The BRIDGE-PMR study: B-cell depletion with Rituximab for Dose reduction of Glucocorticoids: Efficacy in PolyMyalgia Rheumatica

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The proportion of patients in GC-free remission after 20 weeks.

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

Summary

ID

NL-OMON45885

Source
ToetsingOnline

Brief title
The efficacy of rituximab in polymyalgia rheumatica

Condition

- Autoimmune disorders

Synonym
polymyalgia, polymyalgia rheumatica

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: Sint Maartenskliniek

Intervention

Keyword: efficacy, glucocorticoid sparing, polymyalgia rheumatica, Rituximab

Outcome measures

Primary outcome

To evaluate the efficacy of RTX 1*1000 mg in newly diagnosed PMR patients fulfilling the ACR-criteria by determining the proportion of patients in complete GC-free remission at week 20;

Secondary outcome

-To determine the cumulative GC dose at 20 weeks;

-To assess the mean change of ESR and CRP from baseline to 20 weeks;

-To assess the change in the PMR-AS;

-To evaluate the efficacy of RTX with regard to the inner core domain set for outcome measures (systemic inflammation, physical function, pain, stiffness) of PMR as proposed by the OMERACT;

-To assess the functional status before and after treatment with RTX by using the Health Assessment Questionnaire Disability Index(HAQ-DI), health related quality of life survey (EQ5D-5L), Short Form health survey (SF-36) and the transition and Patient Acceptable Symptom state (PASS) questionnaire

-To evaluate 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;

-To assess the percentage of patients with RTX antibodies at week 20;

-To determine the frequency and types of GC- and RTX-related adverse events

during the study

Study description

Background summary

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. PMR is closely related to giant cell arteritis (GCA) -a form of large vessel vasculitis (LVV)- as 16% to 21% of PMR patients have concomitant GCA, and 40% to 60% of patients diagnosed with GCA have concomitant PMR.
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 add significant burden for patients. This emphasizes the need for treatment alternatives such as conventional synthetic and biologic disease modifying antirheumatic drugs (csDMARDs and bDMARDs).

The exact value of several csDMARDs in PMR remains unclear. So far most evidence exists for methotrexate (MTX).The most recent guidelines on management of PMR recommend rheumatologists to consider early start of MTX in patients with risk factors for relapses/prolonged GC therapy. It is also recommended to prescribe MTX in patients who relapse under GC therapy and/or who develop GC-related adverse events or have comorbidities that worsen due to GC. The data on the use of concomitant MTX to date is of medium quality and the MTX dosages are low (7.5-10 mg weekly) compared to the dosages in other rheumatic diseases. One randomized controlled trial (RCT) with concomitant MTX 7.5 mg showed no additional GC sparing effect, although there was a high drop-out rate of 48%. Another RCT found that 10 mg MTX weekly was associated with shorter GC treatment and fewer flares. Outcomes from this study at 76 weeks showed that 28 of 32 patients in the methotrexate group and 16 of 30 patients in the placebo group were no longer taking prednisone. (P*= 0.003). Furthermore, patients receiving concomitant MTX received a median cumulative lower GC dose of 0.9 milligram compared to placebo. However, this finding was not significant. Furthermore, no difference in incidence of GC-related side effects was seen. An open randomized trial of 24 non blinded patients found a significant GC-sparing effect of MTX and notably, significantly better bone mineral density when using concomitant MTX. Leflunomide (LEF) is another csDMARD that showed promise of efficacy in two case series with PMR patients and recently a research group in Groningen initiated a double blinded RCT to examine the relapse sparing effect of concomitant LEF with GC as opposed to placebo with GC.

The efficacy of several bDMARDs has been examined in PMR. So far no effect of TNF-alpha blockers infliximab and etanercept has been shown in PMR patients. There is evidence that anti- IL-6 treatment (tocilizumab) is effective in GCA and also in PMR itself, showing a higher chance of remission and faster tapering of GC. Abatacept has also been shown to be effective in patients with GCA. Currently, tocilizumab, sirukumab, infliximab, etanercept are being investigated in RCTs. These efforts reflect the research agenda of the EULAR/ACR on the management of PMR, expressing the need for more studies on the efficacy and safety of bDMARDs in PMR, as none of the studied bDMARDs have been established as alternative to GC in the treatment of PMR due to limited effect, and limited data on safety and costs.

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). One study has shown that a disturbed B-cell homeostasis is present in newly diagnosed untreated PMR and GCA patients. In a case report one patient with refractory GCA came in remission after 1000 mg RTX. Additionally, a patient with refractory Takayasu 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.

Study objective

The proportion of patients in GC-free remission after 20 weeks.

Study design

Our work plan is to conduct a 20 week long uncontrolled open label proof of concept serendipity study with a total of 40 newly diagnosed patients fulfilling the EULAR/ACR criteria for PMR. All patients will receive RTX 1* 1000 mg * including standard premedication * according to local protocol. A systematic review and meta-analysis of RTX-regimens in RA patients showed that the efficacy of RTX 1* 1000 mg did not differ from 2* 500mg or 2* 1000 mg. We therefore chose 1* 1000mg as the study dose. Additionally, all patients will receive prednisone 15 mg during four weeks. Afterwards prednisone will be tapered to 0 mg by following a rapid tapering schedule up to and including week 16. Patients will be followed for a total of 20 weeks. Outcomes of this explorative study after 20 weeks are the number of patients in GC-free remission, cumulative GC dose, estimates of changes in acute phase reactants, PMR-activity score (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 and function with the HRQoL (health related quality of life) and HAQ (Health Assessment Questionnaire) surveys. Assessments will take place at baseline, 2, 6, 10, 16 and 20 weeks. Additional assessments will be made if patients experience a relapse of symptoms.

Intervention

All patients will receive 1 * 1000 mg rituximab in combination with an accelerated tapering scheme of prednisone.

Study burden and risks

In daily practice, rheumatologists monitor their patients 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 week 2, 6, 10, 16 and 20. At baseline, demographics and disease and treatment related variables will be assessed. Chest X-ray will be taken once, at baseline and ultrasonography of shoulders and hips will be performed at baseline and after 20 weeks. Several blood samples will be collected at all visits. Several short questionnaires will be completed (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 this study is estimated to be approximately 1 hour for the baseline visit and 15 minutes for the follow-up visits. This results in a total of 2:15 hours of extra time required for a patient to take part in the study (excluding travel time).
Risks of participation in this study include the chance of a temporary increase in disease activity in the patients exposed to a accelerated tapering scheme of GC. 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. This research will be conducted according to the principles of the Declaration of Helsinki and all relevant Dutch legislation. METC approval will be requested and the trial will be submitted to the Dutch Trial Registry.

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

·PMR according to the ACR/EULAR 2012 PMR core classification criteria;·Signed written informed consent

Exclusion criteria

·Not being able to speak, read or write Dutch
·Polymyalgia rheumatica diagnosed more than 4 weeks before inclusion in the study
·Exposure to Glucocorticoids or other immunosuppressant treatments in the past 3 months
·Known concomitant giant cell arteritis or other rheumatic diseases such as rheumatoid arthritis, spondylarthropathies, connective tissue diseases, drug-induced myopathies, active and untreated thyroid disorders, Parkinson disorder or fibromyalgia
·Previous hypersensitivity for prednisone, rituximab or murine peptides
·Contra-indications to rituximab 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2019
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	rixathon
Generic name:	rituximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-07-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-11-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2019

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-002641-11-NL
CCMO	NL66847.091.18