Polymyalgia rheumatica

Clinical characteristics and new treatment opportunities

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Raoul Dufy (1877-1953) was a famous French painter who suffered from rheumatoid arthritis (RA) and also one of the first patients who received glucocorticoids (GC) in the pre-biological era. The GC enabled him to paint again; he regained his "joie de vivre".

To express his gratitude, he gifted this painting titled "La Cortisone" (1950) to his treating physician (Freddy Homburger). Unfortunately, he died a few years later due to a massive intestinal hemorrhage, an adverse event due to the combination of GC with aspirin.

Nowadays many RA patients are spared from these glucocorticoid related serious adverse events due to the availability of disease modifying drugs (DMARDs) for RA. However, these developments are in stark contrast to developments in polymyalgia rheumatica, where only few options of GC-sparing agents exist, with limited efficacy. The story of Raoul Dufy relates to one of the aims of this thesis: expanding the GC-sparing treatment options with DMARDS in order to reduce the occurrence of GC-related (serious) adverse events, such as happened with Raoul Dufy.

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Chapter 1

General introduction
General introduction

Epidemiology and immunopathogenesis of polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease usually affecting people older than 50 years.\(^1\) The incidence of disease increases with age, and the highest peak is seen in the age group of 70-79 years.\(^2\) The highest incidence is seen in Northern European countries, varying from 41 to 113 per 100,000 persons.\(^1\) PMR is the second most common inflammatory rheumatic disease after rheumatoid arthritis (RA), and more often occurs in women than men.\(^1\) The lifetime risk for PMR is higher for women than for men; 2.4% versus 1.7%.\(^1\) PMR can occur isolated or in combination with giant cell arteritis (GCA) – a form of large vessel vasculitis (LVV). PMR and GCA are closely related to each other as 40%-60% of GCA patients also have PMR at the time of GCA diagnosis and 16-21% of PMR patients have or will develop GCA.\(^4\)

The cause of PMR remains unknown, but is likely multifactorial and triggered by a combination of genetic predisposition, ageing of the immune system and environmental factors such as infectious diseases.\(^1\) The hypothesis for infectious diseases as a possible trigger for PMR was made because several earlier studies reported simultaneous peaks of onset of GCA / PMR and seasonal pattern of various infectious agents.\(^2,5\) However, most studies were conducted in patients with GCA.\(^1,2\) In order to acquire more evidence for the theory of infectious agents as a disease trigger in PMR, we aimed to investigate whether there was a cyclic pattern of PMR disease onset associated with a seasonal distribution of microbes that were associated with GCA/PMR onset in previous studies. This research is further outlined in chapter 2 of this thesis.

Even though the term “myalgia” refers to muscle pain, PMR appears to be a disorder mainly involving inflammation of the proximal bursa (bursitis), tendons (tenosynovitis) and in lesser extent the large joints (arthritis).\(^6\) Interspinous bursitis of the cervical and lumbar spine has also been reported.\(^1\)

To date the exact pathogenesis of PMR remains unclear and an appropriate understanding of this mechanism may lead to targeted therapies. In the recent years, several studies have tried to uncover the immuno-pathogenesis of PMR. The inflammatory infiltrate in affected synovial membranes obtained by studies involving arthroscopy showed predominantly macrophages and CD4 T-lymphocytes.\(^7\) Additionally, increased interstitial concentrations of several pro-inflammatory cytokines were found in muscles of PMR patients with active disease compared to control patients. The cytokines found are interleukin-1\(\alpha\) and interleukin-\(\beta\), interleukin-1 receptor antagonist, interleukin 6, tumor necrosis factor-\(\alpha\), and monocyte chemoattractant protein 1, and may play an important role in PMR.\(^8\) T-cells and B-cells may also play an important role in the pathogenesis. In both PMR and GCA patients decreased levels of regulatory T- and Th1 cells, and increased levels of Th17 cells were found compared to control subjects. The additional analysis of temporal artery biopsies in GCA patients showed a large infiltration of Th1 and Th17 cells, adding to the evidence that T-lymphocytes are possibly involved in the pathogenesis of PMR and GCA.\(^9\) In addition, PMR is thought to be potentially also a B-cell driven disease for several reasons. Firstly, a disturbed B-cell homeostasis was observed in newly diagnosed and untreated PMR and GCA patients.\(^10-12\) Compared to healthy control subjects, the number of circulating B-cells in newly diagnosed and untreated PMR patients is decreased and recovered after glucocorticoid (GC) therapy in these patients. There was inverse correlation between the number of B-cells and acute phase reactants (APR), and serum B-cell activating factor (BAFF) in untreated patients.\(^10\) Secondly, enhanced B-cell
activity is suggested as an increased presence of auto-antibodies in sera and immunoglobulin deposits in biopsies of PMR and GCA patients was found. Lastly, an association was described between GCA and PMR patients with atypical disease onset – such as normal acute phase reactants at diagnosis – and the use of MTX is high on the research agenda of the 2015 EULAR/ACR guideline for the management of PMR.

Clinical presentation and diagnosis

PMR typically presents with pain and stiffness of the neck, shoulders and hip girdle, caused by inflammation of bursae and / or synovitis of the large joints. It may be accompanied by movement restrictions leading to reduced daily functioning and quality of life if untreated. Morning stiffness may last for more than 45-60 minutes, and in 40-50% of patients constitutional symptoms like low-grade fever, fatigue, asthenia, and weight loss occur. In up to 25% of patients, peripheral arthritis may occur, often in the knee or wrist. Carpaltunnel syndrome and distal tenosynovitis may also be present in patients. Additional laboratory testing usually shows elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), which are also important markers for assessment of PMR activity during follow-up.

To date, there is no golden standard for the diagnosis of PMR although different classification criteria exist for PMR. The most recent classification criteria are the 2012 ACR/EULAR criteria which was evaluated in a prospective cohort of 25 PMR patients and 189 control patients who had musculoskeletal complaints but no clinical PMR diagnosis. The sensitivity and specificity of a score of at least four were 68% and 78% respectively. Using these classification criteria leads to a more homogeneous selection of PMR patients for clinical studies, increasing the comparability and generalizability of studies with each other. However, these classification criteria cannot be used as diagnostic criteria and diagnosing PMR remains challenging as many diseases mimic PMR and PMR often does not present itself with PMR typical features. One of these atypical features are low acute phase reactants (APR). There is scarce but conflicting evidence whether PMR with normal APR at diagnosis exists as it is reported in 1.1 to 22.5% of PMR patients. If PMR with normal APR indeed exists, it remains unclear whether these patients are a distinct clinical subset of PMR with different presentation and prognosis, or whether they are incorrectly diagnosed with PMR. In this thesis, the difficulty of diagnosing PMR in patients with normal APR will be further outlined in chapter 3.

Treatment

To date, glucocorticoids (GCs) remain the cornerstone of treatment of PMR. However, GC treatment is associated with several drawbacks. Firstly, GC increases the risk of development of comorbidities, or are (relative) contra-indicated in certain existing comorbidities such as glaucoma, diabetes or stomach ulcers. These GC-related adverse events (AE) occur quite often, they are reported in up to 65% of patients and occur more often when longer GC treatment is required. Secondly, treatment duration may be long since many patients flare during tapering. These drawbacks of GC emphasize the need for GC sparing agents to enhance treatment efficacy, shorten treatment duration, and reduce GC-related side effects. Use of disease modifying anti-rheumatic drugs (DMARDs) may reduce GC-need and is indeed recommended by the 2015 ACR/EULAR management guideline of PMR.

In light of this, the efficacy of several conventional synthetic (cs) and biological (b) disease-modifying anti-rheumatic drugs (DMARD) has been studied but so far only few DMARDs have shown (varying) efficacy. As regards to csDMARDs, albeit weak there is some evidence for leflunomide and azathioprine. Most evidence exists for methotrexate (MTX). However, the quality of the evidence is still low. The studied MTX dose may also be suboptimal as higher doses are used in other rheumatic diseases such as rheumatoid arthritis (RA). Based on this limited evidence, early introduction of MTX in PMR patients with worse prognosis such as flares, and at high risk for GC-related AE, is recommended by the current EULAR/ACR recommendations for the management of PMR. However, one study by Albrecht et al. showed that MTX is infrequently used in clinical practice. This limited prescription may reflect the uncertainty of the exact role of MTX in PMR, due to the limited and conflicting evidence. Future research regarding the use of MTX is high on the research agenda of the 2015 EULAR/ACR guideline for the management of PMR and therefore we set up two studies to assess the efficacy of MTX in PMR.

First, we set up a retrospective study to assess the efficacy of higher dosed MTX in PMR patients in routine clinical practice concerning the GC-sparing effect and frequency of flares compared to a control group who were eligible for MTX according to the 2015 EULAR/ACR recommendations, but did not receive it. This is outlined in chapter 4. However, due to its nature it is usually not possible to fully correct for unmeasured confounders in retrospective studies and obtain reliable causal inference. Therefore we additionally set up a double blind placebo controlled trial of MTX 25 mg once weekly in patients who were recently diagnosed with PMR, to assess whether higher dosed MTX, started early, is effective in achieving GC-free remission and reducing cumulative GC dose in PMR. The protocol of this study is elaborated in chapter 5 of this thesis.

Concerning bDMARDs, several have been examined and tocilizumab (TCZ) – an IL-6 blocker - showed some promise. However, it is associated with high costs and disease monitoring might be somewhat impaired due to its effect on C-reactive protein (CRP). No efficacy was found for TNF-alpha blockers and several other bDMARDs, such as abatacept, sarilumab, and JAK-stat-inhibitors are currently being tested in randomized trials. Due to the lack of treatment options there remains an unmet need for alternative treatment options in PMR. So far, the effect of B-cell depletion has not been previously studied in PMR. As described earlier in the introduction, in both GCA and PMR a disturbed B-cell homeostasis was observed in untreated patients. Additionally, there are several case reports of large vessel vasculitis (LVI – a subset of GCA) successfully treated with RTX. Because B-cell depletion may be an interesting treatment target, we set up a double blind randomized placebo-controlled trial to examine the efficacy of rituximab (RTX) – a chimeric monoclonal antibody CD20 which causes B-cell depletion - in patients with PMR. This is described in chapter 6.

Objectives and outline of this thesis

The objective of this thesis was to further look at triggering factors for onset of PMR, and PMR patients with atypical disease onset – such as normal acute phase reactants at diagnosis – and to broaden the treatment options in PMR. This thesis therefore aims to answer the following hypotheses:

1. Is there an association between the incidence of onset of PMR symptoms and the seasonal distribution of infectious diseases (Mycoplasma pneumoniae, Chlamydophila pneumoniae, Parvovirus B19 and parainfluenza virus type 3), supporting the theory of an infectious trigger in PMR?

2. Are PMR patients with normal acute phase reactants at diagnosis a) caught early in the disease course b) misdiagnosed, or c) a distinct subset of PMR with different clinical presentation and prognosis?
3. What is the efficacy of MTX in usual care, on a) incidence of flares and b) cumulative GC-dose, compared to patients who were eligible for MTX according to the 2015 ACR/EULAR management guidelines, but were not treated with it?

4. Does MTX 25mg/week compared to placebo lead to a higher proportion of GC-free remission in patients with recently diagnosed PMR who fulfil the 2012 EULAR/ACR criteria?

5. Does rituximab 1 * 1000mg versus placebo lead to a higher proportion of GC-free remission in recently diagnosed and flaring PMR patients who fulfil the 2012 EULAR/ACR criteria?

References


Seasonal influence on incidence of PMR: winter might be coming

Diane E. Marsman
Nathan den Broeder
Calin D. Popa
Alfons A. den Broeder
Aatke van der Maas

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Abstract

Background and objectives

To date, the exact etiology of PMR is thought to be multifactorial, with genetic background, immune senescence and environmental factors, such as infections, among the most important contributors to disease onset. A seasonal pattern of disease onset has previously been indicated in giant cell arteritis (GCA) - a condition often associated with PMR. Concerning PMR patients, there is scarce and conflicting evidence whether infectious diseases play a role in the onset of PMR. Our aim was to assess whether infections associated previously with GCA and/or PMR onset - Mycoplasma pneumoniae, Chlamydophila pneumoniae, Parvovirus B19 and parainfluenza virus type 1 – are related to the pattern of onset of symptoms seen in PMR patients.

Methods

Data from an existing historic cohort of 454 newly diagnosed PMR patients (clinical diagnosis) who visited our outpatient rheumatology clinic between April 2008 and September 2017. The chi-square goodness of fit test was used to determine whether PMR onset was distributed equally throughout the year. Additionally, data on incidence of the infectious agents from the Dutch National Institute for Public Health and Environment (RIVM) was obtained. From this data, the index digits were calculated.

Results

A bimodal seasonal pattern of PMR onset was seen but the chi-square goodness of fit test did not reach statistical significance. Additionally, no coincidence of peaks between onset of PMR symptoms and the proposed agents was seen.

Conclusions

The results of this study are insufficiently suggestive for an infectious trigger as cause of PMR.

Letter to the Editor

Sirs,

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of elderly patients. Symptoms typically consist of pain and stiffness affecting the neck, shoulder- and hip girdles, and elevated acute phase reactants.1 To date, the exact etiology of PMR is thought to be multifactorial, with genetic background, immune senescence and environmental factors, such as infections, among the most important contributors to disease onset.1 Interestingly, a seasonal pattern of disease onset has been previously indicated in giant cell arteritis (GCA) - a condition often associated with PMR.2 Given the close relation between these two conditions - 40%-60% of GCA patients also have PMR at the time GCA is diagnosed and 16-21% of PMR patients have or will develop GCA – one may hypothesize that a similar seasonal pattern could also occur in PMR.3 Various infectious diseases are thought to contribute to the seasonal pattern described in GCA, including Mycoplasma pneumoniae, Chlamydophila pneumoniae, Parvovirus B19 and parainfluenza virus type 1.4-6 These micro-organisms also have been hypothesized to trigger PMR, as simultaneous peaks between the onset of PMR and epidemics of these infectious agents were described.7 Consistent with the seasonal pattern hypothesis, 16% of PMR patients reported a respiratory tract infection or seasonal influenza before the onset of symptoms.8 In contrast, others reported no associations with presence of parvovirus B19, C. pneumoniae, respiratory syncytial virus, measles virus, herpesviruses type 1 and 2, Epstein-Barr virus or human herpesvirus.9-11

A cyclic pattern of disease onset following seasonal distribution may support the theory of infectious agents as disease trigger in PMR.12-13 We therefore aimed to investigate the occurrence of a seasonal effect in incidence of onset of PMR. We examined data from 454 newly diagnosed PMR patients (clinical diagnosis) who visited our outpatient clinic between April 2008 and January 2018. Patients with other active concomitant inflammatory rheumatic disease at baseline were excluded. Six patients were not included because the date of PMR symptom onset was missing, and therefore a total of 448 patients were finally analyzed. Of these patients, 247 (55%) were women and mean age was 66 ± standard deviation (SD) 9 years. Patients’ symptoms started 10 weeks (interquartile range (IQR) 6 to 16 weeks) prior to PMR diagnosis. Patients were further grouped based on the month their symptoms debuted, not on the moment of diagnosis. The chi-square goodness of fit test to determine whether PMR onset was distributed equally throughout the year did not reach statistical significance: p = 0.06. Additionally, we obtained data on incidence of the infectious agents from the Dutch National Institute for Public Health and Environment (RIVM), in which an association was previously described with GCA/PMR. From this data, the index digits were calculated where 100 marks the weighted average of infections at that time point for the years 2007 to 2017. As shown in figure 1, the incidence of PMR symptoms onset is higher in November-January and April through June, with a peak in August. However, these peaks are not compatible with peaks of the proposed infectious agents. In addition, no coincidence of peaks between onset of PMR symptoms and the proposed agents were seen when we analyzed each year separately (data not shown). We conclude that this bimodal seasonal pattern of PMR onset is insufficiently suggestive for an infectious trigger as cause of PMR. Limitations of this study are the retrospective character resulting in absence of blood samples to test whether patients had experienced a recent infection of the proposed infectious agents.
Figure 1. Onset of polymyalgia rheumatica symptoms per month.

References

Polymyalgia rheumatica patients with and without elevated baseline acute phase reactants: distinct subgroups of polymyalgia rheumatica?

Diane E. Marsman
Nathan den Broeder
Nadine Boers
Frank H.J. van den Hoogen
Alfons A. den Broeder
Aatke van der Maas

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Abstract

Objectives
Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease characterized by pain and stiffness of neck, shoulder- and hip girdle, typically with elevated acute phase reactants (APR). However, patients may present with normal APR. Our aim was to explore whether normal APR were due to 1) ‘caught early in the disease’, 2) misdiagnosis, or 3) a distinct subset of PMR with different clinical presentation and prognosis.

Methods
Retrospective cohort study on patients with clinical PMR diagnosis visiting the rheumatologists of the Sint Maartenskliniek from April 2008 to September 2017.

Results
Of 454 patients, 62 patients had normal, and 392 elevated APR. Normal APR patients had longer symptom duration before diagnosis (13 versus 10 weeks; p=0.02), however during follow-up 31% developed elevated APR. In elevated APR patients with previous APR data available while already symptomatic 58% had earlier normal APR. Fewer normal APR patients had peripheral arthritis (2% versus 9%; p=0.04), and anemia (17% versus 43%; p=0.001). More often they had a previous PMR diagnosis (16% versus 8%; p=0.057) and a shorter median time to glucocorticoid-free remission (552 versus 693 days; n=36 versus 160; p=0.02). Route of GC administration differed between groups (p=0.026). Fewer patients received methotrexate; 3 versus 12%; p=0.046). No differences in alternative diagnosis was observed.

Conclusions
PMR patients with long term normal APR seem a milder subset of PMR in clinical presentation and prognosis. Additionally, our data also suggest there is a subgroup with normal APR who are caught early in the disease. Misdiagnosis does not appear to play a role.

Introduction
Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting people usually above 50 years of age. In this age group, the highest incidence is seen in Northern Europe, varying from 41 to 113 per 100,000 person. The cause is unknown and the diagnosis is made on clinical presentation and laboratory testing. Typical symptoms are bilateral pain and stiffness of the neck, shoulder- and hip girdle, with elevated inflammatory parameters. However, there is no golden standard to diagnose PMR and it can be challenging due to its heterogeneous and frequently atypical presentation, especially when patients have normal acute phase reactants (APR) at diagnosis.

A high erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) are important markers for diagnosis and assessment of PMR activity, with considerable negative predictive value for the diagnosis. PMR without increased APR at presentation however has been described. The proportion of patients with clinical diagnosis of PMR and normal APR at baseline was examined in a few observational studies with various quality of evidence and is reported in 1.1 to 22.5% of PMR patients. These studies mostly examined ESR and less frequently CRP.

We hypothesize three different possible reasons for lack of increase of APR in a patient with PMR. Firstly, patients with normal APR at diagnosis might have the same pathophysiology and characteristics as patients with elevated APR, but just caught earlier in the disease course, with an increased APR at a later stage.

A second possibility would be that patients with normal APR are a distinct pathophysiological subgroup of PMR patients with different disease causality and treatment outcomes, representing a milder clinical phenotype, with possibly also a more benign and less refractory course. Indeed, findings of baseline differences reported in previous studies support this hypothesis, as patients with normal APR at baseline were younger, had less systemic signs, a higher mean hemoglobin value, and also had significantly longer duration of symptoms prior to diagnosis. However, there is inconsistency since other studies found no differences in clinical characteristics and disease course in patients with normal and elevated APR. Additionally, comments can be made on quality of evidence, with some studies carried out in very few patients, and/or inclusion of patients with concomitant giant cell arteritis (GCA).

To corroborate the theory of different pathophysiological subgroups it can be hypothesized that there are different disease spectra. Some immunological differences have already been described in patients with PMR versus GCA, maybe this is also the case with normal versus elevated APR patients. Amongst others, differences in localized temporal artery cytokine patterns and serum markers related to immune cells was described in PMR and GCA patients. With regard to differences between normal and elevated APR marked depletion of CD8+ cells in peripheral blood of PMR patients with low ESR has been described, compared to higher levels in PMR patients with high ESR values, and even higher levels in normal controls. In conclusion, there are indications of pathophysiological differences between different disease spectra in PMR.

