Anti-CD20 for the retreatment of primary Sjögren*s syndrome in patients who were included in the placebo-controlled double blinded rituximab study

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Evaluation of the effect of retreatment with rituximab in 20 patients with primary Sjögren syndrome, and evaluation of the intra-individual effect of rituximab compared to placebo, in 10 patients who received placebo in the double blind randomized...

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

Summary

ID

NL-OMON32498

Source
ToetsingOnline

Brief title
Anti-CD20 for retreatment in primary Sjögren*s syndrome

Condition

- Autoimmune disorders

Synonym
Sjogren'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,Roche Nederland BV. Postbus 44 Woerden

Intervention

Keyword: anti-CD20, retreatment, rituximab, Sjögren□s syndrome

Outcome measures

Primary outcome

* Stimulated salivary gland function (stimulated submandibular / sublingual and

parotid saliva)

Secondary outcome

* Functional parameters

* Laboratory parameters

* Subjective parameters

* Histological/Molecular parameters

Study description

Background summary

SS is a chronic inflammatory and lymphoproliferative disease with autoimmune features, characterised by a progressive lymphocytic infiltration of the exocrine glands, notably the lacrimal and salivary glands. The main clinical features are a progressive dryness of the eyes (keratoconjuctivitis sicca) and dryness of the mouth (xerostomia). Furthermore, various extraglandular manifestations may develop, such as neuropathy, arthritis, fatigue, vasculitis, and renal or lung involvement. B-cell activation is a key feature of SS, leading to the production of autoantibodies and hypergammaglobulinemia. Furthermore, SS is also associated with an increased risk of B-cell lymphoma development.
Rituximab, a chimeric humanised monoclonal antibody which binds to the B cell surface antigen CD20, leads to a rapid B cell depletion and may lead to a decrease of SS disease activity. In 2005 a phase II study by our group showed that rituximab was effective in the treatment of primary SS (1). Currently, a double blinded randomized placebo-controlled trial with rituximab is being

performed at our departments. In this trial 20 patients are treated with rituximab, whereas 10 patients received placebo. One patient developed mild serum sickness, which responded well to corticosteroids. Interim statistical analysis after 24 weeks follow-up showed improvement on both objective and subjective variables in the rituximab group compared to the placebo group. However, 48 weeks follow-up data are not available yet.
In RA and SLE repeated courses of rituximab have resulted in good clinical responses (2-4). Since the effect of repeated courses of rituximab in primary SS is not well known, a phase II study will be performed in which patients who have been treated with rituximab before, receive a second course of rituximab treatment. Furthermore, patients who received placebo in the above mentioned trial will also be treated with rituximab, to evaluate the intra-individual effect of rituximab compared to placebo.

Study objective

Evaluation of the effect of retreatment with rituximab in 20 patients with primary Sjögren syndrome, and evaluation of the intra-individual effect of rituximab compared to placebo, in 10 patients who received placebo in the double blind randomized placebo-controlled rituximab trial.

Study design

Phase II trial

Intervention

Rituximab infusions (1000 mg), intravenous infusion of 100 mg of methylprednisolone before infusion of rituximab, together with 60 mg per day of oral prednisone on days 2, 3, 16 and 17, 30 mg per day on days 4, 5, 18 and 19 and 15 mg per day on days 6 and 20.

Study burden and risks

The total duration of this study is 68 weeks. Patients will be seen by their own physicians: their rheumatologist, their eye specialist, and their oral and maxillofacial surgeon prior to the study (regular visit), and after 16, 24, 36, 48 and 68 weeks. Rituximab is given by infusion on day 1 and 15. At these two visits, blood is drawn from the infuse (43 ml) and therefore venapunction is not necessary.
A parotid gland biopsy will be performed prior to the study in patients who received rituximab before, and at 16 weeks in patients who received placebo in the double blind randomized placebo-controlled rituximab trial. 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. This approach makes that all patients have been subjected to in

total three parotid biopsies, viz. the former rituximab patients before the firs t and second trial and at week 12 of the first trial, and former placebo patients before and at week 12 of the first trial, and at week 12 of the second trial.
The visit to the rheumatologist, the eye specialist and the maxillofacial surgeon are all scheduled on the same day. Each specialist visit takes about 20 minutes. At the rheumatology department physical examination is performed and 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 eye specialist performs the Schirmer test and the lisamine green 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, salivary gland function evaluation, schirmer test, lisamine green test, tear break up time) 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.

Experience in oncology showed that rituximab is well tolerated in a variety of settings, with mild-to-moderate infusion related reactions following the first infusion being the most common adverse event (5). Also in RA the most frequently reported adverse events in rituximab treatment were infusion-related, in particular at the first infusion. However, they responded well on intravenous infusion of steroids (6;7). Examples of infusion related event that have been reported in rituximab treatment include pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough, bronchospasm, hypotension and hypertension (2).
Keystone et al (2) performed an open-label extension analysis in patients with active RA. A total of 1039 patients with active RA were treated with repeated courses of rituximab. The most common adverse events, which were mild-to-moderate acute infusion related events, decreased with each course. The serious infection rate after course 1 (5.1 per 100 patient-years) remained stable through additional courses. It was concluded that RA patients treated with repeated courses of rituximab have sustained clinical responses with no new adverse events.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Stimulated whole saliva secretion >= 0,15 ml/min
* Male or female of 18 years or older
* Primary SS according to the revised European - U.S. criteria(22)
* 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 24 months ago)
* Use of reliable method of contraception during the first 48 weeks of the study
* Written informed consent

Exclusion criteria

* The presence of any other connective tissue disease
* Preceding treatment with anti-TNF or other monoclonal antibodies than rituximab
* Use of prednisone, hydroxychloroquine less than 1 month ago
* Use of MTX, cyclophosphamide, cyclosporin, azathioprine and other DMARDS less than * year ago
* Serum creatine > 2.8 mg/dl (250 *mol/l)
* ASAT or ALAT outside 1.5 x upper normal range of the laboratory

* Hb < 9 g/dl (5.6 mmol/l) for males and 8.5 g/dl (5.3 mmol/l) for females
* Neutrophil granulocytes less than 0.5 x 109/l
* Platelet count less then 50 x 109/l
* Positive pregnancy test or breast-feeding
* History of alcohol or drug abuse
* Serious infections
* Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which places the patient at an unacceptable risk for participation in the study
* History of any malignancy with the exception of completely resected basal cell carcinoma of the skin

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2008
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

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	EUCTR2008-004664-39-NL
CCMO	NL24270.042.08