PROTOCOL

TITLE. Rituximab (RTX) Therapy in Patients With Active TAO

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Background

Every year, 2000 patients in Sweden get the diagnosis of a diffuse autoimmune hyperthyroidism (Grave's disease (GD)). About 40% of the patients with GD have some complaints from their eyes indicating thyroid associated ophthalmopathy (TAO) in its mild form. Moderate-severe forms are seen in approximately 5-10% of GD patients. TAO is an autoimmune complication of GD and the inflammation causes swelling of the periorbital fat, muscles and connective tissue. The patient obtains symptoms such as red eyes, pain, epiphora, diplopia and sometimes exophthalmos. This affects the patient's quality of life (QoL) negatively.

Today, the primary treatment of moderate-severe TAO is high doses of intravenous (iv) steroids, with the purpose to suppress the inflammation. High doses of iv steroids cause side effects, therefore, it is motivated only in moderate-severe cases. Even when the treatment is given early in the course of the disease, only 70-80% of the patients respond to the treatment (responders). The treatment effect on the inflammation is most commonly measured with Clinical Activity Score (CAS) – a score recommended by the European Group of Graves orbitopathy (EUGOGO).

Ten years ago, small observational studies reported promising result on Rituximab (RTX) treatment in TAO, given less side-effects. RTX is an immunomodulating drug where antibodies affect B-cells.

Objectives

The primary aim of this study is to evaluate the effect of Rituximab (RTX) in Thyroid Associated Ofthalmopathy (TAO) patients who are non-responsive to treatment with iv GC (NR-RTX), with patients controls that continued with iv GC even though they did not respond (NR-C). A second aim is to compare the NR-RTX patients with the steroid responsive ones (R-GC) and NR-C, regarding background variables (gender, age, smoking status, duration of GD, duration of eye symptoms, thyroid treatment and lab) and efficacy variables (CAS, CAS SU/M, severity, proptosis and subjective diplopia). Lastly, a third aim is to evaluate and compare the QoL between the R-GC and the NR-RTX in the study at given time points.

Research questions

Does RTX lower the CAS of the non-steroid responsive TAO-patients (NR-RTX), in comparison to NR-C, that continued with iv GC, and R-GC? Do the background variables differ between NR-RTX and NR-GC or R-GC? And lastly, does the QoL differ between the R-GC and the NR-RTX at given measuring points?

Material and Methods

Study design

The RTX-study is a non-randomized prospective study that covers patients with moderate-severe TAO with indication for treatment with iv GC. For this study, a control group (NR-C) will be created.

Patients with TAO are evaluated at Department of Ophthalmology at Sahlgrenska University Hospital/ Mölndal's and are asked for participation if eligible. Variables collected at each visit Clinical Activity Score (CAS), Quality of Life (QoL) through ThyPRO self-assessment questionnaire, biochemical tests (fT4, fT3, TSH, TRAb, liver function tests, fasting blood glucose), blood pressure and waist. An oral glucose tolerance test (OGTT) is performed at 12, 18, and 46 weeks, and a short adrenocorticotropic hormone (ACTH) test at 12 and 46 weeks. Dual-energy x-ray absorptiometry (DXA) of the spine is conducted at 0 and 18 weeks.

All patients in the RTX-study start the 12-week scheme of iv GC at baseline. After four weeks of treatment, an evaluation of the treatment outcome is made. If the patients have improved their CAS score by ≥ 2 points, they are classified as responders to iv GC (R-GC) and continue their 12-week iv GC scheme. The remainder of the patients are classified as non-responders to the treatment with iv GC and are switched to 1000 mg iv RTX in week 5 and 7, combined with a weekly oral dose of 12.5 – 15 mg MTX (NR-RTX). The RTX is administered at the department of Rheumatology at Sahlgrenska University Hospital. All included patients have thereafter follow-up visits at week 12, 18, 32, 46 and 68 weeks after baseline.

At week 18 and at all follow-up timepoints thereafter, patients in R-GC group are evaluated for possible relapse. If a patient in R-GC has a CAS ≥ 4 points and CAS has worsened by ≥ 2 points compared to the value measured in the prior evaluation time-point, the patient is

considered having a relapse. Patients with relapse are randomized to either treatment with RTX and MTX or with *per oral* GC and MTX.

All patients included in the study are assessed according to study protocol, but if DON is developed, the affected patient is treated outside the study protocol in order to follow DON treatment regimen. The patients with DON still have the same evaluation time points as the other patients in the study, but they are excluded from the comparisons between groups after the occurrence of DON.

From the group of patients with moderate – severe TAO with indication for treatment with iv GC that do not meet inclusion/exclusion criteria for the RTX-study or declined participation, a control group (NR-C) of non-responders will be created. As they are not included in the RTX study, they continue with their 12 weeks scheme of iv GC treatment.

Data collected at the follow-up timepoints: QoL, safety data and information on adverse events.

Study population

Inclusion criteria for the RTX study: man or woman between 18-70 years old, TAO with 7-point score system of CAS ≥ 4 (less than 3 months old), euthyroid for at least 6 weeks.

Exclusion criteria for the RTX study were: DON, ulcerative corneal involvement, previous treatment with steroids for TAO (except for prophylaxis for TAO in connection with RAI), previous treatment with RTX, positive Hepatitis B or C serology, obtained a living vaccine within 4 weeks prior RTX+MTX to evaluation, history of recurrent significant infection or history of recurrent bacterial infections, assessment by the investigator that the patient may not attend to the protocol, current pregnancy or lactation, significant cardiac disease, including significant or uncontrolled arrhythmia, previous active tuberculosis, bone marrow depression with leukopenia, thrombocytopenia or significant anaemia, allergy to the active substance or any other substance in the medications or murine proteins, active, severe infections (such as tuberculosis, sepsis or opportunistic infections), patients with severe immunosuppression, severe cardiac failure or severe uncontrolled heart disease.

The TAO patients not included in the RTX-study will be identified using the diagnosis-related group (DRG) registry according to the 10th revision (ICD-10) in VGR. In DRG, a combination of different codes was used (TAO [H06.2], Graves' disease [E05.0] and iv infusion [DT016]).

Efficacy variables

In the study, both patients' eyes are evaluated regarding CAS and the score of and any improvement of the worst eye was used.

The proptosis is measured in both eyes using the Hertel exophtalmometer.

The ThyPRO questionnaire is a thyroid specific QoL self-assessment questionnaire. It is one questionnaire that measures QoL within 13 different dimensions: goitre symptoms, hyperthyroid symptoms (constitutes two dimensions), eye symptoms, tiredness, cognitive function, anxiety, depressivity, emotional susceptibility, impairment of social, daily and sex life and lastly cosmetic complaints. ThyPRO consists of totally 84 questions. The scores for each dimension can be presented as raw or normalised score (raw score/max score x 100) that ranges from 0 to 100. A high normalised score indicates decreasing QoL (i.e. more symptoms or greater impact of disease).