A third option is that patients are incorrectly diagnosed with PMR and have another diseases (like amongst others rheumatoid arthritis, osteoarthritis, shoulder bursitis or enthesopathy).
Although most cohorts and case series use course after prolonged follow up as reference standard for the diagnosis to prevent this, there is no golden standard to diagnose PMR or a PMR flare.

In conclusion, evidence remains scarce and it is still unclear whether PMR patients with normal baseline APR are the same as PMR patients with elevated baseline APR but earlier diagnosed in their disease course, whether they represent a distinct subgroup of PMR, or whether they are misdiagnosed patients. We therefore aim to compare baseline and treated diagnosed in their disease course, whether they represent a distinct subgroup of PMR, or whether they are misdiagnosed patients. We therefore aim to compare baseline and treated baseline and treated follow-up characteristics between patients with normal and increased APR at diagnosis.

Methods

Study design
This is a retrospective explorative cohort study of newly diagnosed PMR patients, who visited the outpatient rheumatology clinic of the Sint Maartenskliniek over a ten year period from April 2008 to January 2018. Diagnosis, treatment and follow-up were performed according to local protocol, which follows the EULAR/ACR 2015 recommendations on PMR management.

Patients

Inclusion criteria
All patients with a new clinical diagnosis of PMR or a new episode of PMR who had a follow-up of at least 9 months (minimum duration of GC-treatment) were eligible for inclusion. The date of inclusion in the cohort was the date of diagnosis by the treating rheumatologist, or by the general practitioner, if later confirmed by the rheumatologist. The diagnosis of PMR was made as judged clinically by the treating rheumatologist, and no formal classification criteria were used as inclusion criteria.

Exclusion criteria
We excluded patients who had at baseline a current and active CCA, rheumatoid arthritis, treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs) regardless of indication, if there was uncertainty about the PMR diagnosis as described by the treating physician, or treatment with glucocorticoids (GC) more than four weeks prior to inclusion date (irrespective of reason for prescribing). The justification of not including patients treated with GC for more than four weeks prior to inclusion date was to enhance the quality of the collected data and ensure that collection of ESR and CRP was as complete as possible. If the PMR diagnosis changed within the first 9 months of follow-up, patients were not included.

Assessments
Data was collected from the referral letter from the general practitioner (GP) and the electronic health record. Data from all visits were collected, until censoring of follow-up (January 1, 2018), or until patients were either lost to follow up or deceased. At baseline (either from the GP referral letter or electronic health record) we collected data on previous medical history, clinical symptoms and duration, physical examination, laboratory and additional imaging research, as obtained by the treating physician according to local protocol. We collected the course of the disease (signs and symptoms, CRP/ESR), and treatment, including route of and the GC starting dose in mg at baseline and the GC dose in mg at every follow up visit, and thereby every dosage decrease and increase respectively, and the use of concomitant DMARDs. Baseline APR were collected prior to start of GC.

Laboratory analysis
ESR was determined by the 30 minute automated version of the Westergen method. This method measures the ESR after 30 minutes and extrapolates it to 60 minutes through a specific algorithm, and has excellent agreement with manual 1 hour Westergen. In our study a value above 30 mm/hour was considered elevated for both men and women. High sensitivity CRP was determined by the chemical analyzer Olympus type AU400 (Goffin Meyvis), with an upper limit of normal of 10 mg/l (1 mg/dl).

Sample size calculation
Due to the explorative nature of the study, no formal sample size calculation was made. To calculate the precision that can be reached concerning the primary endpoint, we assumed a proportion of APR negative patients to be 10%, in light of previous studies reporting normal BSE and/or CRP in 1.1-22% of PMR patients. Calculation of the confidence interval around a proportion of 10% normal APR with p +/- 1.96(V(p(1-p))/n) shows that precision of ±3% and ±1% can be reached with a sample size of 384 patients.

Statistical analysis
Descriptive statistics were used [using mean (SD), median (p25-p75) or n (%) as appropriate], and differences between patients with normal versus high APR (CRP >10 mg/L and/or ESR >30 mm/hour) were tested using Fischer’s exact test for categorical data, t-test for normally distributed data and Wilcoxon test for non-normally distributed data. All analysis were performed with STATA/IC v 13.1.

Ethical declaration
We obtained permission from the medical ethical committee of research with human subjects (CMO region Arnhem-Nijmegen, 2017-3056). We informed patients about the study and the research approval committee approved this study (RR-168-PMR). Consent was obtained using an opt out letter procedure, according to Dutch law (WGBO 458.2c). If patients objected to use of their data for this study, their data was not collected.

Results
A total of 880 PMR patients visited the Sint Maartenskliniek between April 2008 to January 2018. Of these 880 patients, 454 (52%) were included. Reasons for exclusion were insufficient baseline data (5%), refractory PMR / second opinion (16%), insufficient follow-up (3%), not fulfilling the inclusion criteria (20%), objection to participating in the study (1%), not able to collect opt-out due to death (4%) and migration (1%). Baseline characteristics of patients with normal versus elevated APR are described in table 1. Sixty-two (14%) patients had normal, and 392 (86%) had elevated APR. Patients with normal APR had a longer median duration of symptoms before diagnosis (13 versus 10 weeks; p=0.02). Also they were more likely to have a previous diagnosis of PMR (16 versus 8%; p=0.06).

Fewer patients with normal APR had peripheral arthritis (2 versus 9%; p=0.04) and anemia at diagnosis (17 versus 43%; p=0.001). The route of GC administration differed between the groups.

A total of 880 PMR patients visited the Sint Maartenskliniek between April 2008 to January 2018. Of these 880 patients, 454 (52%) were included. Reasons for exclusion were insufficient baseline data (5%), refractory PMR / second opinion (16%), insufficient follow-up (3%), not fulfilling the inclusion criteria (20%), objection to participating in the study (1%), not able to collect opt-out due to death (4%) and migration (1%). Baseline characteristics of patients with normal versus elevated APR are described in table 1. Sixty-two (14%) patients had normal, and 392 (86%) had elevated APR. Patients with normal APR had a longer median duration of symptoms before diagnosis (13 versus 10 weeks; p=0.02). Also they were more likely to have a previous diagnosis of PMR (16 versus 8%; p=0.06).

Fewer patients with normal APR had peripheral arthritis (2 versus 9%; p=0.04) and anemia at diagnosis (17 versus 43%; p=0.001). The route of GC administration differed between the groups.
(oral GC only 61 versus 72%, both oral and intramuscular GC 32 versus 27%, intramuscular GC only 6 versus 2%; p=0.026). No differences were found in distal swelling or pitting edema, systemic symptoms, the presence of rheumatoid factor (RF) or anti-citrullinated C-peptide (ACPA), osteoarthritis, cardiovascular disease or diabetes.

Table 1. Baseline characteristics of patients with normal versus elevated APR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal APR (N= 62; 14%)</th>
<th>Elevated APR (N= 392; 86%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female (%)</td>
<td>32 (52)</td>
<td>218 (36)</td>
<td>0.238</td>
</tr>
<tr>
<td>Age in years at diagnosis (SD)</td>
<td>66.0 (15)</td>
<td>66.6 (9.8)</td>
<td>0.594</td>
</tr>
<tr>
<td>History of previous PMR (%)</td>
<td>10 (16)</td>
<td>32 (9)</td>
<td>0.057</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks with PMR symptoms before diagnosis (IQR)*</td>
<td>13 (7-20)</td>
<td>16 (6-16)</td>
<td>0.020</td>
</tr>
<tr>
<td>Neck pain (%)</td>
<td>27 (44)</td>
<td>175 (45)</td>
<td>0.388</td>
</tr>
<tr>
<td>Bilateral shoulder pain/Stiffness (%)</td>
<td>57 (93)</td>
<td>361 (93)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bilateral hip pain/Stiffness (%)</td>
<td>55 (87)</td>
<td>327 (82)</td>
<td>0.352</td>
</tr>
<tr>
<td>Both bilateral shoulder- and hip pain/Stiffness (%)</td>
<td>52 (84)</td>
<td>310 (79)</td>
<td>0.496</td>
</tr>
<tr>
<td>Peripheral arthritis(*)</td>
<td>1 (2)</td>
<td>35 (6)</td>
<td>0.044</td>
</tr>
<tr>
<td>Distal swelling and pitting edema (%)</td>
<td>11 (19)</td>
<td>11 (5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Systemic symptoms ** (%)</td>
<td>27 (44)</td>
<td>172 (44)</td>
<td>1.000</td>
</tr>
<tr>
<td>ESR in mm/hour (IQR)</td>
<td>19 (12-25)</td>
<td>42 (31-53)</td>
<td>0.197</td>
</tr>
<tr>
<td>CRP in mg/l (IQR)**</td>
<td>5 (2-7)</td>
<td>34 (21-57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anemia (*)</td>
<td>8 (13)</td>
<td>33 (58)</td>
<td>1.000</td>
</tr>
<tr>
<td>Morning stiffness&gt;45 min (%)</td>
<td>29 (47)</td>
<td>206 (68)</td>
<td>0.197</td>
</tr>
<tr>
<td>Rheumatoid factor present **** (%)</td>
<td>4 (11)</td>
<td>34 (13)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

| Comorbidities                     |                          |                             |         |
| Osteoarthritis (%)                | 22 (35)                  | 163 (42)                    | 0.406   |
| Hypercholesterolemia (%)          | 10 (16)                  | 86 (22)                     | 0.402   |
| Diabetes mellitus (%)             | 4 (6)                    | 52 (13)                     | 0.149   |
| Hypertension (%)                  | 25 (40)                  | 145 (33)                    | 0.672   |
| Thyroid disease (%)               | 2 (3)                    | 38 (10)                     | 0.136   |
| Ischemic heart disease 1 (%)      | 5 (8)                    | 40 (10)                     | 0.819   |
| Other cardiovascular disease11 (%) | 4 (6)                    | 39 (10)                     | 0.407   |

| Initial treatment                 |                          |                             |         |
| GC treatment *                    | 38 (61)                  | 281 (72)                    | 0.026   |
| Oral GC only (%)                  | 20 (32)                  | 205 (27)                    |         |
| Oral GC + MP i.m. 120 mg (%)      | 4 (6)                    | 6 (2)                       |         |
| Starting dose oral GC in mg (IQR) III | 15 (10-30) | 15 (15-20) | 0.595   |

* Significant with appropriate test
** Fever; night sweats, weight loss, anorexia
*** N=45 in normal APR group; N= 91 in elevated APR group
**** Rheumatoid factor; N= 36 versus N= 257; anti-CCP: N= 33 versus N= 242
1 Angina pectoris, myocardial infarction
2 Cardiovascular disease: cerebrovascular event, peripheral arterial disease, heart failure, thrombosis
3 N=42 in normal APR group; N= 392 in elevated APR group

Follow-up characteristics are described in table 2. After GC initiation, 31% of the patients with normal APR developed elevated APR later during the disease course compared to 59% in the elevated APR group (p=0.0002). No differences were found in response to GC after 4 weeks, time to first flare and total number of flares per patient between groups. However, the total number of flares was higher in the second year of follow-up compared to the first year (34 versus 13%; and 30 versus 20%; p=0.001 in the normal and elevated APR group respectively). In the normal APR group, fewer patients used methotrexate (3 versus 12%; p=0.06). During follow-up, no differences were found in the proportion of patients with an additional new diagnosis of GCA, RA or malignancy. Patients with normal APR at diagnosis were more often referred back to the general practitioner (n= 58 versus 41%; p=0.003) and thereby earlier (85 versus 109 weeks; IQR 61-108 and 73-142 respectively).

Table 2. Follow-up (FU) characteristics of patients with normal versus elevated APR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal APR (N= 62; 14%)</th>
<th>Elevated APR (N= 392; 86%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient response to GC at 4 weeks (%)***</td>
<td>16 (26)</td>
<td>23 (35)</td>
<td>0.411</td>
</tr>
<tr>
<td>Patients who developed elevated APR during FU (%)</td>
<td>19 (31)</td>
<td>221 (59)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median time in weeks to first flare in flare patients (IQR)</td>
<td>41 (19-68)</td>
<td>39 (23-64)</td>
<td>0.964</td>
</tr>
<tr>
<td>Total patients with flares during FU (%)</td>
<td>36 (58)</td>
<td>159 (40)</td>
<td>0.0001</td>
</tr>
<tr>
<td>1 flare (%)</td>
<td>25 (40)</td>
<td>124 (31)</td>
<td>0.271</td>
</tr>
<tr>
<td>2 flares (%)</td>
<td>17 (27)</td>
<td>61 (16)</td>
<td>0.387</td>
</tr>
<tr>
<td>3 or more flares (%)</td>
<td>14 (23)</td>
<td>69 (18)</td>
<td></td>
</tr>
<tr>
<td>Patients with flares during FU*</td>
<td>36 (58)</td>
<td>254 (65)</td>
<td>0.321</td>
</tr>
<tr>
<td>Total (%)</td>
<td>21 (35)</td>
<td>114 (30)</td>
<td>0.289</td>
</tr>
<tr>
<td>DMARD, **</td>
<td>1 (3)</td>
<td>48 (12)</td>
<td>0.064</td>
</tr>
<tr>
<td>Methotrexate (%)*</td>
<td>0</td>
<td>8 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Azathioprine (%)</td>
<td>0</td>
<td>3 (1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Leflunomide (%)</td>
<td>0</td>
<td>1 (0)</td>
<td>0.000</td>
</tr>
<tr>
<td>TCZ (%)</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Other (%) III</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Rheumatoid arthritis (%)</td>
<td>2 (3)</td>
<td>21 (5)</td>
<td>0.755</td>
</tr>
<tr>
<td>Gouty arthritis (%)</td>
<td>1 (2)</td>
<td>7 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Malignancy**** (%)</td>
<td>0</td>
<td>13 (3)</td>
<td>0.230</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>1 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Time in weeks to referral GP in GC-free remission (IQR) *</td>
<td>85 (61-108)</td>
<td>109 (73-142)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* significant with appropriate tests at alpha level 0.05
** Normal APR at 12 months n= 61 and at 24 months n=48, elevated APR n=80, and at 24 months n=309
*** Remission defined by rheumatologist (clinical judgement)
**** Types of malignancy: bladder cancer (2), renal cell carcinoma, ovarian cancer, gravis tumor, leukemia, skin tumor, squamous cell carcinoma, cholecustus carcinoma
1 Patients who flared at 12-24 months was significantly higher than total patients who flared before 12 months, in both normal and elevated APR group
2 Reason for prescribing 'disease modifying drugs (DMARD) in elevated APR: ineffectiveness GC: methotrexate (MTX) 23, azathioprine (AZA) 4, tocilizumab (TCZ) 1, adverse events GC: MTX 7, AZA 2, infliximab 2, adverse events GC: MTX 7, AZA 3, other disease: MTX 4
3 Hydroxychloroquine, sulfasalazine, etanercept and adalimumab were prescribed in 8 patients due to other diseases than PMR

Of the 392 patients with baseline elevated APR, we were able to collect APR previous to PMR diagnosis in 191 patients, during the period in which PMR symptoms already existed, with (up to one year prior to diagnosis). Of these patients, 110 (58%) had no previous elevated APR while having PMR symptoms, and 81 (42%) had previous elevated APR. The median duration of PMR symptoms in these patients was 12 weeks (6-17) and 9 weeks (7-16; p=0.43), respectively.
Discussion

A first conclusion of this study is that a considerable proportion of patients with a clinical PMR diagnosis can indeed present with normal APR at diagnosis. Regarding our hypotheses whether this lack of elevated APR in PMR patients is due to the fact that they a) were caught early in the disease, b) are a distinct subgroup or c) are incorrectly diagnosed with PMR we found most evidence for b), some indication for a), but no support for c).

To start with the hypothesis that patients with normal APR are caught earlier in disease, we found that patients with normal APR had a longer median duration of PMR symptoms prior to diagnosis, even though the frequency of PMR symptoms like neck-, shoulder- and hip girdle symptoms were the same in both normal and elevated APR patients. This time effect in elevation of APR has been studied in two previous small studies. One study reported delayed elevation of ESR/CRP during follow up and after start of GC treatment in 2 out of 26 patients. In another case series of 30 patients with ESR < 35 mm/h who were treated with GC no delayed elevation of ESR was observed during follow up.

Our findings do not support the hypothesis that these PMR patients are caught earlier in their disease course and are therefore APR negative, but rather suggests a delay in diagnosis possibly due to the atypical presentation with normal APR symptoms. This notion is also supported when we looked at prior CRP and ESR values before diagnosis was made in patients with elevated APR at diagnosis, because patients who had prior normal values of CRP and ESR and baseline elevated APR had a longer duration of PMR symptoms than patients who had elevated APR at baseline and prior elevated APR. However, these patients had still presented themselves with symptoms at the physician while APR were normal, so this could also mean that they could have been "caught early" but the diagnosis was not made because of the normal APR. Additionally, the fact that some patients with normal APR at diagnosis were able to develop elevated APR after GC initiation later during the disease course, also suggests that they may have been "caught early".

We found most evidence for the second hypothesis that patients with normal APR represent regular PMR, albeit in a milder clinical phenotype. At diagnosis fewer cases have peripheral arthritis and anemia, but no other differences were observed. A possible hypothesis could be that in patients with more signs of inflammation, for example in patients with additional peripheral arthritis, higher interleukin-6 levels stimulate the production of ESR and CRP. Our results match previous studies that found milder disease presentation at diagnosis. However, not all studies found these differences. And unlike some earlier studies we did not find a differences between systemic signs, gender or age. These contrasts could partly be explained by the smaller sample size in earlier studies. In addition, discrepancies could be explained by the design of the study and selection bias. Some studies used different inclusion criteria, and included patients who had both PMR and GCA, possibly representing a more severe subset of PMR. Our study is conducted with a larger sample size with solely PMR patients, therefore our results may be more precise and less biased. Evidence for this second hypothesis is also shown by the fact that during follow-up patients with normal APR had a better prognosis as more patients were referred back earlier to the GP in GC-free remission. Furthermore, disease modifying anti-rheumatic drugs were prescribed less often in normal APR patients. This finding in line with other studies that found patients with normal ESR/CRP had a shorter treatment duration and higher proportion of patients able to discontinue GC.

One previous study found no differences in proportion and time to remission. We found no difference in flares and relapses, which is consistent with some studies, but not all. No previous study examining differences in patients with versus without normal APR, reported the use of DMARDS in PMR patients.

The results from our study do not support the third hypothesis that patients with normal APR at diagnosis are misclassified as having PMR. Firstly, many patients (31%) develop increased APR when flaring later on in disease course. Also, RA is not more frequently diagnosed during follow-up. However, the nature of our retrospective cohort was such that it was not possible to evaluate other alternative diagnosis such as osteoarthritis. We included patients with a "definitive" PMR, as judged by the treating clinical physician with confirmation also during follow-up, and if a patients’ diagnosis was changed to for example osteoarthritis, this patients would not be included. One other study also reported no alternative diagnoses during follow-up. Strengths of this study are the large sample size, long follow-up, and the fact that we included patients with only clinical PMR and no clinically suspect GCA.

