The efficacy of Methotrexate for glucocorticoid dose reduction in recently diagnosed polymyalgia rheumatica patients: a double-blind randomized placebo controlled multicenter clinical trial.

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Primary Objective: To determine whether in recently diagnosed PMR patients concomitant treatment to glucocorticoids with MTX 25 mg/week compared to a placebo will lead to a higher proportion of GC-free remission at 52 weeks. Secondary Objectives: To...

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

Summary

ID

NL-OMON54851

Source
ToetsingOnline

Brief title
PMR MODE

Condition

- Autoimmune disorders

Synonym
polymyalgia, polymyalgia rheumatica

Research involving

Human

Sponsors and support

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

Intervention

Keyword: glucocorticoïd sparing, Methotrexate, polymyalgia rheumatica, randomized controlled trial

Outcome measures

Primary outcome

The primary study outcome is the proportion of PMR patients in GC-free

remission in both treatments groups compared to each other at week 52.

Secondary outcome

1. The proportion of patients in GC-free remission at week 32;

2. The time to GC-free remission and first relapse;

3. The GC cumulative dose at week 32 and 52;

4. The number of relapses or recurrences during follow up at week 32 and 52;

5. The proportion of patients that relapsed or had a recurrence during follow

up at week 32 and 52;

6. The change in PMR-AS;

7. The change in: ESR, CRP, transition and PASS questions, VAS, EQ-5D, HAQ, and

PROMIS-PF;

8. The frequency and types of GC-related adverse events during the study as

measured by the Glucocorticoid Toxicity Index (GTI);

9. The frequency and types of GC- and MTX-related adverse events

10. The proportion of patients that require a MTX/placebo (dose) adjustment.

Study description

Background summary

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting mostly people older than 50 years (1). The reported prevalence ranges from 0.85% to 1.53% depending on classification criteria and demographic features (2,3). Patients generally suffer from acute onset pain and/or morning stiffness of the neck, bilateral shoulder girdle, and (with less specificity) pelvic girdle. Morning stiffness usually lasts for more than 45-60 minutes (1,4,5). Additionally 40-50% of patients may report constitutional symptoms like low-grade fever, fatigue, asthenia, and weight loss. The duration of the disease can be up to 2-3 years, and during the first year the chance of relapse can range up to 20-55% (1,6). During physical examination, PMR may manifest as a reduction in active motion, but near to normal passive motion of the shoulders, neck, and hip. Furthermore, muscle weakness is not common despite diffuse (muscle) pain (1). Untreated PMR leads to a significant reduction in quality of life (QOL) (7).
In laboratory tests, PMR typically shows a rise in acute phase reactants (5). PMR is closely related to giant cell arteritis (GCA), a large blood vessel vasculitis (LVV) occurring in elderly people, as 16-21% of PMR patients have GCA. Furthermore 40 to 50% of patients diagnosed with GCA have concomitant PMR (1). The cause of PMR remains unknown and there is no golden standard for the diagnosis of PMR (1,8).
Glucocorticoids (GC) remain the cornerstone of treatment of PMR (9). The most recent guidelines recommend a GC initial dosage between 12.5 and 25 mg, depending on patient characteristics and risk factors. Furthermore, different tapering regimens, which have not been adequately investigated, have been suggested (9). However, there are several drawbacks to treatment with GC for PMR, like treatment duration, lack of efficacy, and GC-related side effects. Firstly, GC free remission was achieved in only 27% in a PMR primary care cohort within the first year of treatment (3), and in only 33-50% of a hospital care cohort of PMR patients after two years of treatment (7,10). Secondly, GC-related adverse events (AE) have been reported in a large portion of patients, ranging upwards of 65% dependant on GC dosage (7,11-13). These side effects can be severe, especially when GCs are used for a long period of time. Patients using GCs for longer than 2 years for example are more likely to develop weight gain, osteoporosis, fractures, metabolic and cardiovascular side effects as well as infections (7,11,13-15). Therefore, GC sparing agents are warranted to reduce treatment duration, enhance treatment efficacy, and reduce GC-related side effects.
The exact value of several conventional synthetic disease-modifying

