionnaires concerning sicca features, fatigue and health-related quality of life. Women will be asked to fill in a questionnaire about sexual function at baseline, week 24 and 48. Prior to the study and 4 times during treatment patients will visit their ophthalmologist and oral and maxillofacial surgeon. At the oral and maxillofacial department salivary gland function is evaluated by painless collection of saliva, which takes 15 minutes. A salivary gland ultrasound is performed in week 0, 24 and 48. In patients of who a recent pre-treatment parotid gland biopsy is available and who give informed consent for a follow up biopsy, a second parotid gland biopsy will be performed at 24 weeks. This biopsy is taken in a 15 minutes during procedure, under local anaesthesia through a minor incision around the earlobe. The donor site heals generally without any complications [5] . The ophthalmologist performs the Schirmer test, the tearfilm break-up time test, ocular staining score, tears collection and conjunctival impression cytology to evaluate ocular dryness. The visits to the rheumatologist, the ophthalmologist and the maxillofacial surgeon are all scheduled on the same day. Each specialist visit takes about 20-30 minutes. Visits to the above mentioned specialists and the performed tests are in the regular follow up protocol as well. In the regular protocol, patients visit their specialists at least twice a year. Participants in this trial will therefore bring 8 extra visits to our hospital. No study assessments, administration of the study drug or other study related proceedings will be performed prior to obtaining informed consent from the participant.

An additional assessment, for which patients are specifically asked for consent and which is not mandatory for participation in the study, is the collection of microbiome samples at home. Patients are asked to collect a buccal swab, a mouth wash with 10mL sterile water and a stool sample, all at three time points (before therapy, at week 24 and at week 48). All samples will be collected at home and stored in the freezer of the patient. The patient will bring the samples in a provided freezer bag to the next appointment at the

Rheumatology and Clinical Immunology department. At baseline, a questionnaire with a total of 85 questions has to be completed. Completing this questionnaire takes at most 50 minutes and the patient can do this at home. If a patient is not willing to participate in this specific part of the study, it will not affect any other procedures in the trial.
In our pilot study of IV abatacept treatment in pSS, safety results were comparable with those found in RA patients (4). No SAEs occurred, and no patients withdrew from the study due to AEs. BMS has performed a safety analysis on SC abatacept treatment in RA, which showed that SC abatacept has acceptable safety and tolerability in patients with RA, and safety profiles are consistent with intravenous (IV) abatacept (6). Based on the clinical trial experience in adults, the risks that may be associated with the use of abatacept include infections, some of which may be serious or fatal, infusion-related reactions, and an increase in respiratory adverse events (AEs) and infections in patients with chronic pulmonary obstructive disease.

Whereas for RA a wide variety of traditional and biological disease-modifying anti-rheumatic drugs (DMARD*s) is available, systemic treatment options for pSS are still limited and effective therapeutic interventions are not yet approved. Abatacept treatment of pSS patients has promising efficacy results. Besides decreased disease activity, a major benefit of abatacept treatment is the improved HR-QOL and improvement of daily activities that many patients on this treatment experience, an improvement that not is obtained with traditional DMARDS. Patients that were not able to work anymore or were limited in their daily activities reported that they could restart their work and/or daily activities. Therefore we assume, based on clinical experience and the available literature that the advantages of participation in this trial outweigh the burden and risks involved with this treatment.

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

- Signed written informed consent
- ESSDAI * 5
- Female or male * 18 years
- pSS according to the American European Consensus Group (AECG) classification criteria (6)
- Disease duration * 7 years at the moment of inclusion
- pSS proven by parotid gland biopsy with characteristic features of SS
- Women of child bearing (WOCBP) potential must be using an acceptable method of contraception (i.e. oral, injected or implanted hormonal contraceptives, barrier contraception, intra-uterine devices, or sterilization) to avoid pregnancy throughout the study and for up to 10 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.
- Sexually active fertile men must use effective birth control if their partners are WOCBP

Exclusion criteria

- Presence of any other connective tissue disease.
- Flow rate of stimulated whole saliva * 0.05 ml/min in patients without extraglandular manifestations.
- Positive pregnancy test or breast-feeding women.
- Women with a child-bearing potential who are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period.
- History of alcohol or drug abuse or current alcohol or drug abuse.
- History of any malignancy in the past 5 years, including MALT lymphoma in the last 5 years, or with a current suspicion for cancer, other than non-melanoma skin cell cancers (NMSC), cured by local resection or carcinoma in situ. Existing NMSCs should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.
- Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral

infections at the time of potential enrollment, including subjects with evidence of human immunodeficiency virus (HIV) detected during screening.
- History of chronic or recurrent serious infections. (e.g. chronic pyelonephritis, osteomyelitis or bronchiectasis).
- Subjects with serious bacterial infections within the last 3 month, unless treated and resolved with antibiotics
- Subjects with herpes zoster or cytomegalovirus that resolved less than 2 months before potential enrollment.
- Subjects at risk for TB. Specifically excluded from this study will be subjects with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (* 4 weeks).
- Subjects must not be positive for hepatitis B surface antigen.
- Subjects who are positive for hepatitis C antibody if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay.
- Subjects who have received any live vaccines within 3 months before potential enrollment.
- Underlying cardiac, pulmonary, metabolic, renal, hepatic, gastrointestinal, haematological or neurological conditions, chronic or latent infectious diseases or immune deficiency which places the patient at an unacceptable risk for participation in the study.
- Use of prednisone *10 mg less than 1 month before inclusion.
- Use of pilocarpine, hydroxychloroquine, methotrexate, cyclophosphamide, cyclosporin, azathioprine, mycophenolate mofetil (MMF) and leflunomide less than 1 month before inclusion.
- Use of biologicals:
oUse of abatacept less than 6 months or rituximab less than 12 months before inclusion
oPrevious use of abatacept or rituximab if treatment with abatacept or rituximab was discontinued because of safety reasons or failure of treatment
oPrevious use of other biological DMARDS than abatacept or rituximab, either marketed or under investigation
- Lab abnormalities:
a. Serum creatinine *2.8 mg/dl (250 µmol/l)
b. ASAT or ALAT outside 1.5 x upper normal range of the laboratory
c. Hb *9 g/dl (5.6 mmol/l) for males and 8.5 g/dl (5.3 mmol/l) for females
d. Neutrophil granulocytes less than 0.5 x 109/l
e. Platelet count less than 50 x 109/l
- Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.
- Subjects will be asked if they have allergies or adverse drug reactions. The investigator will withdraw subjects at unacceptable risk for participation from the study.
- Prisoners or subjects who are involuntarily incarcerated.
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.

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):	14-08-2014
Enrollment:	88
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orencia
Generic name:	Abatacept
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-07-2014
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2020
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-000417-31-NL
ClinicalTrials.gov	NCT02067910
CCMO	NL48152.042.14

Study results

Date completed:	15-08-2019
Actual enrolment:	80