Limitations include the retrospective character, introducing possible biases due to missing data. Because of the retrospective character, we could not assess the severity of the different disease activity domains like stiffness or functioning. It could be interesting to see whether these are different in normal versus elevated APR. Another possible limitation of this study is index event bias. For example patients with baseline elevated APR who had previous normal APR while having PMR symptoms, were not recognized as having PMR at that moment, and it is debatable whether the date the patients first went to the doctor with PMR symptoms should have been the index event instead of the date of diagnosis. Furthermore, more patients with normal APR had a previous history of PMR. Unfortunately, it is unknown whether the APR were elevated during the first episode of PMR. Possibly the diagnosis was made easier in these patients due to their previous history and recognition of their symptoms. The generalizability also has its’ limitations, as the findings of this cohort may not be representative to all PMR patients, for example patients treated in the first line. Furthermore, most PMR patients are treated in the first line and only referred to an outpatient rheumatology clinic when there is a good reason in doing so such as uncertainty about the diagnosis (for example normal APR) or a difficult to be treated PMR. This limits the generalizability of this PMR cohort to all PMR patients as this is only a referred subset. It could be possible that the occurrence of normal APR in a referred subset of PMR patients is higher compared to PMR patients treated in the first line only. Also, all referred PMR patients in general could have a more severe and difficult to treat PMR compared to first line patients. Little is known about first line PMR patients and it would be interesting to compare first and second line PMR patients in terms of clinical presentation and prognosis. Furthermore, interestingly only 2% of our PMR patients developed GCA during follow-up. This is far less than the usual reported GCA incidence of 16-20%. Future research on epidemiology of PMR, GCA and concurrence of these diseases could provide answers whether the incidence in the Netherlands is indeed lower than in countries with a different genetic make-up and environmental factors.
In conclusion, this study confirms findings from earlier studies that PMR can indeed present with normal APR and that - even though diagnosing PMR with normal APR remains a challenge, as shown with delayed diagnosis and the lack of a golden standard diagnostic test - clinicians can indeed diagnose PMR when APR are normal. Furthermore, this study confirms with a larger sample size of solely PMR patients that patients with normal APR are indeed a distinct subset with milder disease presentation and prognosis, with possibly a different pathophysiological pathway in the same spectrum of disease.

References

Effect of add-on methotrexate in polymyalgia rheumatica patients flaring on glucocorticoids tapering: a retrospective study.

Diane E. Marsman
Thomas Bolhuis
Nathan den Broeder
Frank H. J. van den Hoogen
Alfons A. den Broeder
Aatke van der Maas

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Abstract

Background and objectives
Guidelines on management of polymyalgia rheumatica (PMR) recommend early introduction of methotrexate (MTX), especially in patients with worse prognosis, although evidence on clinical efficacy of MTX in PMR is limited. Our objective was to assess MTX efficacy in real world PMR care.

Methods
Retrospective data of newly diagnosed PMR patients who started MTX were compared to control patients in whom MTX was not started at the first flare. Main outcomes were number of flares per year (Poisson regression) and weighted daily glucocorticoid (GC)-dose (linear regression), and flare incidence rate in the MTX group only.

Results
240 patients were selected; 39 patients in the MTX group and 201 in the control group. The yearly incidence rate ratio of flares in the MTX versus control group was 0.80 (95%-CI 0.45 to 1.42). The yearly flare rate was 1.22 before and 0.43 after MTX initiation, resulting in an incidence ratio of 0.35 (95%-CI 0.23 to 0.52). Adjusted time weighted daily GC-dose was higher in the MTX versus control group (ratio 1.37, 95%-CI 1.04 to 1.80).

Conclusions
No clear effect of MTX on flares was found and time weighted daily GC-dose was higher, possibly due to residual confounding by indication; however the clearly reduced flare rate after MTX start might be suggestive for a beneficial effect of MTX.

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease in elderly patients typically characterized by pain and stiffness of the neck, shoulder- and hip girdle with elevated inflammatory parameters. Glucocorticoids (GC) remain the cornerstone of treatment. However, around 50% of rheumatologists report flares during tapering and only 35-50% achieve GC-free remission after 2 years. Additionally, approximately 65% of patients experience GC-related adverse events (AE). Use of disease modifying anti-rheumatic drugs (DMARDs) may reduce GC-need and is recommended by the 2015 ACR/EULAR management guideline of PMR. However, evidence on GC-sparing agents is limited and utilization of DMARDs varies widely. Most evidence exists for methotrexate (MTX) and so far only three interventional and three observational cohort studies on MTX for PMR have been published. Data on MTX seem somewhat promising but is of medium quality and the dosages examined are low (7.5-10 mg/week) compared to other rheumatic diseases. Based on this research, recent guidelines on management of PMR recommend early start of MTX in patients with risk factors for flares/prolonged GC therapy, or who flare under GC-therapy.

To add to the evidence on higher dosed add-on MTX, we set up a controlled cohort of PMR patients to assess the effect of add-on MTX on the frequency of subsequent flares and mean GC dose.

Methods

Study design
This is a retrospective controlled cohort study of newly diagnosed PMR patients (clinical diagnosis) who visited the secondary outpatient rheumatology department of the Sint Maartenskliniek from April 2008 to January 2018. The Sint Maartenskliniek is a secondary and tertiary referral clinic with different locations across the Netherlands. All patients received usual care at discretion of the treating physician, guided by our local treatment recommendations (in line with EULAR recommendations).

Patients

Inclusion criteria
In this existing cohort of 454 PMR patients, all patients had a new clinical PMR diagnosis or a recurrence of PMR. This diagnosis was either made by, or confirmed by the treating rheumatologist if the diagnosis was made by the referring primary physician. A clinical diagnosis of PMR was used, instead of classification criteria for PMR, because rheumatoid factor and anti-CCP were missing in many patients. Patients had a minimum follow-up of at least nine months, because GC-treatment is minimally nine months. All patients who started MTX (index event) were regarded as MTX users from that time onward, regardless of MTX duration, follow-up, or assessments. A control group was selected by identifying patients who experienced at least one flare (index event) or more, but received no MTX treatment. A flare was defined as a (clinical) flare judged by the treating physician. Index event was date of starting MTX, or date of the first flare during GC (control group; MTX eligible according to EULAR guidelines).
Exclusion criteria
Baseline use of DMARDs for other indication, development of rheumatoid arthritis (RA) or giant cell arteritis(GCA) during follow-up. The work-up for diagnosis re-evaluation was done retrospectively by collecting information (judgement of the treating rheumatologist) from the electronic patients' health records.

Baseline and follow-up assessments
At baseline (time of index event), data regarding medical history was collected. At baseline and follow-up, data on clinical characteristics, laboratory values, treatment, and comorbidities was collected.

Outcomes
Main outcomes
Main outcomes were the incidence rate (IR) of flares (number/patient/year) and time weighted daily GC-dose compared between MTX patients and controls. A flare was defined as a (clinical) flare judged by the treating physician, with or without elevated acute phase reactants (APR).

The time weighted daily GC dose is defined as the cumulative GC dose in mg divided by the follow-up time. In the MTX group only, we compared the flare IR before and after start of MTX.

Confounding variables
As confounding by indication regarding starting MTX is likely to play a role, we used several covariates to attempt to control for confounding. Based on earlier literature, female gender, baseline elevated inflammatory parameters and peripheral arthritis are potential risk factors for worse prognosis. These and several other demographic and clinical characteristics, that may be associated with worse prognosis at disease onset, were selected for correction of confounding (table 2 and 3).

Secondary outcomes
Secondary outcomes were MTX and GC-related treatment characteristics during follow-up. MTX related outcomes were frequency of flares prior to MTX initiation, MTX dose, reasons for prescribing and discontinuing MTX. GC-related outcomes were daily GC-dose at moment of and one year after index event, and reduction of median daily GC-dose before versus after index event.

Statistical analysis
All analyses were performed using STATA/IC v13.1. Descriptive statistics were used as appropriate. Categorical data were compared using chi-square or Fisher’s exact test. Paired continuous data were compared using Wilcoxon rank or Student’s T-test, as appropriate.

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Statistical analysis
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Ethical declaration and informed consent
The medical ethical committee of research with human subjects (CMO Arnhem-Nijmegen, 2017-3506), judged that no formal review was necessary and the local research approval committee approved this study. Consent was obtained using an opt-out letter, according to Dutch law (WGBO 458.2c).

Results
From an existing cohort of 454 PMR patients, 39 patients were prescribed MTX and 201 patients were eligible for the control group. Patients’ baseline characteristics are shown in table 1.

Table 1. Patients’ demographic and baseline characteristics at time of diagnosis and time of index event*

<table>
<thead>
<tr>
<th>Characteristic at time of PMR diagnosis</th>
<th>MTX (n=39)</th>
<th>Controls (n=301)</th>
<th>Mean difference (95%-CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>19 (49)</td>
<td>117 (58)</td>
<td>-8.0 (-26.0 to 7.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Age at diagnosis, years (SD)</td>
<td>62 (7)</td>
<td>67 (10)</td>
<td>-4.8 (-8.1 to -1.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous history of PMR, n (%)</td>
<td>6 (15)</td>
<td>10 (5)</td>
<td>10 (2 to 18)</td>
<td>0.03</td>
</tr>
<tr>
<td>PMR symptoms, weeks (IQR)</td>
<td>8 (5-16)</td>
<td>8 (6-16)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Bilateral shoulder pain / stiffness, n (%)</td>
<td>39 (100)</td>
<td>191 (95)</td>
<td>5.0 (-1.9 to 11.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hip pain / stiffness</td>
<td>42 (100)</td>
<td>298 (90)</td>
<td>10 (0.8 to 19)</td>
<td>0.03</td>
</tr>
<tr>
<td>Morning stiffness ≥ 45 minutes, n (%)</td>
<td>29 (74)</td>
<td>162 (80)</td>
<td>-6.2 (-20 to 7.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Peripheral arthritis, n (%)</td>
<td>4 (10)</td>
<td>7 (3)</td>
<td>7.0 (-4.4 to 14.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Systemic symptoms, n (%)</td>
<td>18 (46)</td>
<td>85 (42)</td>
<td>4.0 (-1.3 to 20.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Elevated APR, n=38 vs 199 (%)</td>
<td>37 (97)</td>
<td>121 (86)</td>
<td>11.4 (0.4 to 22.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>At time of index event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMR disease duration, weeks (IQR) †</td>
<td>81 (39-112)</td>
<td>52 (27-78)</td>
<td>-</td>
<td>0.00</td>
</tr>
<tr>
<td>Elevated APR n=32 vs 168 (%)</td>
<td>12 (38)</td>
<td>54 (92)</td>
<td>5.0 (-12.5 to 23.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Daily dose of oral GC in mg, n=38 vs 199 (IQR)</td>
<td>10 (5-25)</td>
<td>1 (3.5-9)</td>
<td>-</td>
<td>0.00</td>
</tr>
<tr>
<td>Time weighted daily GC dose in mg (IQR) *</td>
<td>7.4 (6.0-9.3)</td>
<td>5.9 (4.1-7.6)</td>
<td>-</td>
<td>0.00</td>
</tr>
<tr>
<td>Total flares before MTX initiation, n (%)</td>
<td>6 (16)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0</td>
<td>15 (38.5)</td>
<td>1 (46.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2‡</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Reason of prescribing MTX, n (%)</td>
<td>22 (56)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GC-ineffectiveness</td>
<td>4 (10)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GC-related AE</td>
<td>12 (31)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Both GC-ineffectiveness and AE</td>
<td>21 (54)</td>
<td>37 (48)</td>
<td>5.6 (-11.6 to 22.8)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

* Values are mean, median or frequencies
† Systemic symptoms = fever, night sweats, weight loss, anorexia
‡ PMR disease duration = total disease duration from onset symptoms until index event in weeks
MTX denotes methotrexate, CI confidence interval, PMR polymyalgia rheumatic, SD standard deviation, IQR interquartile range, APR acute phase reactants consisting of C-reactive protein and/or erythrocyte sedimentation rate, GC glucocorticoid.
Main outcomes
Due to low proportion of missing values of independent variables (4/240; 2%), we chose to use complete cases analyses, n=236. In the Poisson analysis, the yearly IR of flares did not differ between the MTX versus control groups: IR ratio (IRR) 0.80 (95%-CI 0.45 to 1.42; table 2). Correction for MTX dose did not alter the results, and was therefore not included as confounding variable.

Table 2. Incidence rate ratio of flares between methotrexate and control group using Poisson regression, adjusted for confounding (n=236)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRR</th>
<th>SE</th>
<th>P-value</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.29</td>
<td>0.25</td>
<td>0.15</td>
<td>0.05 to 1.57</td>
</tr>
<tr>
<td>MTX group</td>
<td>0.80</td>
<td>0.24</td>
<td>0.45</td>
<td>0.45 to 1.42</td>
</tr>
<tr>
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<td>0.67 to 1.43</td>
</tr>
<tr>
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<td>0.01</td>
<td>0.97</td>
<td>1.00 to 1.02</td>
</tr>
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<td>History of previous PMR episode</td>
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<td>0.86</td>
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<tr>
<td>PMR disease duration*</td>
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<td>1.00</td>
<td>1.00 to 1.00</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>1.06</td>
<td>0.49</td>
<td>0.42</td>
<td>0.42 to 2.84</td>
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<tr>
<td>Systemic symptoms†</td>
<td>0.87</td>
<td>0.17</td>
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<td>0.59 to 1.27</td>
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<tr>
<td>Baseline elevated APR</td>
<td>0.82</td>
<td>0.22</td>
<td>0.48</td>
<td>0.48 to 1.38</td>
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<tr>
<td>Total time weighted GC dose in mg‡</td>
<td>1.04</td>
<td>0.02</td>
<td>1.00</td>
<td>1.00 to 1.08</td>
</tr>
</tbody>
</table>

* PMR disease duration = Total disease duration from onset symptoms until index event in weeks
† Fever, cold chills, weight loss, night sweats, tiredness
‡ Time weighted GC dose in mg = Total cumulative GC dose divided by treatment time up to index event

In the MTX group, the IR of flares was 1.22 before and 0.43 after MTX initiation, resulting in a (within group) flare IRR of 0.35 (95%-CI 0.23 to 0.52). For this flare IR the outcomes of the crude analysis were used because the outcome did not significantly change after controlling for possible confounding variables, that were used in the other main outcomes. The multivariable linear regression was performed on the log-transformed time weighted daily GC-dose (index event until end of follow-up). After back-transformation, the time weighted daily GC-dose was significantly higher in the MTX versus control group (ratio 1.37, 95%-CI 1.04 to 1.80; table 3).

Secondary outcomes
MTX was started after zero previous flares in six (15.4%), one flare in 15 (38.5%), and two or more in 18 (46.1%) patients. MTX was prescribed due to GC-ineffectiveness (n=22; 56%), GC-related AE (n=4; 10%), both ineffectiveness and GC-related AE (n=13; 33%). Described GC-related AE were Cushingoid face, hair loss, hot flashes, brittle skin, stomach ache, dizziness, weight gain, cataract and osteoporosis. Maximum weekly MTX-dose was 7.5-10mg in 3 (7%), 15-17.5mg in 16 (41%), 20-22.5mg in 8 (21%), and 25mg in 12 (31%) patients. Median duration of MTX use was 56 weeks (IQR 31 to 111), this is an underestimation as some patients were still using MTX at end of follow-up of this study (n=23). Reasons for discontinuing MTX (n=16; 41%) were inefficacy (n= 2; 13%), MTX-related AE (n=12; 75%), both inefficacy and AE (n=1; 6%), and disease remission (n=1; 6%). Reported AE leading to MTX discontinuation were: gastrointestinal complaints, pericarditis, mood alteration, elevated liver enzymes, hair loss, skin rash, upper respiratory tract infection, aversion, extreme fatigue, and renal cell carcinoma. Rescue therapy after MTX failure was leflunomide in two, and tocolizumab in one patient. No statistical difference between groups was observed in patients experiencing a flare, or time to first flare during follow-up.

Discussion
The main results of our study may be interpreted in two opposing ways. Firstly, no beneficial effect of MTX (210mg/week) on reduction of flares was found nor was a GC sparing effect observed: MTX patients had a higher time weighted GC-dose after controlling for confounding. Secondly, however, the trend towards lower flare rate and lower GC-dose after start of MTX, might be interpreted as indicative of some effect. That being said, more robust evidence is clearly necessary to support higher dosed MTX for treatment of PMR.

Table 3. Multivariable regression of difference in time weighted daily GC-dose between MTX and control group (n=234)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-value</th>
<th>95%-CI</th>
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<tr>
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<td>2.07 to 10.39</td>
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<td>1.04 to 1.80</td>
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<td>0.20</td>
<td>0.74 to 1.07</td>
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<td>0.39 to 10.01</td>
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<td>History of PMR</td>
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<td>1.22</td>
<td>0.94</td>
<td>0.69 to 1.50</td>
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<td>PMR disease duration†</td>
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<td>1.00</td>
<td>0.03</td>
<td>1.00 to 1.00</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>0.78</td>
<td>1.27</td>
<td>0.31</td>
<td>0.49 to 1.25</td>
</tr>
<tr>
<td>Systemic symptoms†</td>
<td>0.98</td>
<td>1.10</td>
<td>0.86</td>
<td>0.82 to 1.16</td>
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<tr>
<td>Baseline elevated APR</td>
<td>1.40</td>
<td>1.15</td>
<td>0.02</td>
<td>1.06 to 1.86</td>
</tr>
<tr>
<td>Time weighted GC dose in mg‡</td>
<td>1.04</td>
<td>1.02</td>
<td>0.02</td>
<td>1.01 to 1.07</td>
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</table>

* R²=0.11
† Total disease duration from onset symptoms until index event in weeks
‡ Time weighted GC dose in mg = Total cumulative GC dose divided by treatment time up to index event
GC denotes glucocorticoid, MTX methotrexate, SE standard error, CI confidence interval, PMR polymyalgia rheumatica, APR = acute phase reactants consisting of C-reactive protein and/or erythrocyte sedimentation rate
Several reasons for the lack of efficacy in this study can be conceived. Firstly, the results may reflect a true lack of effect of MTX in PMR. Alternatively, we were unable to find a MTX effect with our study. This could be caused by confounding by indication as the intervention group was selected by date of start MTX and the control group by first flare. It was not possible to fully correct for confounding and prognosis, hampering comparability of groups. The MTX group may have a worse prognosis and possibly this leads to an underestimation of MTX effect, explaining why we did not find a beneficial effect of MTX between groups in our cohort. Several other conditions that may have played a role in not finding a beneficial effect of MTX were the low power of this study as only a limited amount of patients were prescribed concomitant MTX, a non-uniform (clinical) definition of flares which could possibly lead to under or over reporting of flares, different treatment control or measurement of PMR-activity between groups, varying MTX-dose and treatment adherence. The reduction of flare rate within the MTX group may reflect a true beneficial effect, albeit this finding may reflect regression to the mean, and PMR may have the natural tendency to get better in time. Precision of treatment effect between groups was limited but the confidence intervals likely contradict a large effect of MTX. However, the within group flare rate reduction is statistically significant and there was a trend towards flare reduction when compared between groups. Another limitation of this study is that it was a monocenter study. However, the Sint Maartenskliniek has a large rheumatology staff and has outpatient-clinics at different regions of the Netherlands from which patients were included, making the study more generalizable to other secondary rheumatology outpatient clinics.

With regard to the effect on GC use, two previous cohort studies also found no GC-sparing effect of MTX in PMR patients.\(^1,2\) However, the MTX-dose used was lower (varying from 7.5-20mg) and drop-out rate of the trial high. In contrast, three other studies did find a beneficial effect of MTX on GC-dose and flares.\(^3,4,5\) The contrasts of our findings could be explained by the higher methodological quality (intervention trials) of these studies. A strength of our study are that it is conducted with data of PMR patients only – in contrast to most studies that are conducted with patients having both PMR and / or GCA –, and the medium to high MTX dose.

Remarkably, in this large cohort the MTX prescription rate was low even though the ACR/EULAR guidelines recommend MTX early on in patients who flare on GC. It is unknown if this low prescription rate generalizes to other rheumatology practices, but a low prescription rate was also described by one earlier study by Albrecht et al (19%)\(^,5\) A possible reason for this low prescription rate in our cohort may be that the international guideline that recommends early introduction of MTX was published in 2015, whilst our patients were seen in the period of 2008 until 2017. Additionally, patients in the control group had a lower GC dose at index event compared to the MTX group. At a lower GC dose the risks of starting concomitant MTX – with uncertainty regarding efficacy – may not outweigh the benefits.

In conclusion, no clear efficacy of MTX was found although some promising signals were seen, and more robust evidence is clearly necessary to support the efficacy of higher dosed MTX for treatment of PMR patients.

References
PMR MODE: PolyMyalgia Rheumatica treatment with Methotrexate in Optimal Dose in an Early disease phase, a multicentre trial

Diane E. Marsman*
Thomas E. Bolhuis*
Nathan den Broeder
Frank H.J. van den Hoogen
Alfons A. den Broeder
Aatke van der Maas

*Both authors contributed equally to this manuscript

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Abstract

Background
Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting people older than 50, resulting in pain and stiffness of the neck, shoulders, and pelvic girdle. To date, glucocorticoids (GC) remain the cornerstone of treatment, but these have several drawbacks. Firstly, a large proportion of patients do not achieve GC-free remission within either the first (over 70%) or second year of treatment (over 50%). Secondly, GC-related adverse events (AE) occur in up to 65% of patients, and can be severe.

