Abatacept treatment in patients with primary Sjögren*s syndrome: an open label study

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Evaluation of efficacy (as assessed by the stimulated whole saliva flow rate at 24 weeks) and safety of abatacept treatment in 15 patients with pSS.

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

Summary

ID

NL-OMON34695

Source
ToetsingOnline

Brief title
ABATACEPT1

Condition

- Autoimmune disorders

Synonym
Sjorgen's syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Bristol Myers Squibb

Intervention

Keyword: abatacept, sjogren's syndrome, treatment

Outcome measures

Primary outcome

Evaluation of efficacy (as assessed by the stimulated whole saliva flow rate at

24 weeks) and safety of abatacept treatment in 15 patients with pSS.

Secondary outcome

Secondary objectives/endpoint (baseline, 4, 12, 24, 36 and 48 weeks after start

of abatacept treatment):

* Functional parameters.

* Laboratory parameters.

* Subjective parameters.

* Histological / molecular parameters.

Study description

Background summary

Sjögren*s syndrome (SS) is a chronic inflammatory and lymphoproliferative disease with autoimmune features. SS 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 (keratoconjunctivitis sicca) and dryness of the mouth (xerostomia). Furthermore, various extraglandular manifestations may develop of which restricting fatigue is the most common. The fast majority of SS patients (85%) suffers from fatigue [2]. Other extraglandular manifestations that may occur are neuropathy, arthritis, vasculitis, and renal or lung involvement. SS can be primary (pSS) or secondary (sSS), the latter being associated with other autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). The estimated prevalence of SS in the general population is between 0.5-2%, which makes SS, after RA, the most common systemic autoimmune disease [3;4]. Moreover, SS is a disabling disease, particularly in

relatively young patients, of working age. Apart from the symptoms mentioned above, patients may be restricted in their activities and in their participation in society, resulting in a reduced health-related quality of life and an impaired socioeconomic status. The latter results in lower employment rates and higher disability rates compared to the general population [2].
Histopathological findings in SS-patients include focal lymphocytic infiltrates, located mainly around the glandular ducts of the salivary and lacrimal glands and extend to occupy the acinar epithelium, leading to glandular dysfunction [5;6]. The lymphocytic infiltrates mainly consist of activated T-cells, B-cells, and plasma cells. Despite extensive studies, the etiopathogenic factors that lead to the massive infiltration of the exocrine glands in SS are unknown. It is thought that activated (autoreactive) T cells play an integral part in the immunopathology and disease development of pSS, mediating B-cell activation, macrophage activation and cytokine production that, ultimately, lead to glandular inflammation and destruction.
Most of the traditional anti-rheumatic drugs used in RA and SLE, such as corticosteroids, methotrexate (MTX), azathioprine, sulphalazine and leflunomide, have been tried in pSS with unsatisfactory or limited results [7-11]. Currently, biological agents have been introduced in various systemic autoimmune diseases, as rheumatoid arthritis and SLE. Biological agents most frequently applied in autoimmune diseases are monoclonal antibodies (e.g., anti-CD20 (rituximab), anti-CD22 (epratuzumab), anti-BAFF (belimumab), anti-TNF-α (infliximab)) and soluble receptors (e.g., anti-TNF-α (etanercept)). The biological agents enhance or replace conventional immunosuppressive therapy. However, in contrast to rheumatoid arthritis and SLE, no biological agent has yet been approved for the treatment of SS [12]. Moreover, currently no effective systemic treatment modalities are available for SS, although recently, in two randomized placebo controlled phase II studies B-cell depletion with rituximab has shown promising results as improved salivary secretion, reduction of fatigue and extraglandular manifestations, and reduction of subjective symptoms as xerostomia and ocular dryness [13;14].
Abatacept, a biological agent not yet tested in SS, 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 the T cell dependent activation of B cells. Abatacept is currently used for the treatment of rheumatoid arthritis and it appears to be safe and effective [15]. Abatacept might also be a promising treatment for various other autoimmune diseases. Given the novel mechanism of action of abatacept and the recognized role of activated T-cells in the immunopathology of pSS, selective modulation of costimulation represents a rational therapeutic approach in pSS patients. Abatacept could be a good alternative for B-cell depletion therapy, possibly also in patients in whom B-cell depletion is not well tolerated or ineffective. Furthermore, abatacept is a fusion protein, and may therefore have a more favourable side effect profile than rituximab, which is a chimeric monoclonal antibody.
Therefore, the aim of the proposed open label phase II study is to assess whether abatacept therapy will reduce the objective signs and subjective

