Study on the efficacy of rituximab in patients with polymyalgia rheumatica

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27507

Source
NTR

Brief title
BRIDGE-PMR

Health condition

polymyalgia rheumatica

Sponsors and support

Primary sponsor: None. This is an investigator initiated trial
Source(s) of monetary or material Support: Self financing: Sint Maartenskliniek

Intervention

Outcome measures

Primary outcome

A preliminary estimate of the GC-sparing effect of RTX by comparing the proportion of PMR patients with GC-free remission (PMR-AS <7 as described in section 3.1.1) in both groups

Secondary outcome

To compare in both groups:

-GC cumulative dose after 21 weeks;

-Proportion of patients achieving a relatively safe low dose of GC (5 mg or less) after 21 weeks

-Change in ESR and CRP, PMR-AS, inner core domain set as proposed by the OMERACT, SF-36, EQ5D-5L, HAQ-DI from baseline to 21 weeks;

-Change in BAFF, IL-6

-Presence of anti-ferritin antibodies and RTX antibodies;

-Frequency and types of GC-related adverse events during the study by using the GTI

-Frequency and types of GC- and RTX-related adverse events during the study

Study description

Background summary

Background

Polymyalgia rheumatica (PMR) is a debilitating inflammatory rheumatic disorder which typically occurs in patients older than 50 years and is characterized by pain and stiffness of the neck, bilateral shoulder, hip girdle and often elevated inflammatory parameters. Glucocorticoids (GC) are the cornerstone of PMR treatment, however, 29-45% of PMR patients do not sufficiently respond to GC treatment after 3-4 weeks and only 33-50% of PMR patients treated in secondary clinics achieve sustained GC-free remission after 2 years. GC related side effects occur in about 50% of PMR patients and are a significant burden for patients. This emphasizes the need for treatment alternatives such as conventional synthetic and biologic disease modifying antirheumatic drugs (csDMARDs and bDMARDs). One interesting mode of action that has not yet been studied is the efficacy of B-cell depletion in PMR. Rituximab (RTX), a chimeric mAb against CD20 which causes B-cell depletion, has proven to be an effective treatment in rheumatoid arthritis (RA). There are several indications that B-cells have a role have a role in PMR (and the related disease giant cell arteritis, GCA). One study has shown that a disturbed B-cell homeostasis is present in newly diagnosed untreated PMR and giant cell arteritis patients. In a case report one patient with refractory GCA came in remission after 1000 mg RTX. Additionally, a patient with refractory Takayasu disease (a large vessel vasculitis (LVV) comparable with GCA) was treated with RTX and showed remarkable clinical and laboratory improvement after 500 and 1000 mg RTX. So far no additional case reports or a proof of principle study on RTX in PMR patients has been described. As the need for more treatment alternatives in PMR is clear and in line with the

EULAR/ACR research agenda for PMR, it is important to evaluate whether a bDMARDs such as RTX is an effective alternative for GC in PMR patients.

Objectives

The primary objective is to evaluate the efficacy of RTX 1*1000 mg in newly diagnosed PMR patients fulfilling the Chuang criteria by comparing the proportion of patients in complete GC-free remission at week 21 in the RTX versus placebo group. Secondary objectives are comparing the cumulative GC dose at 21 weeks, the mean change of ESR and CRP from baseline to 21 weeks, the change in the PMR-activity score (AS), the efficacy of RTX with regard to the inner core domain set for outcome measures of PMR as proposed by the OMERACT, the functional status before and after treatment with RTX by using the HRQOL (health related quality of life), HAQ (Health Assessment Questionnaire), the effect of RTX on biomarkers such as total B-cell count, B-cell activating factor (BAFF), interleukin 6 (IL-6), T-cell count and anti-ferritin antibodies, the percentage of patients with RTX antibodies at week 21 and the frequency and types of GC- and RTX-related adverse events during the study.

Methods

We will conduct a 21 week double blind placebo controlled proof of concept serendipity study with a total of 50 newly diagnosed patients fulfilling the Chuang criteria for PMR. Patients will be randomized in a 1:1 ratio to either receive RTX 1* 1000 mg – including standard premedication – according to local protocol, or placebo. We chose this dose because earlier studies showed that the efficacy of RTX 1* 1000 mg did not differ from the registered 2* 1000 mg in RA patients. Additionally, all patients will receive standard PMR treatment of prednisone 15 mg during four weeks Afterwards prednisone will be tapered to 10 mg according to usual care and to 0 mg at week 17 by following a rapid tapering schedule. Patients will be followed for a total of 21 weeks. Outcomes of this explorative study after 21 weeks are the number of patients in GC-free remission, cumulative GC dose, estimates of changes in acute phase reactants, PMR-AS, inner domain of the OMERACT outcome measures for PMR, biomarkers (B-cells, T-cells, IL-6, anti-ferritin antibodies) RTX- and GC-related adverse events, level of serum anti-RTX anti-bodies, function and health related quality of life surveys. Assessments will take place at baseline, 2, 4,11, 17 and 21 weeks. Additional assessments will be made if patients experience a relapse of symptoms.