The current EULAR/ACR guidelines for PMR recommend early introduction of methotrexate (MTX) as a GC sparing agent in patients at risk for worse prognosis. However, earlier trials of low to medium quality only studied MTX dosages of 7.5–20 mg/week with none to modest effect. These doses may be suboptimal as MTX is recommended in higher doses (25 mg weekly) for other inflammatory rheumatic diseases. The exact role, timing and dose of MTX in PMR remains unclear. The objective of this trial therefore is to study the efficacy of MTX 25 mg once weekly in recently diagnosed PMR patients.

Methods
We set up an investigator driven, double blind, randomized, placebo-controlled superiority trial (PMR MODE) to assess the efficacy of MTX 25 mg/week versus placebo in a 1:1 ratio in 100 patients recently diagnosed with PMR according to the 2012 EULAR/ACR criteria. All patients will receive prednisolone 15mg/day, tapered to 0 mg over the course of 24 weeks. In case of primary non-response or disease flare prednisolone dose will be temporarily increased. Assessments take place at baseline, 4, 12, 24, 32, and 52 weeks. The primary outcome is the difference in proportion of patients in glucocorticoid-free remission at week 52.

Discussion
In this trial design an accelerated tapering scheme was chosen in order to more easily spot a GC-sparing effect. A composite endpoint of GC-free remission was chosen as this is in our eyes a clinically relevant endpoint for both patients and rheumatologist. Data on the efficacy of MTX 25 mg/week will contribute to better management of PMR. A positive finding will lead to better GC sparing management, and a negative finding may lead to cessation of a futile treatment, thus preventing needless harm.

Trial registration
Dutch trial registration, NL8366, registered on 2020-02-10 (CMO Regio Arnhem-Nijmegen NL69979.091.19, approval date 2020-02-23).

Background and rationale (6a)
Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting mostly people older than 50 years. Patients generally present with subacute onset pain and stiffness of the neck, bilateral shoulder-, and pelvic girdle, and elevated acute phase reactants. Additionally 40–50% of patients experience constitutional symptoms. Disease duration while on treatment may last up to 2–3 years, and during the first year the chance of relapse ranges between 20–55%. PMR is closely related to giant cell arteritis (GCA), a large blood vessel vasculitis occurring in elderly people. The cause of PMR remains unknown and there is no golden standard for the diagnosis of PMR. Untreated PMR leads to a significant reduction in quality of life (QOL).

To date, glucocorticoids (GC) remain the cornerstone of treatment of PMR. Several different tapering regimens exist, but there is no data on which regimen is optimal, as these have not been adequately investigated. There are several drawbacks to GC treatment for PMR. Firstly, there may be a long treatment duration due to lack of a true disease modifying effect; GC-free remission was achieved in only 27% in a PMR primary care cohort within the first year of treatment, and in only 33-50% of a hospital care cohort of PMR patients after two years of treatment. Secondly, GC-related adverse events (AE) are frequent, and have been reported in up to 65%, dependent on GC dosage. Patients using GCs longer than 2 years are more likely to develop weight gain, osteoporosis, fractures, metabolic and cardiovascular side effects as well as infections. This emphasizes the need for GC sparing agents to enhance GC efficacy, shorten treatment duration, and reduce GC-related side effects.

The efficacy of several conventional synthetic disease-modifying antirheumatic drugs (DMARD) as GC sparing agents has been studied but the exact role in PMR remains unclear. There is some evidence for leflunomide and azathioprine but the evidence to date is weak. Of biological DMARD treatment tocilizumab (TCZ) showed some promise, although it is associated with high costs and due to its effect on C-reactive protein (CRP) disease monitoring might be somewhat impaired.

The most evidence – three small RCTs – for a GC-sparing treatment exists for Methotrexate (MTX). However, the quality of the evidence is still low. Firstly, the examined doses varied between 7.5–10 mg once weekly, and no studies are available on standard dosed (25 mg) MTX for other inflammatory rheumatic diseases such as rheumatoid arthritis (RA). Furthermore, the studies were small, and limited by high drop-out rates and in some studies open label MTX use. The results of these studies are conflicting, as only one study with 10 mg showed some efficacy by reduced flare rate and GC-dose, and the other two studies did not show an effect. Of biological DMARD treatment tocilizumab (TCZ) showed some promise, although it is associated with high costs and due to its effect on C-reactive protein (CRP) disease monitoring might be somewhat impaired.

However, based on this limited evidence, the current EULAR/ACR recommendations for the management of PMR advise an early introduction of MTX in patients with worse prognosis such as flares, and in whom GC-related AE are more likely to occur. Clinical practice, however, MTX is infrequently used, as reported by a national database study of Albrecht et al, who found that only 19% of patients with PMR received concomitant MTX. Limited prescription may reflect the uncertainty of the exact role of MTX in PMR, due to the limited and conflicting evidence. Therefore, further research regarding the use of MTX is high on the
research agenda of the 2015 EULAR/ACR guideline for the management of PMR.4

In conclusion, evidence on GC-sparing treatment for PMR patients remains scarce and MTX seems to be a reasonable candidate to study. We therefore set up a double blind placebo controlled trial of MTX 25 mg once weekly in early PMR patients to assess whether higher dosed MTX, started early, is effective in achieving GC-free remission and reducing cumulative GC dose in PMR.

Objectives (7)
The main objective of this study is to determine whether add-on MTX 25 mg/week is efficacious in increasing the proportion of patients in GC-free remission compared to placebo in patients with recently diagnosed PMR, after 52 weeks. Secondary outcomes are other outcomes related to disease activity, physical function, health related quality of life, and GC- and MTX related AE, at different time points in the study. See paragraph “Outcomes (12)” for a more detailed description of the chosen outcomes.

Trial design (8)
This is an investigator driven, double blind, randomized, placebo-controlled superiority trial of recently diagnosed PMR patients fulfilling the 2012 EULAR/ACR preliminary classification criteria. On 05-07-2021 the trial protocol was amended on the following points: addition of the outcomes low-dose GC remission and direct healthcare costs, visits (except for week 32 and 52) may be performed digitally (due to COVID), intention-to-treat, per-protocol, and missing data analysis, a secondary cost-utility analysis, and removal of the baseline chest X-ray. At this moment, 31 patients have been included in the trial and five have completed follow-up.

Methods: Participants, interventions and outcomes

Study setting (9)
The study is a monocenter study that is conducted in the Sint Maartenskliniek (at the outpatient rheumatology clinics located in Nijmegen, Woerden, Boxmeer, Geldrop). Patients are recruited over a course of 18 months, but as timely recruitment may be challenging, we are aiming to include other centers in this RCT.

Eligibility criteria (10)
Inclusion criteria
For this study, we include patients with recently (within the last 12 weeks) diagnosed PMR according to the 2012 EULAR/ACR preliminary classification criteria.

Exclusion criteria
Our main exclusion criteria are GC exposure for > 8 weeks; GC treatment with > 30 mg/day, and exposure to other systemic immunosuppressant treatment other than GC 3 months prior to inclusion in the study. We chose for a short GC exposure duration since we want to know the additive effect of MTX given early in the disease course, and this shorter period also increases homogeneity of patients. Additionally, we think that a GC need > 30mg/d requires considering different diagnoses. The decision to exclude patients treated with other DMARDs 3 months prior to inclusion is because we want to be certain that any GC-sparing effect we see in our study is only due to MTX. Also, to ensure adequate assessments we exclude patients with active concomitant GCA or other rheumatic diseases such as RA, spondylarthropathies, connective tissue diseases, drug-induced myopathies, neuropathies or other conditions that might interfere with pain or movement evaluation of PMR, or interfere with treatment choices with respect to GC and DMARDs.

Who will take informed consent? (26a)
The research physician will take informed consent in duplicate and one copy will be given to the patient. Patients may withdraw their informed consent at any time.

Additional consent provisions for collection and use of participant data and biological specimens (26b)
Separate informed consent is taken for collecting additional (biobanking) samples when blood is taken, further elaborated upon in SPIRIT header (33). Separate approval will be sought for PMR related research regarding these samples.

Interventions

Explanation for the choice of comparators (6b)
In RA, MTX is the first choice of DMARD, and one of the most prescribed drugs in comparison to other DMARDs.24,25 Furthermore, MTX has been noted as a "potential steroid saving" drug in the treatment of PMR in the EULAR/ACR guidelines.4 Two earlier studies have compared the effect of MTX with placebo with an accelerated prednisone scheme, but the MTX dose used may have been suboptimal.20,21 In this study we prefer oral MTX over MTX injections for several reasons. Firstly, in discussion with patients they indicated a preference for oral MTX as there was a reluctance against MTX injections. Secondly, the MTX and placebo capsules are less expensive compared to subcutaneous injections. To mitigate the potential lower efficacy of oral MTX compared to subcutaneous and increase bioavailability, oral MTX is spread out over the course of a day.27 In this study we chose for GC-tapering through an accelerated protocol (of 24 weeks) – which is approximately twice as fast as usual care - for several reasons. Firstly, optimal GC-tapering in PMR is unknown as this is based on limited evidence of low to medium quality.20-23 Secondly, minimizing GC treatment may minimize AE.13 Thirdly, minimizing GC treatment can make it easier to spot a possible effect of MTX on GC use and GC free remission.

Intervention description (11a)
After inclusion patients are randomly allocated into one of two arms with a 1:1 ratio. Patients allocated to the treatment arm will receive oral MTX 15 mg per week, which will be increased to 25 mg per week after 4 weeks, for the remainder of the study period if no clinically relevant MTX-related side effects occur (Table 1). Patients assigned to the placebo arm will receive an identical amount of indistinguishable placebo capsules, containing MTX omg, once weekly. MTX will be dosed in capsules of 5mg as this allows easier dose adjustment without the risk of un-blinding with regard to treatment allocation in the case of AE. Also, it will be easier to split the dose over the course of the day to increase bioavailability. After the 52 week study period study medication will be stopped.
All patients in this study start with a prednisolone dose 15-20mg once daily, followed by an accelerated tapering scheme over the course of 24 weeks, with a dose reduction every 4 weeks of 2.5mg per day. (Table 1). Prednisolone will only be tapered after acquiring an adequate initial response and in the absence of a disease relapse. If primary non-response occurs during the first 4 weeks the prednisolone dose will be increased to 25mg/day for 2 weeks, followed by 20mg/day for 2 weeks and subsequently 15mg/day followed by the study tapering protocol (Figure 1).

Figure 1. Treatment protocol flowchart \{11b\}

When no primary response is obtained during treatment with 25 mg/day, alternative diagnoses such as GCA will be ruled out. If a patient does not respond after a maximum of 4 weeks, prednisolone can be raised further to 30mg/day for 1 week. If a patient does not respond in this time, they will be excluded from the study, because we think an alternative diagnosis is more likely. This patient will be replaced by an extra recruited patient. If a relapse occurs after initial primary response, prednisolone dose will be increased to the pre-relapse dose, followed by tapering in the case of response, or further raising of the dose in the case of non-response. If this is the first relapse, tapering will occur according to the study tapering protocol. If a second relapse occurs tapering will occur according to usual care. See figure 2 for a detailed description of the relapse protocol.

Figure 2. Relapse flowchart \{11b\}

Additionally, all patients will receive folic acid 5mg twice weekly, to reduce potential MTX related side effects.\textsuperscript{28} Osteoporosis prophylaxis for prevention of GC-related osteoporosis will be given if indicated.\textsuperscript{29}
leukocyte count is < 3,0 * 10^9/L, or platelet count is < 100 * 10^12/L then testing will be repeated (30). If ALAT serum levels are more than 3 times the upper bound of the normal values, is done by ALAT serum levels and blood count by hemoglobin level, leukocyte count and platelet count. Since MTX can lead to hepatotoxicity or blood count abnormalities, monitoring of hepatoxicity is an outcome assessed half a year after the earliest possible end of GC treatment (at week 24). Thus, we think this reflects the more relevant longer term efficacy. Furthermore, since relapse occurs frequent (and increased taper speed further increases chance of relapse) and prednisolone is raised and tapered in case of a relapse, we chose a point sufficiently far enough that patients with a relapse can still achieve GC-free remission. Additionally, we chose GC-free remission instead of an outcome like GC cumulative dose, because in our opinion GC-free remission is more clinically relevant and pragmatic, both for patients and physicians, as it also enables calculating Numbers Needed to Treat. This has additional value because earlier literature report a higher risk of relapse at lower doses of GC. In PMR there is no validated measure for disease activity but, since most evidence exist for the PMR-AS, we chose for a PMR-AS based score to define remission. The PMR-AS is discussed in more detail in the paragraph on assessments with SPIRIT header (18a).

Secondary outcomes are the proportion of patients in GC-free remission at week 32; the time to GC-free remission and first relapse; the GC cumulative dose at week 32 and 52; the number of relapses or recurrences during follow up at week 32 and 52; the proportion of patients that relapsed or had a recurrence during follow up at week 32 and 52; the change in: ESR, CRP, transition and PASS questions, VAS, EQ-5D, HAQ, and PROMIS-PF; the frequency and types of GC-related adverse events during the study as measured by the Glucocorticoid Toxicity Index (GTI); the frequency and types of GC- and MTX-related adverse events; and the proportion of patients that get MTX/placebo dose adjustment during follow up at week 52. Other variables that will be assessed and evaluated for a possible effect on primary and secondary outcomes: age, gender, smoking, alcohol use, BMI, comorbidities, GC-cumulative dose before inclusion, CRP/ESR at baseline, time to response, and the number of additional visits. After approval of the amendment of the trial by the Medical Ethics Review Committee, the following secondary outcomes were added to the trial: the proportion of low-dose GC (≤ 5mg daily) remission at week 32 and 52, and cost-utility (based on EQ-5D and direct healthcare costs). These outcomes were added as we thought they are asignificant contribution to a confirmatory aspect of the study. The choices of several of these secondary outcomes are based on the proposed inner core domains (systemic inflammation, physical function, pain, and stiffness) for PMR by the OMERACT working group. Furthermore, we chose multiple patient reported outcomes (PROs) to get a better insight in the quality of life and functioning of PMR patients.

We chose to use the GTI developed by Miloslavsky et al. because this enables a detailed and standardized assessment of GC-related AE. In PMR trials there is much heterogeneity regarding outcome measures; in our opinion, using the inner core domain as proposed by the OMERACT working group and the GTI will increase the chance of homogeneity and comparability of this trial with other (future) trials of PMR.

Participant timeline (13)
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 takes 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. Approximately 5-6 patients per month will be recruited to achieve 100 study participants within this time period.

### Criteria for discontinuing or modifying allocated interventions (11b)

Since MTX can lead to hepatotoxicity or blood count abnormalities, monitoring of hepatotoxicity is done by ALAT serum levels and blood count by hemoglobin level, leukocyte count and platelet count conform the Dutch Rheumatologist Association guidelines for methotrexate treatment (30). If ALAT serum levels are more than 3 times the upper bound of the normal values, leukocyte count is < 3.0 * 10^9/L, or platelet count is < 100 * 10^12/L then testing will be repeated within 7 days to determine whether these values improve, stabilize, or worsen. If laboratory abnormalities are still clinically relevantly elevated, as judged by treating physician, then MTX dose may be skipped for that week. Furthermore, laboratory values will be monitored the week thereafter and MTX dose can either be adjusted to a minimum of 10mg/week or continued. If clinically relevant lab abnormalities persist, MTX or placebo will be stopped, and patients will remain in the study. Treatment of other AE is at the discretion of the treating physician.

### Strategies to improve adherence to interventions (11c)

Patients are encouraged to adhere to the treatment regimen. If patients are not able to adhere to the treatment protocol, the reasons will be asked and noted by the treating physician. To improve MTX/placebo treatment adherence, in case the relatively frequent side-effect nausea occurs, ondansetron 4mg 1-2 times daily can be prescribed. Other side effects will be treated as judged by the treating physician.

### Relevant concomitant care permitted or prohibited during the trial (11d)

Patients are not allowed to take part in a competing clinical study whilst enrolled in this study. Patients are allowed to use paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) during the trial. Patients are encouraged to discuss any new medications, or medication changes, during the trial.

### Provisions for post-trial care (30)

After completion of the trial, usual care will be provided. This might include open label MTX, or other treatment according to management guidelines.

### Outcomes (12)

The primary outcome of this study is the between group difference in proportion of PMR patients in GC-free remission at week 52. This outcome captures both the state of disease activity and absence of GC-use. Combining these two in one composite measure is in our eyes a relevant and efficient way to measure the efficacy of MTX. Also, the 52 week endpoint is an outcome assessed half a year after the earliest possible end of GC treatment (at week 52). Thus, we think this reflects the more relevant longer term efficacy. Furthermore, since relapse occurs frequent (and increased taper speed further increases chance of relapse) and prednisolone is raised and tapered in case of a relapse, we chose a point sufficiently far enough that patients with a relapse can still achieve GC-free remission. Additionally, we chose GC-free remission instead of an outcome like GC cumulative dose, because in our opinion GC-free remission is more clinically relevant and pragmatic, both for patients and physicians, as it also enables calculating Numbers Needed to Treat. This has additional value because earlier literature report a higher risk of relapse at lower doses of GC. In PMR there is no validated measure for disease activity but, since most evidence exist for the PMR-AS, we chose for a PMR-AS based score to define remission. The PMR-AS is discussed in more detail in the paragraph on assessments with SPIRIT header (18a).

### Table 1. Treatment set-up for initial responders without relapse

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<td>0</td>
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<tr>
<td>2.5</td>
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<td>1.5</td>
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</tbody>
</table>

| **MTX (mg/week)** | 15 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Folic acid (mg/week)** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
Sample size

We calculated our sample size for our primary outcome, the proportion of patients in GC-free remission. Based on two previous RCTs studying the efficacy of MTX with regards to GC-free remission we assumed conservative, but still a clinical important, GC-free remission proportions of 70% versus 40% at week 52 (MTX versus placebo respectively). To calculate sample size, STATA/IC version 13 for windows was used, a Chi-Square test with a power of 0.80, a two-tailed alpha of 0.05, a 1:1 allocation ratio, and correction for continuity. This resulted in a total sample size of 98 patients, 49 per treatment arm. We calculated the sample size for different GC-free proportions in both groups. As shown in table 2, with a sample size of at least 98 we are on the safe side of finding a clinically relevant difference between groups, but also still on the feasible side. We increased the sample size to 100 as we expect a maximal drop-out of < 5%, as has been the experience in our center before.

Table 2. Patients needed for different effect sizes

<table>
<thead>
<tr>
<th>proportion of GC-free remission</th>
<th>Placebo group</th>
<th>MTX group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>55</td>
<td>0.8</td>
</tr>
<tr>
<td>0.45</td>
<td>65</td>
<td>0.75</td>
</tr>
<tr>
<td>0.4</td>
<td>70</td>
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</tr>
<tr>
<td>0.3</td>
<td>72</td>
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<tr>
<td>0.25</td>
<td>74</td>
<td>0.6</td>
</tr>
<tr>
<td>0.2</td>
<td>72</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Note: STATA/IC 13, a two tailed $\alpha$ of 0.05, power of 0.80, correction for continuity

Recruitment

To stimulate patient enrolment we will place information regarding the study on the website of ReumaNederland and the Sint Maartenskliniek. Every year, the diagnosis PMR is made approximately times in the Sint Maartenskliniek and around 50 patients a year fulfill the 2012 EULAR/ACR criteria. Because not every patient will want to, or is eligible to, participate in this trial, other centers and general practitioners are encouraged to refer patients to the Sint Maartenskliniek. Furthermore, collaboration with other rheumatology clinics will be sought to enhance patient enrolment. In case of exclusion of subjects if another diagnosis appears to more likely, additional subjects will be recruited, to ensure a minimum of 100 evaluable patients in the analysis.