antirheumatic drugs (DMARD) in PMR remains unclear. To date there is no proven efficacy or data is insufficient on azathioprine, cyclophosphamide, cyclosporin and dapsone (16). For leflunomide there are two case series that showed some promise of efficacy in PMR patients (17,18). The evidence regarding biological DMARD treatment is even scarcer. An open label trial with tocilizumab showed some promise, although study size was very small and treatment is associated with high costs (19,20).
The most evidence - three small RCTs - for a GC-sparing treatment exists for Methotrexate (MTX) (9,16). One RCT with concomitant MTX 7.5 mg showed no GC-sparing effect, although the high drop-out rate of 48% might be a factor in this negative finding (21). A RCT with 10 mg concomitant MTX showed fewer relapses, but no significant difference in GC related AE (22). Long term outcomes of this trial showed that patients receiving concomitant MTX received a lower cumulative GC dose compared to placebo, but this finding did not reach statistical significance (23). Furthermore, no difference in long term GC-related AE was found, although authors confirm data obtained retrospectively from elderly patients can be questioned (23). Finally, a small open RCT found that 24 patients treated with 10mg of concomitant MTX showed a significant reduction in GC cumulative dose, fewer relapses and earlier discontinuation of GC (24). No studies using higher dosages of MTX comparable to those used in RA (up to 25-30 mg per week) have been performed (25,26).
Based on this limited data, the current EULAR/ACR recommendations for the management of PMR advise an early introduction of MTX 7.5 - 10 mg weekly in patients prone to relapse or prolonged GC-therapy, as well as in patients where GC-related AE are more likely to occur, e.g. females, a high initial ESR/CRP, hypertension, diabetes, cardiovascular disease, and osteoporosis (6,9,27). In clinical practice, however , MTX is scarcely used, presumably in part because of the limited evidence. A national database study of German rheumatology clinics reported that only 19% of patients with PMR received concomitant MTX (13). In addition, the EULAR/ACR recommendations for the management of PMR also advise further research regarding MTX (9).
In conclusion, evidence on GC-sparing treatments for PMR patients remains scarce and MTX seems to be the most promising and best examined treatment. However, well-designed blinded studies using higher dosages of MTX are lacking. We therefore set out to study if optimally dosed weekly MTX is indeed effective in achieving GC-free remission and reducing cumulative GC dose in PMR.

Study objective

Primary Objective: To determine whether in recently diagnosed PMR patients concomitant treatment to glucocorticoids with MTX 25 mg/week compared to a placebo will lead to a higher proportion of GC-free remission at 52 weeks.

Secondary Objectives: To assess in, and compare between, both groups (MTX versus placebo):
1. The proportion of GC-free remission at week 32;

2. The time to GC-free remission and first relapse;
3. The proportion of low-dose GC (<= 5mg daily) remission at week 32 and 52;
4. The GC cumulative dose at week 32 and 52;
5. The number of relapses or recurrences during follow up at week 32 and 52;
6. The proportion of patients that relapsed or had a recurrence during follow up at week 32 and 52;
7. The change in PMR-AS;
8. The change with the core domain sets for outcome measures of PMR as proposed by the OMERACT, including:
a. Systemic inflammation;
b. Physical Function;
c. Pain;
d. Stiffness;
9. The change in Patient Reported Outcomes (PROs): transition and Patient Acceptable Symptom states (PASS) questions, Visual Analog Scales (VAS), the health related quality of life (EQ-5D-5L), Health Assessment Questionnaire (HAQ), and Patient Reported Outcome Measures Information System Physical-Function (PROMIS-PF);
10. The frequency and types of GC- and MTX-related adverse events;
11. The proportion of patients that require MTX/placebo (dose) adjustment.
12. Direct healthcare costs at week 52

Study design

This study is a double blind, randomized placebo-controlled superiority trial of recently diagnosed PMR patients fulfilling the 2012 EULAR/ACR classification criteria. Patients will mainly be recruited from the Sint Maartenskliniek (patients recruited at locations Nijmegen, Woerden, Boxmeer, CWZ, Geldrop) and Gelre Ziekenhuizen over the course of 18 months.
After inclusion patients will randomly be allocated into one of two arms with a 1:1 ratio. Patients allocated to the treatment arm will receive oral MTX and patients assigned to the other arm will receive placebo. All patients will receive prednisolone using an accelerated tapering protocol (see *Treatment of subjects* for more details).
The pre-recruitment phase of the study is scheduled to take 6 months . The recruitment and inclusion phase is expected to take 18 months. Follow-up will take 12 months for each recruited patient. Data analysis, reporting, and submitting the written article of the study is scheduled to take 6 months. Total study time is approximately 42 months (Figure 1).