complains in pSS patients (see below for the primary and secondary objectives and endpoints to be studied).

Study objective

Evaluation of efficacy (as assessed by the stimulated whole saliva flow rate at 24 weeks) and safety of abatacept treatment in 15 patients with pSS.

Study design

fase 2 study, open label

Intervention

Abatacept will be given at week 0, 2, 4 and every 4 weeks there after by infusion (in total 8 infusions).

Study burden and risks

The total duration of this study is 48 weeks. Abatacept is administrated in a 30-minute intravenous infusion on day 1, 15, and 29 and every 28 days thereafter for 5 months. At these visits, blood is drawn from the infuse (43 ml) and therefore venapunction is not necessary. Patients will be seen by their own physicians: their rheumatologist, their ophthalmologist, and their oral and maxillofacial surgeon prior to the study (regular visit), and after 4, 12, 24 and 36 weeks.
A parotid gland biopsy will be performed prior to the study and within 2 weeks after the 24 weeks visit. 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 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. At the rheumatology department physical examination is performed. When no infusion is scheduled on the day of the visits, blood is drawn (43ml) for analysis. At the oral and maxillofacial department salivary gland function is evaluated by painless collection of saliva, which takes 15 minutes. The ophthalmologist performs the Schirmer test, the Lissamin green test and the tearfilm break-up time test to evaluate ocular dryness. Patients will receive a questionnaire, concerning sicca features, fatigue and health-related quality of life.
Visits to the above mentioned specialists and the performed tests (phycial examination, venapunction on visit days that no infusions are scheduled, salivary gland function evaluation, Schirmer test, Lissamin green test, tearfilm break-up time test) are in the regular follow up protocol as well. In the regular follow up protocol patients visit their specialists once or twice a year. Patients that participate in this trial will therefore bring 4 extra

visits to our hospital, besides the visits for the infusions.
Sibilia and Westhovens [16] performed an integrated safety analysis of five randomized, placebo controlled double-blind abatacept clinical trials in RA patients that encompassed a total of 1687 patient-years of abatacept exposure. This analysis suggested that abatacept has acceptable safety and tolerability in patients with RA.
Overall frequencies of adverse events (AEs; 88.8% vs. 85.1%), serious AEs (SAEs; 14.0% vs. 12.5%) and malignancies (1.4% vs.1.1%) were similar in abatacept- versus placebo-treated patients, respectively (regardless of the potential relationship to the study therapy). The AEs were considered to be at least possibly related to the study therapy in 52.2% and 46.1% of abatacept- and placebo reated patients, respectively, leading to discontinuation in 3.4% and 2.2% of patients (14). The most frequently reported AEs in the abatacept and placebo groups, regardless of their potential relationship to the study therapy, were: headache (18.3% vs. 12.7%, respectively), upper respiratory tract infection
(12.7% vs. 12.1%), nausea (11.6% vs. 10.6%), nasopharyngitis (11.6% vs.9.1%), diarrhea (9.9% vs. 10.0%) and dizziness (9.5% vs. 7.0%).
Discontinuations due to SAEs were 2.8% in the abatacept group vs. 1.6% in the placebo group. The frequency of serious infections was low overall (3.0% vs. 1.9% in abatacept- versus placebo-treated patients, respectively). Acute infusional AEs (9.8% vs. 6.7% in the abatacept versus placebo groups, respectively) were mostly mild-to-moderate in intensity. Safety data through cumulative exposure were consistent with those from the double-blind periods; there was no evidence of an increase in the incidence of serious infections or malignancies with increasing exposure to abatacept. Abatacept was associated with low levels of immunogenicity, with no detectable association between immunogenicity and safely or efficacy. Abatacept treatment did not result in a higher rate of seroconversion for anti-nuclear or anti-dsDNA antibodies versus placebo, and was associated with a similar frequency of autoimmune events versus placebo (1.4% vs. 1.8*, respectively). Moreover, treatment with abatacept may not markedly impair the response to vaccination in healthy volunteers or RA patients.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* pSS according to the revised European - U.S. criteria(22).
* Male or female * 18 years.
* Stimulated whole saliva secretion * 0.15 ml/min.
* Positive autoantibodies (IgM-Rf *10 and SS-A and/or SS-B).
* Parotid gland biopsy (paraffin material and fresh frozen tissue) with characteristic features of SS performed at time of inclusion (no longer than 12 months ago).
* In female patients: use of reliable method of contraception during the study and at least until 14 weeks after the last infusion, in women of child bearing potential.
* In male patients: use of reliable method of contraception during the study and at least until 14 weeks after the last infusion by partner of patient, in case the partner of the patient is a female of child bearing potential.
* Written informed consent.
* Patients are allowed to continue artificial tears and/or artificial saliva provided that the dosage and schedule regime are stable, and that the usage will be stopped one day prior to each evaluation.