Assignment of interventions: allocation

Sequence generation

The treatment allocation sequence will be generated by computer-generated random numbers and we will stratify in 4 groups based on sex and either an ESR ≥ 70 mm/h or a CRP ≥ 25 mg/L. Previous studies show that sex and serum level of inflammatory parameters before treatment may be predictors of PMR relapse during the first year of treatment, thus we wanted to make sure these variables were balanced between the MTX and placebo group. A variable block size will be used to reduce predictability of the randomization sequence, while maintaining balance in numbers. The details of this randomization sequence and treatment allocation will be unknown to all personnel part of the research team and only known to colleagues of the pharmacy.

Concealment mechanism

After removal of the label identifying MTX and placebo medication, MTX and placebo pills will be identical in packaging. Furthermore, the capsules will be identical to each other in appearance. Patients will receive the study medication from the pharmacy that is located at the Sint Maartenskliniek Nijmegen.

Implementation

The treating physicians will enroll patients. The interventions will be assigned by the pharmacy who have the document with the allocation sequence.

Assignment of interventions: Blinding

Who will be blinded

Patients and all caregivers, including researchers, nurses, and physicians, will be blinded for 52 weeks.

Procedure for unblinding if needed

If MTX is not tolerated during the trial period of 4 weeks (as assessed by laboratory values and AE), the dosage is not raised further or dose can be lowered without unblinding patients or caregivers. MTX capsules of 5mg will be used to allow easier dose adjustment without unnecessarily unblinding participants or caregivers. Unblinding is only done on request of a treating physician when this is needed for adequate treatment. This request will be made to the pharmacist and subsequent unblinding will be done by the pharmacist.

Data collection and management

Plans for assessment and collection of outcomes

See figure 3 for all the assessments and collection of outcomes that will take place during this study.
At baseline patient characteristics and physical examination will be performed. Patient characteristics include age, gender, smoking habits, alcohol use, and previous medical history. Disease characteristics that will be assessed include PMR specific symptoms and regions, the duration of symptoms prior to inclusion, involvement of systemic symptoms, and treatment prior to inclusion. Physical examination will include at least: length, weight, blood pressure, pulse rate, and temperature.

At baseline and every follow-up visit the PMR-AS will be assessed. To date there is no consensus based measure for disease activity in PMR. However, most evidence exists for the PMR-AS and earlier research has shown it may be possible to use this to discriminate remission from relapse in clinical practice if a cut-off point of ≥10 is used.33,37 The PMR-AS is calculated from CRP measurements (mg/dl), the duration of morning stiffness (MST, minutes), the ability to raise the arms (Elevation upper limb; EU1; 3 to 0: 3= no elevation possible; 2= elevation possible below shoulder girdle; 1= up to shoulder girdle; 0= full elevation possible), physician's global assessment (physician's visual analogue scale (VAS ph); 0 to 10), and the patients' assessment of pain (patient's visual analog scale (VAS p); 0 to 10). The total score will be calculated with the formula as described by Leeb et al.33 Primary response will be defined as ≥70% improvement from baseline in: PMR Visual Analogue Scale, duration of morning stiffness, and normal CRP or ESR. Remission during the visits will be defined as a PMR-AS < 10.33,37,38 Relapse will be defined as judged by the treating physician. AE will be assessed at every visit. Additionally GC-related AE are assessed by using the Glucocorticoid Toxicity Index (GTI).35

**COVID19 study visits**

Due to the COVID pandemic, study visits without physical appointments will be done where needed. Study visits at week 0, 32 and 52 will be done physically as these are necessary to accurately assess and analyze primary and secondary outcomes. Other study visits will be performed by digital means and laboratory assessment may be performed at local laboratories, based on physician and patient shared decision making. We think this is possible since the (main) physical examination, the EU1, and other parameters (e.g. pain and morning stiffness) may be done by telephone or video.

**Plans to promote participant retention and complete follow-up (18b)**

Contacting the research physician will be made easily accessible for patients. Patients will be seen as soon as possible when they experience a relapse. Furthermore, it will be made clear that prednisolone dose can (quickly) be raised in case of a relapse. The reason for withdrawal will be asked but patients do not need to provide the answer if they prefer not to disclose their reason.

**Data management (19)**

A CASTOR EDC database will be used to store all study data anonymously. CASTOR also enables an audit trail. Data entry will be done by a research assistant. Data will be checked by double entry in 20% of patients. Before analysis data will be checked on completeness and range checks will be made to detect any (potential) outliers. Data will be stored for 25 years after the end of the study.

**Confidentiality (27)**

All data will be collected and stored anonymously in a CASTOR database. Data will be coded and kept based on the rules for good clinical practice (GCP) and Dutch law. Only the trial researchers will have access to the CASTOR database through a personal password.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (23)**

Study Data will be stored for 25 years after the end of the study period. Blood samples for this study will be stored for the duration of this study period to do additional testing if necessary. Additional permission will be asked to use data and additional blood samples for future research in the field of PMR, as described in the patient information brochure. Blood samples for future research will be stored for 10 years. Blood samples will be sent to the hematology laboratory of the SMK and anonymously coded and delivered. The database managers keep a unique code list at a secured location which is only accessible to the database manager and the principal investigator. Additional research on material will only take place after medical ethical approval.

**Statistical methods**

All statistical analyses will be performed using STATA/IC version 13 for Windows. Results will be analysed on a intention-to-treat approach, and an additional per protocol sensitivity analysis will be done as described under spirit header (20c). Descriptive statistics will be provided using mean and standard deviation (SD, median and interquartile range (IQR) or frequencies / percentages as appropriate.

**Statistical methods for primary and secondary outcomes (20a)**

The primary outcome, the proportion of patients in GC-free remission after a total of 52 weeks, will be compared using a Cochran–Mantel–Haenszel. Reason for stratification are a possible
different prognosis between men and women, and in patients with higher values of ESR and/ or CRP. Of the secondary outcomes, the proportion of patients in GC-free remission at week 32; the proportion of patients with low dose GC, 15mg at week 32 and 32; proportion of the patients that have a relapse during follow up; proportion of patients that had MTX/placebo dose adjustment at week 32 will be analyzed in the same manner. Time to remission and time to first relapse will be compared using Kaplan-Meier analysis. GC cumulative dose will be compared using an independent t-test or Mann-Whitney test. Number of relapses will be compared using Poisson regression. Change in ESR and CRP, PMR-AS, transition and PASS, VAS, EQ-5D, HAQ, and PROMIS-PF will be compared using an independent t-test or Mann-Whitney test; Glucocorticoid Toxicity Index will be compared using an independent t-test or Mann-Whitney test; number of AE will be compared using an independent t-test or Mann-Whitney test. A p-value of p<0.05 will be considered significant.

Interim analyses (2zb)

No preplanned interim analyses will take place. On request of the DSMB, an interim analysis can be performed for safety reasons.

Methods for additional analyses (e.g. subgroup analyses) (20b)

We will stepwise study the correlation between covariates and the primary (and secondary) study parameter(s) by starting with a model with the (various) dependent outcome variables and independent treatment variable, and thereafter adding and removing covariates one at a time. We will first study the correlation with the stratification factors: sex and ESR and CRP level before treatment as covariates. Thereafter we will take into account the stratification of sex and pre-treatment CRP/ESR in a model, and stepwise add and remove age, smoking, alcohol use, BMI, and time to initial response as covariates.

Economic evaluation will be performed in a secondary (healthcare sector perspective) cost-utility study guided by national recommendations. Costs will be determined by multiplying units of medication and rheumatology appointments by costs per unit. QALY will be calculated using an Area Under the Curve (AUC) method using utility scores converted from the EQ-5D-5L.43,44

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)

Patients in which an alternative diagnosis is considered more likely during primary response evaluation due to lack of response to prednisolone, are excluded from the primary analyses (as discussed under spirit header {15a}) and replaced by a new inclusion. After this exclusion, patient data will primarily be analyzed in an Intention-To-Treat (ITT) manner. Efficacy related outcomes will also be analyzed in a Per-Protocol (PP) manner. Patients will be excluded from the PP analysis if they either: deviated from the tapering protocol more than eight weeks, are treated with prednisolone ≥ 20mg/day for 2 weeks due to other complaints than PMR (after initial response to prednisolone) or are allocated to MTX group and were not treated with at least MTX 15mg/week for at least 6 months. Potential reasons for drop-out will be noted and assessed with regards to the rise of attrition bias due to los to follow-up.

The number of missing values and the role of the corresponding variables will be assessed. Missing value patterns will be analyzed using visualization (e.g. histograms), potential causes for missing (e.g. treating physician and PP adjustments) will be examined, and supportive testing using Little’s test for Missing Completely At Random will be used42. If missing values are limited in number and importance (of the corresponding variable) a complete case analyses, per analysis per outcome, can be considered. If missing values occur more often, or the corresponding variable is deemed important, and we assume data to be Missing (Completely) At Random, then an imputation technique will be considered. Imputation will be considered separately for ITT and PP analyses. The imputation technique used will depend on the missing values, with a preference for multiple imputation (using chained equation) as opposed to single imputation, like Last Observation Carried Forward45.

Plans to give access to the full protocol, participant level-data and statistical code (31c)

Full public access to the full protocol will be granted. After the initial analyses of study data, access to anonymized participant-level dataset and statistical code may be granted upon request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee (5d)

The coordinating center is the Sint Maartenskliniek. In case more centers will participate in the future, The Sint Maartenskliniek will be coordinating and steering the other participating centers (principal investigator is dr. Aatke van der Maas, rheumatologist and coordinating investigator is Thomas Bolhuis, MD).

Composition of the data monitoring committee, its role and reporting structure (21a)

Stringent monitoring is not formally necessary as this study is classified as negligible/low risk. Nevertheless, an independent Data Safety Monitoring Board (DSMB) will be installed to monitor the inclusion progress of the study every six months. Members of the DSMB are independent from the study and include a pharmacist, an internist, a rheumatologist, and a methodologist. Their role is to monitor the feasibility and safety of the study, e.g. inclusion rate and the occurrence of (serious) adverse events(SAE) . Meetings will be planned every 6 months from the time of first inclusion. The principle and coordinating investigators will be present during meetings.

Adverse event reporting and harms (22)

All(S)AE reported spontaneously by the subject or observed by the investigator will be recorded. The (S)AE will be timely reported to the medical ethical authorities according to Dutch legislations. An annual safety report will be written and submitted to the competent authority throughout the duration of the clinical trial. Furthermore, AE will be discussed in the DSMB (as discussed under spirit header {21a}) and checked by the monitor (as discussed under spirit header {23}).

Frequency and plans for auditing trial conduct (23)

As this is a low risk study, monitoring of the trial will be performed once per year. The assigned monitor is independent from the study and ‘BROK’ certified conform Dutch guidelines. Monitoring will consist of checking rate of inclusion, drop-out, the investigator site file, informed consent for 25% of participants, in- and exclusion criteria for 10% of participants,
source data of ≤10% of participants, SAE in 1% of participants, and verify SAE in 10% of SAE. The monitor will write a report, which will be assessed and signed by the principal investigator.

**Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)**

Any protocol amendments will first be communicated to the medical ethical committee. After approval by the medical ethical committee, the protocol amendments will be communicated to the study participants if the amendments apply to the patients. Depending on the degree of amendments, they will also be communicated to all other relevant parties such as the treating physicians, research personnel, trial registries and regulators.

**Dissemination plans**

The main findings of clinical trials will be authored by investigators of the Department of Rheumatology from the Sint Maartenskliniek and submitted for publication in a peer-reviewed journal within 12 months of study completion. Researchers who have made significant contributions to the study will be included in the list of authors. In addition, key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry. Furthermore, a layman’s summary of the results will be posted on a free-to-access, publicly available, searchable institutional website of the Sint Maartenskliniek and will also be disseminated to all patients who participated in the study.

**Discussion**

With this double-blinded placebo controlled superiority design our aim is to investigate whether MTX 25mg/week is efficacious and leads to disease remission and GC-sparing in PMR. Several choices for the design are motivated above, but we would like to discuss some aspects and challenges of the study design in more detail below.

First of all, the selection of patients: in an ideal setting we would like to include all patients with clinical PMR in the study. However, a clinical diagnosis of PMR may be less specific for PMR than the EULAR/ACR classification criteria and there may be much heterogeneity among rheumatologist regarding clinical diagnosis. Thus using these criteria will – although generalizability and inclusion will be somewhat hampered - improve homogeneity, both within the study, and when comparing with other studies. Of note, these criteria have a moderate sensitivity and specificity for PMR. Therefore not all patients with clinically diagnosed PMR can be included, e.g. patients with normal acute phase parameters. However, these patients may represent a subset of PMR patients with a different (more benign) disease course, possibly benefitting less from add-on MTX. Inclusion criteria for this trial are less strict when compared to other PMR trials in the Netherlands (a Leflunomide trial (clinical trial identifier: NCT0376794) and a Sarilumab trial (clinical trial identifier: NCT03600818)). Firstly, newly diagnosed PMR for this trial is defined as GC use ≤ 8 weeks, which we assume more feasible and reflecting the true newly diagnosed PMR patients we see in daily clinical practice, as opposed to a shorter treatment duration (e.g. more pragmatic approach versus explanatory). Secondly, exclusion based on conditions interfering with pain and movement evaluation is left to treating rheumatologists, for example fibromyalgia is not a hard contra-indication, unless this might interfere with assessments. We assume these exclusion criteria to be more pragmatic, improve feasibility, and increase generalizability. Lastly, eligibility for treatment with MTX is left to judgement of the treating rheumatologist/research physician. This was decided, because there is a lot of experience with MTX in rheumatology practice, and this choice is supported by the Dutch guidelines for MTX treatment which does not formulate absolute contra-indications.

We have considered also including patients relapsing during tapering of GC. Indeed, to date, even though it is recommended in the international guidelines for management of PMR, the evidence of GC-sparing effect of concomitant MTX in PMR patients who relapse is not strong. Including PMR patients who relapse in our study would have the advantage of a higher inclusion rate. However, in this study we decided not to include PMR patients who relapse for several reasons. Firstly, it is uncertain if the MTX efficacy will be the same in both subgroups of PMR, and effect modification may occur. Secondly, it is unknown what the optimal GC-dose cut-off point is at moment of relapse for starting concomitant MTX. This is because at lower GC doses the possible benefits of MTX may not outweigh the risks. Therefore our study will be conducted with recently diagnosed PMR patients only.

Another point we would like to address is the selection of the primary outcome in light of this GC tapering based strategy study. We deliberately chose a composite endpoint of disease activity (remission defined as PMR-AS<10 AND treatment (GC free), as this is in our eyes a more meaningful outcome than an outcome of disease activity or treatment alone. The remission defined as PMR-AS<10 is both a subjective and objective outcome, and including both patients’ and physicians’ view of PMR disease activity. Also, earlier strategy studies conducted in rheumatoid arthritis have shown that, when adjusting treatment based on disease activity alone, the outcome tends to converge at the endpoints of the study. In our study if patients experience a relapse, this will be ameliorated by increasing GC to the pre-relapse dose. This may lead to second order effects such as increased cumulative GC dose, number of relapses or being symptom free but still on medication. In our eyes, being on treatment or not is also a meaningful outcome as treatment is related with adverse events. Therefore we chose to use the GC-free remission as our primary outcome, as it captures both disease activity and treatment outcomes at once.

Concerning the intervention, the choice for using MTX capsules instead of injections has already been motivated in the text above, the accelerated GC-tapering on the other hand will be discussed further here. In this study we chose an accelerated GC-tapering regime of 24 weeks, which is approximately twice as fast as usual care. With this tapering speed it is more likely to find a treatment effect of MTX if it exists. Also, as two previous RCTs examined MTX using an accelerated GC tapering scheme, the results of our study may be more easily compared with results of these other studies. Also, it may lead to better insight in the ideal length of a GC tapering scheme. One aspect we did not discuss before is the possible increased chance of relapsing during tapering. In discussions with patients in the design phase of our study, patients were willing to accept this risk if contact with the physician is easily accessible and prednisolone may promptly be raised to the pre-relapse dose. The diagnosis has already been made and both the patient and research physician will be able to identify relapses quicker.
Another challenge in this study is the COVID-19 pandemic as both inclusion and follow-up of patients may be hampered by distancing measures. To guarantee patient safety and reduce risk of COVID-19 infection and spread study visits are performed digitally where possible. In spite of limited physical appointments we do think that adequate study assessments will be made as most assessments can be collected reliably by telephone and the visits where physical appointments is required for assessments are limited.

In conclusion, both a negative and positive outcome of this trial will have significant implications for the management of PMR. To date there is insufficient data on treatment of PMR with MTX. However, as it is recommended by the international guidelines for PMR, a negative result might alter this recommendation and it might prevent unnecessary exposure to adverse events of MTX. If this trial does indeed prove efficacy of MTX in PMR patient in an early phase of the disease, it will lead to improved treatment of PMR.

Trial status
Protocol version 1.1, date 26-11-2019. Recruitment started at 02-03-2020 and is expected to be completed by 08-2022.

References


Efficacy of rituximab in polymyalgia rheumatica patients: a double blind randomized placebo controlled proof of concept trial

Diane E. Marsman
Nathan den Broeder
Frank H. J. van den Hoogen
Alfons A. den Broeder
Aatke van der Maas

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Abstract

Background
Glucocorticoids remain the cornerstone of polymyalgia rheumatica treatment, but their use has several drawbacks such as long treatment duration and glucocorticoid-related adverse events. Effective glucocorticoid-sparing agents with a strong evidence base are absent. As B-cells are implicated in the pathogenesis of polymyalgia rheumatica, we evaluated the efficacy of rituximab for the treatment of polymyalgia rheumatica.

Methods
In a 21-week double-blind placebo controlled exploratory study, 47 polymyalgia rheumatica (Caucasian) patients (recently diagnosed \(n=38\) / relapsing on prednisolone \(\geq 7.5\) mg/day \(n=9\)) fulfilling the 2012 EULAR/ACR criteria, were randomized 1:1 to intravenous rituximab \(1 \times 1000\) mg \((n=23)\) or placebo \((n=24)\), with a 17-week long glucocorticoid co-treatment. Primary outcome was glucocorticoid-free remission at week 21. Secondary outcomes were glucocorticoid ≤5 mg/day, patient reported outcomes and adverse events.

Results
In the rituximab versus placebo group mean age (standard deviation (SD)) in years was 64 (8) and 66 (10), and proportion of women was 11/23 (48%) versus 13/24 (54) respectively. Glucocorticoid-free remission was achieved in 48% (rituximab) versus 21% (placebo), difference: 27% (one-sided 95%-CI 4%; \(p=0.049\)), and glucocorticoid ≤5 mg/day in 100% versus 54%, absolute difference: 46% (one-sided 95%-CI 20%; relative risk 1.8 (1.3); \(p=0.005\)). Mean (SD) changes in polymyalgia rheumatica activity score were -13.8 (2.9) and -3.8 (3.6), with an absolute difference of -10 and one-sided 95% CI of at most -2.2, \(p=0.02\). In the rituximab versus placebo group 10 and 3 infusion related complaints occurred, incidence rate 3.47, one-sided 95% CI of 13. No significant differences were observed regarding other outcomes.

Conclusions
Rituximab was shown to be effective in combination with 17-week glucocorticoid-treatment to achieve glucocorticoid free remission in polymyalgia rheumatica (funding: Sint Maartenskliniek; no external funding; Dutch trial number NL7414).