Relevance

The results of this pilot study will be of importance and is in line with the research agenda of the 2015 EULAR/ACR collaborative initiative for the management of PMR. Recently in 2018, treatment options with GC sparing agents in PMR and GCA has been listed as an important knowledge hiatus and is of high priority on the research agenda of the Nederlandse Vereniging van Reumatologie (NVR; Dutch Society for rheumatology) as well.

Nature and extent of the burden and risks associated with participation

In daily practice, rheumatologists monitor their patients with PMR on an ongoing basis once

every two, three or six months. During these regular visits, disease activity is measured and blood samples are collected. In this study patients will be scheduled to a visit at weeks 2, 4, 11, 17 and 21. At baseline demographics, and disease and treatment related variables will be assessed. Chest X-ray will be taken at baseline and ultrasonography of shoulders and hips will be performed at baseline and after 21 weeks. Blood samples will be collected at all visits. Patients will complete several short questionnaires (HAQ-DI, SF-36, EQ5D-5L, transition question, PASS question) and patients will be asked for other medication use and the occurrence of GC- and RTX-related adverse events, during all visits. The extra time required for the patient by participating in this study is estimated to be approximately 1 hour for the first visit and 15 minutes for the other visits. This results in a total of 2:15 hours of time required for a patient to take part in the study (excluding travel time).

Possible risks of participation in this study include the chance of a temporary increase in disease activity in the patients exposed to an accelerated tapering scheme of GC, especially in de placebo group. However, if this happens, the increase in disease activity will probably be short-lived as the rheumatologist will immediately act upon it by increasing GC dose. On the other hand, possible benefits include a reduced chance of GC- related side effects and shorter treatment duration for all patients RTX. Though it has to be taken into account that RTX does have side effects, including dose-dependent risk of infection and infusion related side effects such as headache, cough, nausea, stomach complaints, rash, muscle stiffness and numbness. Still, there is sufficient experience with RTX as it is registered for other indications where it has a relatively safe adverse events profile with possibly fewer infections compared to GC. Furthermore, earlier studies have shown that RTX is well tolerated by patients and in our study we also prescribe a lower dose than registered for RA. We therefore expect a minimal risk for patients treated with RTX. This research will be conducted according to the principles of the Declaration of Helsinki and all relevant Dutch legislation. METC approval has been granted and the trial has been submitted to the Dutch Trial Registry.

Study objective

RTX 1*1000 mg compared to a placebo controlled group leads to a higher proportion of patients in glucocorticoid remission at week 21 in newly diagnosed PMR patients fulfilling the Chuang-criteria

Study design

Visits at week 0 (baseline), 2, 4, 11, 17 and 21. All patients will be followed for 21 weeks

Intervention

rituximab 1*1000mg

Contacts

Public

Scientific

Eligibility criteria

Inclusion criteria

·PMR according to the Chuang PMR classification criteria

·Signed written informed consent

Exclusion criteria

·Not being able to speak, read or write Dutch

·PMR diagnosed >4 weeks before inclusion in the study

·Exposure to GC or other immunosuppressant treatments in the past 3 months more than 2 weeks and more than a week before inclusion of the study

·Known concomitant GCA or other rheumatic diseases such as RA, spondylarthropathies, connective tissue diseases, drug-induced myopathies, active and untreated thyroid disorders, Parkinson disorder or severe fibromyalgia

·Previous hypersensitivity for prednisone, RTX or murine peptides

·Contra-indications to RTX such as active current infection, including hepatitis B or tuberculosis infection, state of severe immunodeficiency, severe heart failure (NYHA-class IV)

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2019
Enrollment:	50
Type:	Anticipated

Ethics review

Positive opinion

Date:	26-11-2018
Application type:	First submission

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
NTR-new	NL7414
NTR-old	NTR7639
Other	eudract 2018-002641-11 : CMO number: 2018-4609

Study results