Intervention

5.1 Investigational product/treatment
Patients will randomly be allocated into two arms with a 1:1 ratio. Patients allocated to the treatment arm will receive oral Methotrexate 15 mg per week for the first 4 weeks, followed by 25 mg per week for the following 48 weeks if

they did not develop significant MTX-related side effects (Table 2). The placebo arm will receive a placebo of MTX 0mg per week. MTX will be dosed in capsules of 5mg, allowing both splitting of doses over the course of the day (to improve bioavailability) and easier dose adjustment without un-blinding with regards to treatment arm.
5.2 Use of co-intervention (if applicable)
All patients will receive treatment with regular prednisone once per day starting at 15mg and tapering through an accelerated protocol over the course of 24 weeks: every 4 weeks a reduction of 2.5mg per day. Tapering will only occur after an adequate initial response and subsequently if the disease is in remission at visits (Table 2 and Figure 2). In case of primary non-response during the first 4 weeks (as defined later) the prednisone dose will be increased, to 25mg/day, for 2 weeks. After response to this dose, prednisone will be dosed at 20mg/day for 2 weeks, followed by 15mg/day and the accelerated tapering protocol as stated above.
When no primary response is obtained during treatment with 25 mg/day, alternative diagnoses such as giant cell arteritis (GCA) will be ruled out; if a patient does not respond after 4 weeks, prednisone can be raised further and the patient will be excluded from the study.
If a patient flares for the first time, prednisone will be increased to the pre-flare dose for 4 weeks. If response follows prednisone will then again be tapered through the accelerated tapering protocol (Figure 3). If a patient flares for the second time, prednisone will be increase to the pre-flare dose for 7 weeks. If response follows prednisone will then be tapered through a local hospital usual care tapering protocol. If response does not follow after raising of prednisone to the pre-flare dose, prednisone dose can then be increased with increments of 5-10 mg for 4 weeks until there is either response or prednisone is at 25mg/d. If no response is obtained during treatment with 25mg/day, alternative diagnoses will again be ruled out and if the patient does not respond after 4 weeks the patient will be excluded from the study.

Study burden and risks

During this study, patients will be assessed at 6 visits, after the baseline assessment, over the course of 52 weeks. At baseline, demographics and patient and disease characteristics are assessed. Additionally, imaging and a several laboratory tests will be run. At follow-up, blood samples will be collected to assess acute phase reactants and possible adverse events, patients will complete questionnaires, and rheumatologists will assess disease activity and potential adverse events. Compared to usual care, consisting of a visit ranging from once a month early on to once per 2, 3, or 4 months later on, this means approximately 2 extra visits for the purpose of this study. The study questionnaires and measurements will take on average an additional 20 minutes per visit.
Potential risk associated with participation includes an increase in disease activity due to the accelerated GC tapering protocol, especially in the placebo group. In case this happens, patients are instructed to contact their treating

rheumatologist, who will increase GC dose accordingly. Potential side-effects of MTX are mainly gastro-intestinal of nature, including nausea, abdominal pain, diarrhea, hematological or liver enzyme abnormalities, and non-basal-cell skin cancer. However, there is sufficient evidence that indicates that MTX has a relatively safe treatment profile, and it is registered for a number of indications. Therefore we expect a minimal risk for patients treated with MTX. 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 and EuropeanTrial Registry.

Contacts

Public
Sint Maartenskliniek

Hengstdal 3
Ubbergen 6574 NA
NL
Scientific
Sint Maartenskliniek

Hengstdal 3
Ubbergen 6574 NA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• PMR according to the 2012 EULAR/ACR classification criteria, diagnosed within

the last 12 weeks. Mandatory criteria:
o an age > 50,
o bilateral shoulder pain,
o elevated CRP/ESR (dependent on local testing procedure),
• Patients must score at least 4 points in the following 2012 EULAR/ACR criteria:
o Morning stiffness > 45 mins (2 points),
o absence of (rheumatoid factor) RF or Anti-citrullinated protein antibodies (ACPA) (2 points),
o hip pain or limited range of motion (1 point),
o absence of other joint involvement (1 point);
• Patients must be eligible for treatment with MTX or placebo and show a willingness to follow the study protocol as judged by treating rheumatologist;
• Signed written informed consent.

Exclusion criteria

• Not being able to speak, read or write Dutch;
• PMR-related GC treatment prior to inclusion consisting of either:
o GC exposure for > 8 weeks;
o GC treatment with > 30 mg/day;
o No further information regarding GC treatment;
• Exposure to other systemic immunosuppressant treatments other than GC 3 months prior to inclusion in the study;
• Active concomitant GCA or other rheumatic diseases such as RA, spondylarthropathies, connective tissue diseases, or drug-induced myopathies;
• Neuropathies or other conditions that might interfere with pain or movement evaluation of PMR, as judged by the treating rheumatologist;
• Previous hypersensitivity for prednisolone or MTX.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2020
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jylamvo
Generic name:	Methotrexate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-01-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-02-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-12-2023

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

ID: 22681
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-002413-18-NL
CCMO	NL69979.091.19
OMON	NL-OMON22681