Introduction
Polymyalgia rheumatica is an inflammatory rheumatic disease that usually affects people older than 50 years. The incidence varies from 41 to 133 per 100,000 persons, and is highest in Northern European countries. Typical symptoms are bilateral pain and stiffness of the neck, shoulder- and hip girdle, with elevated inflammatory parameters. The cause and pathogenesis of the disease remain largely unknown, and polymyalgia rheumatica may lead to morbidity and significant reduction of quality of life.1-3

Glucocorticoids are the cornerstone of polymyalgia rheumatica treatment but have several unfavorable aspects.1 Firstly, a considerable number of patients have contra-indications to glucocorticoids and/or experience glucocorticoid-related adverse events which can be severe, especially after prolonged treatment.3-6 Secondly, around 50% of patients experience one or more flares during glucocorticoid tapering.4 Flares leads to a substantially prolonged treatment duration, with around 40% of patients needing glucocorticoid ≥4 years.7

The 2015 European league against rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines on management for polymyalgia rheumatica recommend concomitant glucocorticoid-sparing agents in patients with worse prognosis or contra-indications for glucocorticoids.3 Several conventional synthetic and biological disease modifying anti-rheumatic drugs have therefore been studied in polymyalgia rheumatica,1,3 but benefits were absent or limited.3,8-9 Research on glucocorticoid-sparing agents therefore remains high on the international research agenda of polymyalgia rheumatica.3

So far, B-cell targeted treatment in polymyalgia rheumatica has not been studied. Because it is not clearly associated with autoantibodies, polymyalgia rheumatica does not appear to be a typical B-cell driven disease.1,10-13 However, B-cells are part of the inflammatory cascade and produce interleukine-6, which is involved in the pathogenesis of polymyalgia rheumatica.1,14 A disturbed B-cell homeostasis was found in newly diagnosed untreated polymyalgia rheumatica and giant cell arteritis (a large vessel vasculitis associated with polymyalgia rheumatica).14 In addition, one case report of giant cell arteritis with polymyalgia rheumatica successfully treated with rituximab has been published.15 Therefore, although this is not supported by strong evidence, B-cells might play a pathophysiological role in polymyalgia rheumatica.

One B-cell targeting treatment is rituximab, a chimeric monoclonal antibody against CD20. There is sufficient clinical experience with other inflammatory rheumatic diseases showing that rituximab is well tolerated.16 Advantages include a safe, and patient-friendly drug, although rituximab has infusion related side effects and a small dose-dependent risk of infection.16 We therefore aimed to explore whether rituximab has a glucocorticoid-sparing effect in recently diagnosed and relapsing polymyalgia rheumatica patients in a double blind randomized controlled trial.
Methods

Study design and participants

Study design and ethical conduct

This 21-week long, double-blind placebo-controlled trial explored the efficacy of rituximab 1 x 1000 mg in patients with polymyalgia rheumatica who were either recently diagnosed, or relapsed on prednisolone treatment 2.5 mg/day. The glucocorticoid tapering scheme is shown in supplement 1, section 1. The study was conducted at the Rheumatology Department of the Sint Maartenskliniek, The Netherlands. Medical ethical approval was obtained from the Medical ethical committee of the region Arnhem-Nijmegen (NL66847.091.18; 2018-4609). The trial is registered in the European EudraCT (2018-002641-11) and Dutch trial database (NL7414).

Of note, after registration the trial protocol was amended concerning the following points: the cut-off point of remission by the polymyalgia rheumatica-activity score, the classification criteria used for study inclusion, the inclusion of not only glucocorticoid naïve patient but also patients on a short glucocorticoid treatment and relapsing patients: (see supplement 1, section 2 for description and rationale, changes also described in the protocol and statistical analyses plan document). The amendment was approved on 18th of April 2019, after the eighth patient was enrolled and before the first patient reached the end of follow-up. However, due to human error the trial register was not updated to reflect these amendments in time and only noticed after the last patient had completed follow-up. All participants and research personnel were still blinded to the allocated intervention and results. All participants received study information including possible benefits/risks involved in study participation and gave written informed consent. The trial was monitored according to good clinical practice. A Data Safety Monitoring Board held three-monthly meetings to safeguard study feasibility and participant safety.

Patients

Participants were referred by their treating rheumatologists or general practitioner. We recruited both newly diagnosed and relapsing patients according to the following inclusion criteria:

Newly diagnosed patients:
• polymyalgia rheumatica fulfilling the 2012 EULAR/ACR classification criteria (excluding the ultrasound criteria)
• diagnosed within three months before study inclusion
• glucocorticoid naïve, or
• glucocorticoid treatment ≤6 consecutive weeks before study inclusion, with a maximum dose of 30mg if treatment duration was <1 week, and a maximum dose of 20mg otherwise

Relapsing patients:
• polymyalgia rheumatica fulfilling the 2012 EULAR/ACR classification criteria (excluding ultrasound criteria)
• clinical relapse (including elevated ESR (>30mm/hour)/CRP (>5mg/L)) at glucocorticoid dose of 2.5mg/day

Main exclusion criteria:
• daily dose of oral glucocorticoid >30mg
• exposure to other immunosuppressants in the four months before study inclusion
• other concomitant inflammatory rheumatic diseases or diseases hampering assessment of polymyalgia rheumatica

A more detailed description of inclusion and exclusion criteria is shown in supplement 1, section 3.

Randomisation and masking

Rituximab and placebo were randomly allocated in a 1:1 ratio. An independent pharmacist generated the randomization scheme by computerized procedure with varying block size (two blocks of 20, one block of 10 subjects). Patients, care and research personnel were blinded to treatment assignment and randomization sequence. Treatment allocation was revealed to patients at least one year after rituximab infusion. Researchers were unblinded only after analyses of the primary efficacy outcome. Rituximab and placebo were prepared based on randomization number by the local hospital pharmacy. It was not possible to discern rituximab from placebo, and all patients received similar care and pre-medication during the infusion.

Procedures

Interventions

Within three weeks of study enrollment, patients received either 1 x 1000 mg rituximab or placebo infusion intravenously. We chose 1 x 1000 mg as the study dose, since a systematic review and meta-analysis of rituximab-regimens in rheumatoid arthritis showed similar efficacy of rituximab 1 x 1000 mg; 2 x 1000 mg and 2 x 500 mg and 1 x 1000 mg was associated with fewer adverse events. A higher dose than in rheumatoid arthritis was deemed unnecessary in polymyalgia rheumatica. Two vials of each 50 mL containing concentrated 500mg of rituximab were diluted in in 500mL sodium chloride 0.9% (Rixathon; Sandoz bv; ATC code: L01X C02). Prior to infusion, standard premedication according to local treatment protocol in rheumatoid arthritis (single dose intravenous 50 mg methylprednisolone, oral acetaminophen 1000 mg and cetirizine 10 mg) was given in both groups to ensure blinding for intervention.

Co-medication

All patients received the same prednisolone treatment from the day of intervention (supplement 1, section 1). Since data in rheumatoid arthritis demonstrates a delay in efficacy after rituximab infusion, we did not expect rituximab to show relevant efficacy before 11 weeks in most polymyalgia rheumatica patients. Therefore, we started with a regular glucocorticoid tapering scheme, which was accelerated after 11 weeks. When a patient experienced a relapse after initial response (secondary non-responder), prednisolone was increased up to the last effective dose for two weeks and the accelerated tapering scheme resumed when remission was achieved again. If a second relapse occurred, the prednisolone was again increased to the last effective dose and after two weeks subsequently tapered according to the slower local usual care tapering scheme. In case of recurrence of disease after glucocorticoid cessation, prednisolone was reintroduced and subsequently tapered according to above mentioned manner (accelerated or usual care depending on it being the first or second relapse during the
Visits and assessments

Visits and assessment of study outcomes took place at baseline, and week 2, 4, 11, 17 and 21 after rituximab infusion. Extra visits were planned if necessary. Data on patient, disease characteristics, measurements, laboratory values, disease activity and functional and health related questionnaires were collected (described in more detail below). Alternative diagnoses were ruled out by an extensive history taking, physical exam (always including palpation of temporal artery and lymph nodes), routine laboratory tests including hepatitis serology, chest X-ray and if needed additional laboratory tests or imaging. During follow-up, patients were monitored by careful review and physical exam to rule out concomitant giant cell arteritis or conversion into other rheumatic disease for example rheumatoid arthritis.

Outcomes

The primary outcome was proportion of glucocorticoid-free remission at week 21 after rituximab infusion. Remission is defined as polymyalgia rheumatica activity score <10, indicating low disease activity as proposed by earlier studies. This score is a composite score of the following items: C-reactive protein (CRP) level (mg/dl), duration of morning stiffness (MST), elevation of upper limbs (EUL); 3-0: 3=no elevation possible; 2:elevation below shoulder girdle; 1=elevation up to shoulder girdle, 0=elevation above shoulder girdle), physician’s global assessment by visual analogue score (physician’s VAS (VASph); 0 to 10), and the patients’ assessment of pain (patient’s VAS (VASp); 0 to 10). This leads to the following equation: CRP + VASp + VASph + (MST *0.1) + EUL. Relapse was defined as judged by the treating physician, if symptoms and raised erythrocyte sedimentation rate (ESR) and/or CRP recurred attributable to polymyalgia rheumatica.

Preplanned secondary outcomes at week 21 were group differences in (change in) proportion of patients achieving glucocorticoid dose ≤ 5mg, cumulative glucocorticoid (total oral, intravenous, intramuscular and intra-articular glucocorticoids) dose, ESR/CRP and B-cell count, polymyalgia rheumatica activity score, and relapsing patients. Additionally, differences in functional status and quality of life were assessed by using the HAQ disability index, patients’ global, pain, fatigue and stiffness VAS. Post-hoc analyses included proportion of glucocorticoid-free remission judged by treating rheumatologist (clinical assessment of patients’ complaints with or without elevated acute phase reactants; with the following possible categories: glucocorticoid-free remission, remission with glucocorticoids, doubtful glucocorticoid-free remission, doubtful remission with glucocorticoids, and flare), proportion of glucocorticoid-free remission (polymyalgia rheumatica activity score <10) and glucocorticoid dose ≤ 5mg stratified by disease phase. To ensure optimal assessment reliability, visits were done by one research physician, with one other research physician as backup.

Assays of CRP, ESR and CD19 + B-lymphocytes are described in supplement 1, section 4 and 5.

Safety and adverse events

All types of glucocorticoid- and rituximab-related adverse events were collected during the study. An elaborate assessment of glucocorticoid-related toxicity was assessed at baseline, visit 4 and 6 using the glucocorticoid toxicity index. At baseline and follow-up, signs for alternative diagnoses such as malignancy or aortic abnormalities, were assessed.

Sample size calculation

The proportion of glucocorticoid-free remission at 21 weeks after monotherapy prednisolone is unknown and scarce literature reports different percentages. Taking into account a 5% drop-out, we selected a sample size of 50 patients (25 per treatment-arm) using Fisher’s exact test and one-sided alpha of 0.05, this sample size has at least 86% power to assess a clinically relevant difference of 40% in advantage of rituximab (supplement 1, section 6). As described in the original protocol, a one sided p-value was used as we expected only one possible and relevant direction of efficacy of rituximab because both groups were treated with concomitant glucocorticoids.

Statistical analysis

Statistical analyses were performed using STATA/IC 13 for Windows. Descriptive values are presented as mean +/- standard deviation (SD), median (p25-p75) or frequencies/percentages, depending on type and distribution of data. Primary endpoint was compared using Fishers’ exact test. Secondary outcomes were compared using either Welch t-test, Wilcoxon rank sum or Fishers’ exact test depending on data type and distribution. One-sided p-values <0.05 and one-sided 95%-confidence intervals not containing zero were considered statistically significant. Imputation of missing CRP values is described in section three of the supplement.
Results

Forty nine patients were enrolled from January 2019 through March 2020. The participants’ flow chart is shown in figure 1.

Figure 1. Participant flow diagram following CONSORT guidelines

Ultrasound criteria for the 2012 EULAR/ACR classification criteria of polymyalgia rheumatica were ultimately not used due to the logistical difficulties of organizing ultrasound of shoulders and hips and because most patients had already started glucocorticoid treatment before inclusion. Study inclusion ended somewhat prematurely due to the COVID-19 pandemic: 47 patients were enrolled and completed the study of 21 weeks. The population included 38 with recently diagnosed polymyalgia rheumatica, and 9 patients with relapsing disease. Demographic and baseline clinical characteristics are shown in table 1.

<table>
<thead>
<tr>
<th>Table 1. Demographic and baseline clinical characteristics</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age years – mean (SD)</td>
</tr>
<tr>
<td>Female – no. (%)</td>
</tr>
<tr>
<td>Male – no. (%)</td>
</tr>
<tr>
<td>Body-mass index – mean (SD) *</td>
</tr>
<tr>
<td>Newly diagnosed polymyalgia rheumatica – no. (%)</td>
</tr>
<tr>
<td>Relapsing polymyalgia rheumatica – no. (%)</td>
</tr>
<tr>
<td>Disease duration</td>
</tr>
<tr>
<td>Newly diagnosed polymyalgia rheumatica in weeks - median (IQR) †</td>
</tr>
<tr>
<td>Relapsing polymyalgia rheumatica in months - median (IQR) ‡</td>
</tr>
<tr>
<td>Morning stiffness in minutes - median (IQR)</td>
</tr>
<tr>
<td>Systemic symptoms – no. (%) §</td>
</tr>
<tr>
<td>CRP in mg/l at diagnosis – median (IQR)</td>
</tr>
<tr>
<td>CRP in mg/l at baseline visit - median (IQR)</td>
</tr>
<tr>
<td>ESR in mm/hour at diagnosis – mean (SD) ‡</td>
</tr>
<tr>
<td>ESR in mm/hour at baseline visit - mean (SD)</td>
</tr>
<tr>
<td>Polymyalgia rheumatica activity score – mean (SD) ¶</td>
</tr>
</tbody>
</table>

* Body-mass index = weight (kilograms) divided by height (meter) squared
† Disease duration from onset symptoms until PMR diagnosis, in weeks
‡ Disease duration from diagnosis until study inclusion, in months
§ Fever, cold chills, weight loss, night sweats, fatigue
¶ Polymyalgia rheumatica activity score = total score is calculated with the following equation: CRP (mg/dl)+VAS patient (0–10)+VAS physician (0–10)+morning stiffness (min)*0.1+elevation of upper limbs (3–0)

The research physician was accidentally unblinded to the likely treatment allocation of seven patients due to B-cell counts mistakenly uploaded into the laboratory output of patients’ electronic health records. Subsequent visits of these patients were thereafter done by another physician who remained blinded to treatment allocation. Also, both the patients study number and allocation labels were coded during the analysis phase to safeguard blinding of the research team during analysis of primary outcome. Further information on protocol violations is described in supplement 1, section 7.

Compared to placebo, significantly more patients receiving rituximab achieved glucocorticoid-free remission (polymyalgia rheumatica-activity score<10) at 21 weeks: 48% (12/25) versus 21% (5/24), absolute risk difference 27% (one-sided 95%-CI 4%), relative risk 2.3 (one-sided 95%-CI 1.1, p=0.049. The course of mean polymyalgia rheumatica-activity score is shown in Figure 2. The course over time of each separate polymyalgia rheumatica-activity score item is shown in supplement 1, section 8. Other secondary outcomes are described in table 2. Scores of the glucocorticoid toxicity index are shown in supplement 1, section 9.
Figure 2. Mean Polymyalgia Rheumatica Activity Score at each visit.

Table 2. Treatment, disease characteristics and quality of life related secondary outcomes at week 21*

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n=23)</th>
<th>Placebo (n=24)</th>
<th>Absolute difference (one sided 95%-CI)</th>
<th>Relative risk (one sided 95%-CI)</th>
<th>One sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose glucocorticoid ≤5 mg – no (%)</td>
<td>21 (100)</td>
<td>13 (54)</td>
<td>8 (46)</td>
<td>1.8 (1.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cumulative glucocorticoid dose in mg</td>
<td>1506 (151)</td>
<td>1406 (189)</td>
<td>-100 (34)</td>
<td>-0.16</td>
<td></td>
</tr>
<tr>
<td>Median CRP in mg/l (median, IQR) ‡</td>
<td>3 (1 to 5)</td>
<td>3 (1 to 12)</td>
<td>2 (1 to 12)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (median, IQR)</td>
<td>-1.5 (-9 to 2) [22]</td>
<td>-5 (-13 to 0) [21]</td>
<td>3.5 (CI N/A)</td>
<td>-0.16</td>
<td></td>
</tr>
<tr>
<td>Mean ESR in mm/hour</td>
<td>18 (13) [21]</td>
<td>18 (13) [21]</td>
<td>0 (7)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Relapsing patients during follow-up – no (%)†</td>
<td>7 (30)</td>
<td>8 (33)</td>
<td>-3 (20)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Median PMR-AS</td>
<td>3 (1 to 5)</td>
<td>11 (5)</td>
<td>-8 (9)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>23 (18) [21]</td>
<td>23 (18) [21]</td>
<td>2 (1)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Mean physicians’ VAS</td>
<td>17 (14) [21]</td>
<td>18 (17) [21]</td>
<td>11 (9)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>30 (9 to 30) [21]</td>
<td>30 (9 to 30) [21]</td>
<td>0 (CI N/A)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean patients’ morning stiffness VAS</td>
<td>24 (28) [21]</td>
<td>24 (28) [21]</td>
<td>0 (CI N/A)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>5 (0 to 10) [21]</td>
<td>13 (8) [21]</td>
<td>-8 (7)</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>Morning stiffness in minutes (median, IQR)</td>
<td>5 (0 to 10) [21]</td>
<td>13 (8) [21]</td>
<td>-8 (7)</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>30 (9 to 30) [21]</td>
<td>30 (9 to 30) [21]</td>
<td>0 (CI N/A)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Mean patients’ fatigue VAS</td>
<td>35 (31) [21]</td>
<td>38 (36) [21]</td>
<td>3 (3)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>41 (20) [21]</td>
<td>42 (20) [21]</td>
<td>1 (1)</td>
<td>-0.37</td>
<td></td>
</tr>
<tr>
<td>Mean patients’ global VAS</td>
<td>34 (30) [21]</td>
<td>35 (31) [21]</td>
<td>1 (1)</td>
<td>-0.37</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>41 (20) [21]</td>
<td>42 (20) [21]</td>
<td>1 (1)</td>
<td>-0.37</td>
<td></td>
</tr>
<tr>
<td>Mean HAQ-DI</td>
<td>0.66 (0.6)</td>
<td>0.45 (0.6)</td>
<td>0.21 (0.49)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.68 (0.6)</td>
<td>0.49 (0.6)</td>
<td>0.26 (0.49)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Mean EQ5D-5L total score</td>
<td>0.67 (0.12)</td>
<td>0.58 (0.12)</td>
<td>0.09 (0.47)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.67 (0.6)</td>
<td>0.68 (0.6)</td>
<td>0.01 (0.47)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Use of NSAID (standard / on demand) – no (%)</td>
<td>9 (39)</td>
<td>10 (43)</td>
<td>1 (9)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.00 (0.02) [21]</td>
<td>1.00 (0.02) [21]</td>
<td>0.00 (0.02) [21]</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Mean CD19+ B-cell count (cells/μL)</td>
<td>0.00 (0.02) [21]</td>
<td>0.00 (0.02) [21]</td>
<td>0.00 (0.02) [21]</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>

* Values are means, SD, unless specified otherwise. Numbers of observations is indicated between brackets [ ]. No correction for type I error was performed.
† Relapse = as judged by research physician
‡ Wilcoxon rank sum (Mann-Whitney) test
CRP denotes C-reactive protein, IQR interquartile range, N/A not applicable, ESR erythrocyte sedimentation rate, PMR-AS polymyalgia rheumatica activity score, VAS visual analogue score with higher scores indicating worse outcome (range 0 to 100), HAQ-DI health assessment questionnaire disability index with higher scores indicating worse function and greater disability (range total score 0 to 3), EQ5D5L EuroQol five dimension scale with higher scores indicating more severe or more frequent problems (range of total score for the Netherlands 0.446 to 1), NSAID non-steroidal anti-inflammatory drugs

* No correction for type I error was performed.
† Relapse = as judged by research physician
‡ Wilcoxon rank sum (Mann-Whitney) test
CRP denotes C-reactive protein, IQR interquartile range, N/A not applicable, ESR erythrocyte sedimentation rate, PMR-AS polymyalgia rheumatica activity score, VAS visual analogue score with higher scores indicating worse outcome (range 0 to 100), HAQ-DI health assessment questionnaire disability index with higher scores indicating worse function and greater disability (range total score 0 to 3), EQ5D5L EuroQol five dimension scale with higher scores indicating more severe or more frequent problems (range of total score for the Netherlands -0.446 to 1), NSAID non-steroidal anti-inflammatory drugs
Disease phase appeared to be an effect modifier, as effect of rituximab versus placebo on primary outcome was greater in recently diagnosed patients (58% (12/21) versus 21% (4/19), absolute risk difference 37% (one-sided 95% CI 10% of relative risk 2.8 (one-sided 95% CI 1.3); p=0.02), compared to relapse patients (0 versus 20% (1/5), absolute risk difference 20% (one-sided 95% CI -57%; relative risk not applicable; p=0.56), but this could not be formally shown in the limited sample size. The effect of rituximab versus placebo on glucocorticoid ≤5mg/day was also greater in recently diagnosed patients: 100% (19/19) versus 47% (9/19), absolute risk difference 53% (one-sided 95% CI of difference 29%), relative risk 2.1 (one-sided 95% CI of difference 1), p<0.001 compared to relapse patients (75% (3/4) versus 80% (4/5), absolute risk difference 5% (one-sided 95% CI -54% relative risk 0.9 (one-sided 95% CI 0.5), p=0.72).