Exclusion criteria

* Disease duration * 5 years.
* The presence of any other connective tissue disease.
* Clinically significant serious abnormalities on electrocardiography or chest X ray.
* Lab abnormalities:
o Serum creatine > 2.8 mg/dl (250 *mol/l);

o ASAT or ALAT outside 1.5 x upper normal range of the laboratory;
o Hb < 9 g/dl (5.6 mmol/l) for males and 8.5 g/dl (5.3 mmol/l) for females;
o Neutrophil granulocytes less than 0.5 x 109/l;
o Platelet count less than 50 x 109/l.
* Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases (e.g., patients with hepatitis B or C, patent tuberculosis or latent tuberculosis non-adequately treated) or immune deficiency which places the patient at an unacceptable risk for participation in the study.
* History of cancer, including mucosa associated lymphoid tissue (MALT) lymphoma in the preceding 5 years (except adequately treated basal cell carcinoma of the skin and carcinoma in situ of the skin).
* Positive pregnancy test or breast-feeding.
* Planned major surgery (e.g. joint replacement) within the duration of the treatment period of the study.
* Serious infections in the preceding month.
* Opportunistic infection in the preceding 3 months.
* Subjects with evidence of active or latent bacterial infections at the time enrollment, including subjects with evidence of Human Immunodeficiency Virus (HIV) infection.
* Subjects with current clinical or laboratory evidence of active tuberculosis (TB).
* Subjects with a history of active TB treated within the last 3 years.
* Subjects who received treatment for active TB greater than 3 years ago may be eligible for inclusion in this study if there is documentation of the prior anti-TB treatment confirming that it was appropriate in duration and type.
* Subjects with latent TB which was not successfully treated.
* Subjects with a positive TB screening test indicative of latent TB will not be eligible for this study unless active TB infection has been ruled out and they have been initiated treatment for latent TB with isoniazid (INH) for at least 4 weeks prior to dosing of Abatacept and they have a negative chest x-ray for active TB at enrollment. Such subjects should complete 9 months of INH treatment.
* Subjects with herpes zoster that resolved less than 2 months prior to enrollment.
* Preceding treatment with anti-TNF, rituximab or other monoclonal antibodies
* Use of prednisone and/or pilocarpine less than 2 weeks ago
* The use of hydroxychloroquine, azathioprine, cyclofosphamide, cyclosporine, MTX and other DMARDs should be discontinued at least 1 month prior to the first infusion of abatacept.
* History of alcohol or drug abuse.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-08-2010
Enrollment:	15
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:	29-04-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	28-07-2010
Application type:	First submission
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	EUCTR2009-015558-40-NL
CCMO	NL31137.042.09