Glucocorticoid-free remission by clinical judgement of treating physician in the rituximab versus placebo group was 30% (7/23) versus 25% (8/32), remission in combination with glucocorticoid use was 17% (4/23 and 4/24) in both groups, doubtful remission without glucocorticoid use was 22% (5/23) versus 0%, doubtful remission with glucocorticoid use was 9% (2/23) versus 21% (5/24); and overt clinical flare was 31% (7/23) versus 38% (9/24). Four glucocorticoid-free patients were classified as in glucocorticoid-free remission by the polymyalgia rheumatica-activity score <10 definition, but were classified as doubtful remission by clinical judgement of the treating physician. The primary outcome, disaggregated by biological sex is shown in supplement 1, section 10. Concerning the use of non-steroidal anti-inflammatory drugs (NSAIDs), this was used in week 21 in the rituximab versus placebo group in 9/23 (39%) and 10/24 (42%) respectively, absolute risk difference -3% (one-sided 95% CI of difference -31%), relative risk 0.9 (one-sided 95% CI of difference 0.9), p=0.55. In the rituximab group, NSAIDs were prescribed in 3/21 (27%) of the patients who achieved glucocorticoid-free remission (PMR-AS<10), and in 6/12 (50%) who did not achieve GC-free remission (PMR-AS<10). In the placebo group, NSAIDs were prescribed in 3/5 (60%) of the patients who achieved GC-free remission (PMR-AS<10), and in 7/23 (37%) who did not achieve GC-free remission (PMR-AS<10). In supplement 1, section 11, a table is presented with data from patients who did, and who did not achieve GC-free remission within the intervention groups. It concerns the distribution of sex, baseline CRP and ESRs, the PMR-AS and its separate components.

### Safety and adverse events

One serious adverse event was reported in one patient receiving rituximab: a pulmonary embolism. Infusion related and other adverse events of special interest are shown in table 3.

#### Table 3. Summary of total number of adverse events per treatment group

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n=23)</th>
<th>Placebo (n=24)</th>
<th>Rate ratio rituximab compared to placebo (one-sided 95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>136</td>
<td>148</td>
<td>0.96 (0.8)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections ‡</td>
<td>15</td>
<td>8</td>
<td>1.96 (1.0)</td>
</tr>
<tr>
<td>Serious infections 2 grade 3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infusion related complaints §</td>
<td>10</td>
<td>3</td>
<td>3.47 (1.3)</td>
</tr>
<tr>
<td>Serious infusion related complaints 2 grade 3 †</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* All adverse events that occurred during the study period were included in the analyses. Adverse events numbers are number of events, not number of patients with events. Safety outcomes were compared by chi-squared test (cumulative incidences). No correction for type I error was performed. For all adverse events grading was performed according to Common Terminology Criteria for Adverse Events version 5.0, grade range 0–5 with higher scores indicate worse events.

† The serious adverse event that occurred was a pulmonary embolism in one patient

‡ Labelled as such by the research physician. In the rituximab group: upper respiratory tract infection in eight patients (documented by anamnesis patients), lower respiratory tract infection in two patients (diagnosed and treated by general practitioner, urinary tract infection in two patients (diagnosed and treated by general practitioner), herpes zoster in one patient (diagnosed and treated by dermatologist), and eczema with secondary infection in one patient (diagnosed and treated by general practitioner). In the placebo group: upper respiratory tract infection in three patients (documented by anamnesis patients), influenza-like symptoms in two patients (documented by anamnesis patients), acne in one patient (physical examination by research physician), stomach flu in one patient (documented by anamnesis patients).

§ Labelled as such by the research physician. Reported infusion related complaints in the rituximab group: restlessness n=1, malaise n=1, hypersonia n=1, palpitations n=1, hot flashes n=1, fatigue n=1, hypotension n=1, cough n=1, maculo-papular rash n=1. Reported infusion related complaints in the placebo group: palpitations n=1, fatigue n=1, hot flashes n=1.

CI denotes confidence interval.

#### Discussion

To the best of our knowledge, this is the first clinical study on B-cell targeted treatment in polymyalgia rheumatica.

The marginally statistically significant efficacy of rituximab seen regarding the primary outcome in our study is supported by positive effects on secondary outcomes such as proportion of patients with glucocorticoid ≤5mg, lower mean change of polymyalgia rheumatica-activity score in the rituximab group, and persisting polymyalgia rheumatica-activity score value below 10 after accelerated glucocorticoid tapering commences. No previous studies with B-cell depleting treatment in polymyalgia rheumatica have been published, but the results of our study are in line with previous preclinical studies showing that B-cells may play an important role in the pathogenesis of polymyalgia rheumatica. The safety profile of rituximab in our small study is similar to that seen in rheumatoid arthritis, although the study was not powered to detect differences in safety profile.
Concerning other biological disease modifying anti-rheumatic drugs in polymyalgia rheumatica, so far no clear effect of TNF-alpha blockers has been shown in case reports and series, small open label studies or randomized controlled trials of limited sample size. A small placebo controlled study could not demonstrate short term efficacy of secukinumab and canakinumab but they might have some steroid sparing effect.

Tocilizumab has shown efficacy in polymyalgia rheumatica in case series and small open label studies. In the studies, efficacy was shown in the outcomes low disease activity scores defined by polymyalgia rheumatica activity score >10, and glucocorticoid-free remission (judged by physician) with one study also demonstrating long term remission after monotherapy. However, although promising, a considerable amount of patients withdrew from some of the tocilizumab studies due to adverse events or inefficacy, and randomized blinded studies with tocilizumab are lacking. Additionally, tocilizumab has some conceptual disadvantages such as the difficulty of monitoring disease activity using CRP and frequent administration of the drug.

Strengths of our study are the adequate (although small) sample size, double-blind, randomized and placebo controlled design, as well as blinding during the analyses, minimizing risk of bias. Also, none of the patients was lost to follow-up. In addition, the primary outcome glucocorticoid-free polymyalgia rheumatica activity score remission is a composite outcome measure reflecting both objective and subjective symptoms of disease activity, and both patients’ and physicians’ perspective. Lastly, the glucocorticoid toxicity index was used making the registration of any adverse event very sensitive, also resulting in the relatively high rate of adverse events recorded in both study groups.

This study has limitations and challenges that need to be considered. Firstly, partly by premature ending due to the COVID-pandemic, the sample size is limited and the positive results could be due to chance. However, the reasonably large effect size is somewhat reassuring in this, as are the effects on some of the secondary findings and exploratory post-hoc analyses. No statistically significant differences were found in the cumulative glucocorticoid dose and some other secondary outcomes, and in the subgroup of relapse patients. With regard to the cumulative glucocorticoid dose, this could be expected to be different after longer follow up, because the prednisolone induction and tapering schedule does not allow for large differences to occur within the timeframe of the current study. Of note, the benefits and risks of rituximab and glucocorticoids should adequately be weighted in polymyalgia rheumatica, which is not a life-threatening disease. Both repeated infusions of rituximab (dose-dependent and after a few cycles) and long-term use of glucocorticoids are associated with increased risk of infection. Now that a first signal of rituximab efficacy in polymyalgia rheumatica has been found, a larger confirmatory study should be conducted with due regard to weighing benefits and risks, targeting long-term effects, effects of rituximab (1 x 1000 mg) retreatment, and effect on secondary outcomes including glucocorticoid use.

A more general limitation in polymyalgia rheumatica clinical studies is the lack of a better standard for the diagnosis polymyalgia rheumatica, as classification criteria lack specificity to some degree, and this might lead to erroneous inclusion of patients in the study. Two patients developing clinically suspect rheumatoid arthritis were indeed excluded from the study, but further misclassification cannot be fully ruled out. However, misclassification can only lead to a overestimation of the effect when rituximab is effective in the misclassified disease, and this could only realistically be true for rheumatoid arthritis.

The same holds true for measuring disease activity. The polymyalgia rheumatica-activity score has, although partially validated, not universally been adopted as a core outcome measure. Indeed, a clear consensus core outcome measure is lacking in polymyalgia rheumatica. However, this measure is by and large the most frequent used outcome in recent and ongoing randomized clinical trials in polymyalgia rheumatica. In addition, as in polymyalgia rheumatica research in general, this study was challenged by the non-uniform definition of relapse in polymyalgia rheumatica.

It should be noted that most patients had received (short-term) glucocorticoid treatment prior to study inclusion. Although this may have resulted in lower baseline polymyalgia rheumatica activity score, ESR and CRP values, and other patient reported outcomes. Balancing this, enrolling patients who have recently commenced glucocorticoids is reflective of usual care and thus increases the generalizability of our study and would not lead to higher risk of a false positive result. Interestingly, it is still unknown whether glucocorticoid treatment results in a shorter disease course, or that they only have a disease modifying effect in polymyalgia rheumatica while being used. The outcomes of this study likely contradict the former, as glucocorticoid-free remission was seen infrequently in the control group after 17 weeks prednisolone.

In conclusion, this proof of concept study showed marginally statistically significant efficacy of rituximab in patients diagnosed with polymyalgia rheumatica. A larger phase III trial with longer follow-up, possibly with rituximab retreatment on indication, is indicated to confirm these results.
References


Supplementary Appendix: The efficacy of rituximab in polymyalgia rheumatica

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Section 1. Prednisolone tapering schedule, dose in mg, initiated at date of rituximab / placebo.

<table>
<thead>
<tr>
<th>Week</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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</tr>
</tbody>
</table>

* All patients were administered intravenous methylprednisolone 50 mg, acetaminophen 1000mg and cetirizine 10 mg prior to infusion of rituximab / placebo to prevent allergic reactions of the intervention, following local protocol of rituximab infusions.

Section 2. Summary of protocol changes (second amended versus first protocol) and rationale. Date of approval of amendment protocol from medical ethical committee: 18th of April 2019.

1. Cut-off point remission defined by polymyalgia rheumatica activity score (section 3.1.1)

Instead of the cut-off point for remission of the polymyalgia rheumatica activity score (>7, we used a cut-off point <10 as a literature research showed that a cut-off point <10 better discriminates a state of remission from a state not in remission. This also enhances comparability of the BRIDGE-PMR trial to other studies with polymyalgia rheumatica patients.

2. Classification criteria for polymyalgia rheumatica (section 3.2.1)

The classification criteria used in version 1.0 were the Chuang classification criteria for polymyalgia rheumatica. Due to new insights, we choose to use the 2012 EULAR / ACR classification criteria for polymyalgia rheumatica because this improves comparability with other polymyalgia rheumatica studies and increases generalizability of our study population to the general polymyalgia rheumatica population as these criteria are less stringent.

3. Inclusion criteria: including patients with short prednisolone treatment instead of glucocorticoid-naive patients only (section 3.2.1 and 3.2.2)

In practice it is very difficult to enroll glucocorticoid naive polymyalgia rheumatica patients into the study. Most patients eligible for this study were prescribed prednisolone by their treating general physician or rheumatologist. For the reason of timely alleviating of the burden that the symptoms cause (knowing that baseline disease activity scores in the study do not reflect real time disease activity without prednisolone treatment), and thus also for generalizability to clinical practice, we allowed recently diagnosed polymyalgia rheumatica a short treatment with glucocorticoids. We made sure to enroll and assign patients the study intervention as soon as possible.

4. Inclusion criteria: including patients with relapsing polymyalgia rheumatica (section 3.2.1)

In addition to new patients, we choose to also include patients with relapsing polymyalgia rheumatica who were unable to taper to a prednisolone dose lower than 7.5mg/day. Because doses of 7.5mg/day or higher for a longer period of time are associated with increased risk of glucocorticoid-related adverse events, we thought that this is also an import subgroup of polymyalgia rheumatica patients that could benefit greatly from glucocorticoid-sparing agents.
Section 3. In- and exclusion criteria of patients with polymyalgia rheumatica for the BRIDGE-PMR study.

Inclusion criteria
1. Recently diagnosed polymyalgia rheumatica (within the past 3 months) according to the 2012 EULAR/ACR polymyalgia rheumatica classification who either:
   a. Are glucocorticoid naive, or,
   b. Used glucocorticoid for less than 6 consecutive weeks before study inclusion with a maximum daily dose of 20mg, or,
   c. Short treatment of 30mg for 7 days and/or methylprednisolone intramuscular not more than 120 mg in the past 3 months
2. Polymyalgia rheumatica patients diagnosed with longer-standing polymyalgia rheumatica according to the 2012 EULAR/ACR polymyalgia rheumatica classification criteria but who relapse and are unable to taper their prednisolone below 7.5 mg
3. Signed written informed consent

Exclusion criteria
1. Not being able to speak, read or write Dutch
2. Patients who were prescribed a daily dose of oral glucocorticoid of more than 30 mg
3. Exposure other immunosuppressant treatments in the past 4 months before inclusion of the study
4. Known active 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’s disease or severe fibromyalgia
5. Previous hypersensitivity for prednisolone, rituximab or murine peptides
6. 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)

*Prior to the study intervention, patients were actively screened for hepatitis B or tuberculosis (by hepatitis B serology / Quantiferon-tuberculosis test).

Section 4. Assays of CRP, ESR and B-lymphocytes.

High sensitivity CRP was determined by the chemical analyzer Olympus type AU400 (Coffin Meyvis), with an upper limit of normal of 5 mg/L, until October 2019. From October 2019 onwards the laboratory in our hospital switched to the chemical analyzer Cobas C111 (Roche) using a turbidimetric method also with an upper limit of normal 5 mg/L. ESR was determined by an automated and accelerated Westergen method (StaRRsed Auto-Compact, Sysmex) (37). A value above 30mm/hour was considered elevated for both men and women. The absolute amount of peripheral CD19+ B-lymphocytes was determined by flow cytometry (FACS Calibur flowcytometre, Becton Dickinson) using APC-labeled anti-CD19 antibodies (Becton Dickinson) and Trucount tubes (Becton Dickinson). Samples were measured using the software program Multiset.

Section 5. Imputation of CRP.

At baseline visit, CRP was missing completely at random in one patient because it was not analyzed by the laboratory. At the last study visit, CRP was missing at random in three patients due to the COVID-19 pandemic as patients were not able to visit the hospital or diagnostic centers for blood collection. CRP was missing in four patients at either visit three, four or five, due to either the COVID-19 crisis or accidently not having been analyzed by the laboratory. Unfortunately, a multiple imputation method was not possible because there is no Fischers’ exact test option with multiple imputation in STATA version 13. Single imputation was used instead as only 2% of CRP values (n=6) of all visits (n=282) were missing, and none of the three patients with missing CRP at last visit were glucocorticoid-free. Therefore, regardless the imputed values of CRP at the last visit, single imputation does not affect the result of the primary outcome. Variables used for the imputation model were ESR, duration of morning stiffness, physician’s global assessment and the patients’ assessment of pain of all visits. Other outcome variables were not imputed as they were not needed for primary analyses and missings were rare.

Section 6. Power of one-sided Fisher exact test with alpha 0.05 with a sample size of 25 patients per group with different effect sizes and response percentages on prednisolone alone.

<table>
<thead>
<tr>
<th>Response in placebo group</th>
<th>Treatment effect (risk difference of response in favor of rituximab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>20%</td>
<td>36</td>
</tr>
<tr>
<td>30%</td>
<td>34</td>
</tr>
<tr>
<td>40%</td>
<td>34</td>
</tr>
<tr>
<td>50%</td>
<td>34</td>
</tr>
</tbody>
</table>

66
Section 7. Protocol violations during the trial.

Inclusion criteria

Two patients were younger than 50 years of age at time of diagnosis
- One newly diagnosed patient of 49.7 years (rituximab group)
- One patient with flaring polymyalgia rheumatica of 49.3 years (rituximab group)

One patient with recurring polymyalgia rheumatica (previous disease episode was eight years ago) was classified as recently diagnosed polymyalgia rheumatica upon enrollment into the study (rituximab group)

Exclusion criteria

One patient received oral prednisolone between six to seven weeks prior to study inclusion (rituximab group)

One patient received methylprednisolone 120 mg intramuscular twice prior to study inclusion (rituximab group)

During follow-up

Five patients received a local intra-articular or sub-acromial injection due local bursitis / tendinitis / carpal tunnel syndrome / local arthritis* (four in placebo, one in rituximab group)

Three patients received glucocorticoid more than pre-relapse dose due to the severity of symptoms (one in placebo, two in rituximab group)

Four patients received intramuscular methylprednisolone† (three in placebo, one in rituximab group)

* The glucocorticoid administered through local or intramuscular injections were added to the total cumulative glucocorticoid dose count
† One patient received methyl-prednisolone at visit five due to arthritis not responding to a local injection, and three at the last study visit (visit 6)

Section 8. Mean course of each separate polymyalgia rheumatica-activity score item per visit

Section 8a. Mean CRP (mg/L) per visit

Section 8b. Mean VAS physician per visit

* CRP denotes C-reactive protein, CI confidence interval
* VAS denotes Visual Analogue Scale, CI confidence interval
Section 8c. Mean VAS pain per visit

Section 8d. Mean morning stiffness in minutes per visit

Section 8e. Mean score of elevation of upper limbs (range 0 to 3, higher indicating worse state) per visit
Section 9. Glucocorticoid toxicities, domain and total scores of composite glucocorticoid toxicity index at week 11 and 21*

<table>
<thead>
<tr>
<th>Toxicity domain</th>
<th>Rituximab, number of patients (%)</th>
<th>Placebo, number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (BMI)</td>
<td>Improvement No change Moderate increase Major increase</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
</tr>
<tr>
<td>Grade</td>
<td>(n=23)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>Improvement</td>
<td>18 (83)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>No change</td>
<td>5 (22)</td>
<td>6 (25)</td>
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<tr>
<td>Moderate increase</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major increase</td>
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<td>0</td>
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<tr>
<td>Total BMI score – mean (SD)</td>
<td>1.0 (6.2)</td>
<td>1.1 (6.3)</td>
</tr>
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<td>Glucose tolerance</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
</tr>
<tr>
<td>Grade</td>
<td>(n=23)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>Improvement</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>6 (26)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Worsening</td>
<td>13 (57)</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Worsening despite treatment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total glucose score – mean (SD)</td>
<td>2.2 (12.4)</td>
<td>3.5 (4.3)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
</tr>
<tr>
<td>Grade</td>
<td>(n=23)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>Improvement</td>
<td>2 (9)</td>
<td>16 (67)</td>
</tr>
<tr>
<td>No change</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Worsening</td>
<td>19 (83)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Worsening despite treatment</td>
<td>11 (48)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Total blood pressure – mean (SD)</td>
<td>2.1 (8.5)</td>
<td>2.1 (10.6)</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
<td>Improvement No change Worsening Worsening despite treatment</td>
</tr>
<tr>
<td>Grade</td>
<td>(n=23)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>Improvement</td>
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<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>9 (39)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Worsening</td>
<td>2 (9)</td>
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</tr>
<tr>
<td>Worsening despite treatment</td>
<td>18 (78)</td>
<td>18 (75)</td>
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<tr>
<td>Total lipid score – mean (SD)</td>
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<tr>
<td>Glucocorticoid myopathy</td>
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<td>Mild Moderate or severe</td>
</tr>
<tr>
<td>Grade</td>
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<td>(n=24)</td>
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<tr>
<td>Mild</td>
<td>21 (95)</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Moderate or severe</td>
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<td>2 (10)</td>
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<tr>
<td>Severe</td>
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<td>0</td>
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<tr>
<td>Total myopathy score – mean (SD)</td>
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<tr>
<td>Skin toxicity</td>
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</tr>
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<td>(n=24)</td>
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<td>Mild</td>
<td>17 (77)</td>
<td>21 (87)</td>
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<td>Moderate or severe</td>
<td>5 (23)</td>
<td>2 (9)</td>
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<tr>
<td>Severe</td>
<td>0</td>
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<tr>
<td>Total skin score – mean (SD)</td>
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<td>0.7 (2.3)</td>
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</tr>
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<td>(n=24)</td>
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<tr>
<td>Mild</td>
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<td>17 (71)</td>
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<tr>
<td>Moderate or severe</td>
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<td>2 (9)</td>
</tr>
<tr>
<td>Severe</td>
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<td>0</td>
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<tr>
<td>Total neuropsychiatric score – mean (SD)</td>
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<td>8.9 (10.3)</td>
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<td>Infections</td>
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<tr>
<td>Grade</td>
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<td>(n=24)</td>
</tr>
<tr>
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<td>31 (135)</td>
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<tr>
<td>Oral or vaginal candidiasis</td>
<td>1 (4)</td>
<td>21 (87)</td>
</tr>
<tr>
<td>Noncomplicated atypical*</td>
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</tr>
<tr>
<td>Grade 3 infection or greater</td>
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<td>0</td>
</tr>
<tr>
<td>Total infection score – mean (SD)</td>
<td>4.2 (18.6)</td>
<td>0.0 (4.1)</td>
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<tr>
<td>Total C1RF score – mean (SD)</td>
<td>17.3 (39.7)</td>
<td>20.8 (54.6)</td>
</tr>
</tbody>
</table>

*Scores of week 11 are total scores of changes compared to baseline, scores of week 21 are total scores of changes compared to week 11. Only scores of patients with values for every domain are calculated (complete case analysis). Lower scores indicate better outcomes, higher scores indicate worse outcomes. Values are means, SD, unless specified otherwise. DEXA scan not included due to trial duration less than one year, therefore scores ranging from -36 to 439 instead of -36 to 439. For a detailed description of interpretation of the glucocorticoid toxicity index we refer to the article of Miloslavsky et al (1)

Section 10. Primary outcome at week 21, disaggregated by biological sex*

<table>
<thead>
<tr>
<th>Glucocorticoid-free remission</th>
<th>Rituximab (n=23)</th>
<th>Placebo (n=24)</th>
<th>Absolute difference (one sided 95%-CI)</th>
<th>Relative risk (one sided 95%-CI)</th>
<th>One sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female* – no (%)</td>
<td>7 (31)</td>
<td>3 (13)</td>
<td>4 (0.2) (0.02 to 0.8)</td>
<td>1.4 (0.9 to 2.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Male* – no (%)</td>
<td>7 (58)</td>
<td>3 (27)</td>
<td>4 (1.0 to 6.0)</td>
<td>1.0 (0.5 to 2.0)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*Primary outcome is defined by being glucocorticoid-free en a polymyalgia rheumatica activity score of 10.

References

Chapter 7
Summary and general discussion
Chapter 1

Summary

The aim of this thesis is to address several unmet needs in polymyalgia rheumatica (PMR). Even though PMR is an inflammatory rheumatic disorder, globally not much research has been done in this field. PMR is not a deadly disease but it is associated with a significant burden and negative impact on quality of life for afflicted patients.1

There are several specific challenges in PMR diagnosis and treatment. Amongst others these include the unelucidated pathogenesis of PMR, and factors triggering its onset such as previous infections with pathogens.2 Also, diagnosing PMR can be difficult as no golden standard exists and the disease is clinically heterogeneous or atypical in presentation - such as normal acute phase reactants - with a large differential diagnosis as many diseases may mimic PMR.2-4 Glucocorticoids (GC) are the cornerstone treatment in PMR and it is generally thought that prednisolone is a relatively safe and effective treatment in a considerable proportion of PMR patients and that patients are usually cured within two years.5,6 However, this is not always the case as around 50% of patients experience one or more flares during GC tapering. This leads to a substantially prolonged treatment duration, with only 33-50% of PMR patients in hospital care achieving sustained GC-free remission after two years of treatment, and around 40% of patients needing GC ≥4 years.7-9 This increases the risk of GC-related adverse events as patients receiving GC treatment for longer than 2 years are more likely to develop weight gain, osteoporosis, fractures, cataract, metabolic and cardiovascular side effects and infections.8-11 To date, GC-sparing treatment options are limited as not many therapeutic clinical trials have been done in PMR and data on GC-sparing treatments is inconclusive or negative on efficacy.12-24 GC-sparing agents are therefore warranted and they remain high on the research agenda of the EULAR/ACR on management of PMR.5

The aim of this thesis was to target several of these unmet needs in PMR, including its atypical clinical presentation, triggering factors, and broadening non-GC treatment options in PMR.

Main findings

Chapter 2: No association found between previous proposed infectious triggers and the onset of polymyalgia rheumatica.

The immunopathogenesis of PMR largely remains unknown and is thought to be multifactorial, including genetic background, immune senescence and environmental factors.2 One particular environmental factor of interest for trigger of PMR onset is an infection, and seasonal patterns between infection and onset of PMR / GCA have been suggested for Mycoplasma pneumoniae, Chlamydia pneumoniae, Parvovirus B19 and parainfluenza virus type 1.25-27 However, existing evidence shows conflicting results.25-29 In chapter 2 we therefore analyzed data from 448 patients by using a chi-square goodness of fit test to determine whether PMR onset was distributed equally throughout the year. Additionally, data on incidence of the infectious agents from the Dutch National institute for Public health and Environment (RIVM) was obtained. From this data, the index digits were calculated where 100 marks the weighted average of infections at that time point for the years 2007 to 2017. Results show a non-significant bimodal seasonal pattern of PMR onset. Additionally, no coincidence of peaks
between onset of PMR symptoms and the proposed agents were seen. Therefore, the results of this study are insufficiently suggestive for any infectious trigger as cause of PMR. The main limitations of this study were the retrospective character and the fact that only PMR patients in secondary care, and not PMR patients treated in the first line, were included in this study.

Chapter 3: PMR patients with an atypical presentation such as low acute phase reactants at diagnosis do indeed exist, and these are distinct subsets of PMR with somewhat different clinical presentation and prognosis.

In chapter 3 we found evidence that supports the hypothesis that there are indeed PMR patients with an atypical presentation such as low acute phase reactants (APR). They form a distinct and milder subset of PMR with different clinical presentation and prognosis. In order to answer these hypotheses, we set up a retrospective study with 454 PMR patients (clinical diagnosis by the treating rheumatologist) in order to explore whether normal APR in new PMR patients was due to a) patients being “caught early in the disease course”; b) a different subset of PMR patients with different clinical presentation and prognosis; or c), a misdiagnosis of PMR. We found most evidence supporting hypothesis b, some indication for hypothesis a, and insufficient evidence for c. Hypothesis b is corroborated by similar clinical characteristics of patients with normal APR compared to elevated APR, albeit milder in clinical presentation and prognosis. At baseline fewer patients with normal APR had peripheral arthritis or anemia at diagnosis. Their prognosis was better as fewer patients with normal APR were prescribed disease modifying antirheumatic drugs and more patients were referred back earlier to the general practitioner in GC-free remission. Another factor substantiating this hypothesis is the fact that some patients with normal APR at diagnosis developed elevated APR at a flare during follow-up. This fact also provides some evidence for hypothesis a, as patients could be considered “caught early in disease” as APR only occurred later during the disease and after diagnosis. In addition, when looking into the subgroup of patients with elevated APR, the patients who had had normal APR prior to the diagnosis (when APR was elevated), had a longer symptom duration compared to the subgroup of patients who had had elevated APR prior to the moment the diagnosis was made. Patients with normal APR at diagnosis also had a longer duration of symptoms compared to patients with elevated APR at diagnosis. This rather suggests a delay in diagnosis. Insufficient evidence was found for hypothesis c as a considerable proportion of patients with normal APR developed elevated APR when they flared during follow-up. In addition, in the normal APR group rheumatoid arthritis was not diagnosed more frequently during follow-up compared to the elevated APR group. However, in our study only patients who did not develop a more likely alternative diagnosis during the first nine months of follow-up were included. Therefore hypothesis c cannot be truly ruled out due to our study design. The results of this study strongly suggest that a considerable proportion of PMR patients can indeed present with normal APR at diagnosis (14%), and this fits with reports of PMR patients with normal APR at diagnosis in other studies (1% to up to 22%). The strength of our evidence is limited by the retrospective character of the study and the lack of more objective diagnostics such as ultrasound, MRI, or PET-CT to assess bursitis / arthritis of the shoulders and / or hips. In addition, index event bias is likely to play a role, and generalizability may be limited to PMR patients seen in secondary / tertiary clinics only. Strengths of this study are the reasonably large sample size, and the fact that it is conducted in patients with PMR only, unlike other studies which mostly study PMR in combination with GCA.29 30

Chapter 4-5: Methotrexate is prescribed infrequently in daily clinical practice at the rheumatology department of the Sint Maartenskliniek between the period 2008-2017. The efficacy and role of methotrexate in polymyalgia rheumatica is unclear and further research is needed to assess the efficacy of higher dosed methotrexate.

Earlier studies on MTX have shown conflicting results, have a small sample size or are methodologically suboptimal.29-31 Data on efficacy of MTX in usual rheumatology care is scarce.32-34 In chapter 4, we therefore investigated the prescription rate and efficacy of methotrexate (MTX) by using data from an existing retrospective cohort of 454 newly diagnosed PMR patients (clinical diagnosis). Of these patients, 240 were selected: 39 were prescribed MTX and 201 patients were eligible for the control group. Patients were eligible for the control group if they were MTX naïve and had at least one flare. The first flare was considered the index event. The choice for this specific control group was made because the 2015 EULAR / ACR guidelines on management of PMR recommend starting MTX in patients who flare. The main outcomes were number of flares per year (Poisson regression), weighted daily GC-dose (linear regression), and flare incidence rate in the MTX group only. The yearly incidence rate ratio of flares in the MTX versus control group was 0.80 (95%-CI 0.45 to 1.42). The yearly flare rate was 1.22 before and 0.43 after MTX initiation, resulting in an incidence ratio of 0.35 (95%CI 0.23 to 0.52). Adjusted time weighted daily GC dose was higher in the MTX versus control group (ratio 1.37, 95%-CI 1.04 to 1.80). In conclusion, no clear effect of MTX on flares was found and time weighted daily GC-dose was higher. However, the strongly reduced flare rate after MTX start might be suggestive for a beneficial effect of MTX. The prescription rate of MTX for PMR in the total PMR cohort is low: only 9% (39 / 454). Only one other study reported the prescription rate of MTX in daily rheumatology practice, reporting MTX prescription in 19%.35 Several reasons for this low prescription rate in our cohort can be conceived. Firstly, patients were enrolled into this cohort in the years 2008 until 2017, whilst the guidelines on management of PMR were published in 2015.35 The low prescription rate could also reflect the uncertainty of the exact role of MTX in PMR. Secondly, the control group had a lower GC dose at index event, suggesting that MTX is more frequently prescribed to patients with a higher need for GC. The main limitation of this cohort is the retrospective and non-randomized character. Therefore, residual confounding and confounding by (contra-)indication likely play large roles. The evidence this study adds on the exact role and timing of MTX in PMR remains limited. Thus, a well sized double-blind placebo-controlled trial is needed with optimal dosed MTX in PMR patients.

Chapter 6: Rituximab (RTX) shows promise as a safe and non-GC treatment in PMR as it is effective in achieving GC-free remission and low-dose GC in PMR patients.

In chapter 5 we assessed the efficacy of RTX in a 21-week double-blind placebo controlled trial with 47 polymyalgia rheumatica patients (recently diagnosed n=38 / relapsing on prednisolone ≥7.5mg/day n=9) fulfilling the 2012 EULAR/ACR criteria. Patients were randomized 1:1 to receive either intravenous RTX (1 x 1000 mg; n=23) or placebo (RTX 1 x 0mg; n=24), in combination with a 17-week long GC co-treatment. Regarding the primary outcome GC-free remission (PMR-AS ≤10) at week 21, this was achieved by more patients in the RTX compared to the placebo group: 48% (11/23) versus 21% (5/24), absolute risk difference 27% (one-sided 95%-CI 4%), relative risk 2.3 (one-sided 95%-CI 1.1, p=0.049). Regarding the secondary outcomes, more patients in the RTX compared to the placebo group achieved GC ≤5mg/day: 100% (23/23) versus 54%
(13/24), absolute risk difference 46% (one-sided 95%-CI of difference 20%), relative risk 1.8 (one-sided 95%-CI of difference 1.3), \( p < 0.001 \), patients in the RTX group achieved a greater median (IQR) decline in morning stiffness in minutes: \(- 60 (-120 \text{ to } -5) \) versus \(-20 (-60 \text{ to } 0)\); absolute difference -40 (CI not applicable), one-sided \( p = 0.02 \). In addition, a greater reduction of PMR-AS was achieved in patients with RTX compared to placebo: \(-13.8 (2.9) \) versus \(-3.8 (3.6)\), absolute difference -10 (one-sided 95%-CI of difference -2.2), \( P = 0.02 \). In the RTX group, more infusion related complaints occurred compared to the placebo group: 10 versus 3, rate ratio 3.47, one-sided 95%-CI 1.3. No significant differences were observed regarding other outcomes.

Several post-hoc analyses showed that disease phase was an effect modifier and that recently diagnosed PMR patients fared better. In the recently diagnosed patients GC-free remission was achieved in (RTX versus placebo): 58% (11/19) versus 21% (4/19), absolute risk difference 37% (one-sided 95%-CI 10% relative risk 2.8 (one-sided 95%-CI 1.3); \( p = 0.02 \); GC ≤5mg/day: patients 100% (19/19) versus 47% (9/19), absolute risk difference 53% (one-sided 95%-CI of difference 29%), relative risk 2.1 (one-sided 95%-CI of difference 1), \( p < 0.001 \). No significant differences were observed in the relapsing PMR patients. In conclusion, RTX has shown efficacy in PMR patients. Now, the efficacy of RTX should be investigated in a larger confirmatory trial with recently diagnosed PMR patients. If confirmed efficacious in this larger trial, RTX is a safe and effective GC sparing agent, and may be considered first choice treatment in PMR.

General discussion

Challenges and methodological considerations in polymyalgia rheumatica research

The research presented in this thesis represents the beginning of a new research line of polymyalgia rheumatica (PMR) in the Sint Maartenskliniek. During this Ph.D. trajectory, several challenges and methodological issues were encountered, which are described in more detail below.

Hurdles in subject recruitment for clinical trials in PMR

Recruitment of PMR patients for research is quite difficult. Although it is not as rare as GCA, it is a relatively rare disease — with an incidence varying between 41 to 113 per 100,000 persons.\(^2,3\)\(^7\) The average Dutch general practitioner diagnoses a patient with PMR approximately once a year. A large proportion of PMR patients are treated by general practitioners and only a minority are referred to second line care, which in the Netherlands can either be an internist or rheumatologist.\(^3\)\(^8\) To increase referral of PMR patients to rheumatology outpatient clinics, a fast track clinic for suspected PMR patients could be set up. This does not only enhance patient referral but could also improve PMR management as previous research has shown that a fast track clinic also allows for a more timely diagnosis and lower GC dose compared to patients who were referred to rheumatologists in usual care.\(^3\)\(^9\) Positive experiences with fast track clinics also exist with GCA, where permanent visual loss occurred less frequently and was more economical as the fast track clinic led to fewer hospital visits.\(^4\)\(^7\)

Also, rheumatologists, internists and general practitioners could collaborate in developing the referral protocols together and make agreements on when and which patients should be referred to the rheumatologists.

Another reason for the arduous recruitment of sufficient PMR patients for clinical studies could be the use of strict inclusion or exclusion criteria. This may lead to exclusion of patients who would otherwise benefit from GC-sparing treatments. This also negatively influences the generalizability of study results to the entire PMR population. For example, one manner to ease inclusion criteria is to include patients with short GC treatment duration prior to study inclusion. In the original set-up of the “B-cell depletion with Rituximab for Dose reduction of Glucocorticoids: Efficacy in PolyMyalgia Rheumatica” (BRIDGE-PMR) study only GC-naive patients were eligible for study inclusion. However, in hindsight this did not reflect daily clinical practice as almost all patients with PMR who were referred to the BRIDGE-PMR study or outpatient department of the Sint Maartenskliniek had already used GC. This was most likely because in usual care most general practitioners and rheumatologist referring patients for the BRIDGE-PMR study deemed it unethical, even for a short period of time, to withhold GC treatment in patients suffering from PMR symptoms. An amendment was made to also include patients with a short GC treatment duration prior to study participation. In my opinion, this also increases the generalizability of results.

The use of the PMR-AS in clinical trials with PMR patients

Prior to the development of the PMR-AS, disease activity of PMR patients was monitored by the acute phase reactants and global assessment only.\(^4\) Because a uniform and validated disease activity score was lacking in PMR, Leeb et al developed the PMR-AS.\(^4\) The score is calculated by the patients visual analogue score (VAS) of pain (0-10), the physicians’ VAS of disease activity...
We thought the PMR-AS was most appropriate as a primary outcome measure in the BRIDGE-PMR study and “PolyMyalgia Rheumatica treatment with Methotrexate in Optimal Dose in an Early disease phase” (PMR-MODE) study for several reasons. First, we see it as a clinically meaningful outcome as it is a direct patient-relevant outcome and all components reflect disease (in)activity and it allows for both subjective and objective, and both patients’ and physicians’ endpoints. Second, the PMR-AS has a relatively high reliability (Cronbach’s alpha between 0.91 and 0.88) and all five components contribute significantly to the overall outcome, with patients’ pain and physicians’ assessment of disease contributing the greatest. Third, it is in line with the core domain outcome set that was considered mandatory in clinical trials with PMR patients, by the Outcome Measures in Rheumatology (OMERACT) working group. The PMR-AS includes all the outcome domains that were considered essential by the OMERACT working group: acute phase reactants, patients’ stiffness, pain and physical function. The patients’ global assessment of disease was considered as important, but not mandatory. Fourth, even though it consist of several components, it is easy to use in daily clinical practice as was the experience in the BRIDGE-PMR and PMR-MODE study. Fifth, it is a composite outcome and that is associated with several advantages. Composite outcomes are increasingly used in randomized controlled trials in PMR it is a useful strategy because there is no obvious choice for a primary outcome with multiple clinically relevant outcomes. Using a composite outcomes increases study power, which in turns sample size and trial duration. In addition, the outcome is more precisely estimated because more data is used. However, multiple testing is also avoided or reduced as multiple outcomes are combined into one single outcome. Lastly, using the PMR-AS would lead to enhanced comparability and facilitates systematic reviews and meta-analysis of clinical trials in PMR.

Concerning the PMR-AS, there are some caveats to be addressed. First, the measurement properties of the PMR-AS and each of its components have not been comprehensively been assessed and may be suboptimal. Concerning the elevation of upper limbs, it may not fully reflect physical impairment in PMR and the physical impairment can differ on different time points during the day. Also, measures of pain or stiffness attributable to PMR may not be reliable when co-existing conditions such as osteoarthritis are present. Therefore, further clinimetric studies are needed to assess the reliability, validity and responsiveness of the PMR-AS and its components. Second, because the PMR-AS is a composite outcome, it is more vulnerable for missing data, which occurs regularly in clinical trials. This often requires multiple imputation, which can be technically difficult and the optimal imputation method remains unknown.

Concerning the BRIDGE-PMR trial, there were relatively few missing data, except for occasionally the CRP value due to the COVID-19 pandemic. This allowed us to use a simple imputation method. This could be a point of concern for future PMR trials as missing data in randomized controlled trials of inflammatory rheumatic disease with composite measures is not rare. However, when CRP is not available or missing, there are alternatives that have a high agreement with the PMR-AS. Another pitfall of composite outcomes is that it can sometimes lead to misleading results as a treatment may have effect on one of the components, but not the other components (e.g. opposite or absent effect). However, I would expect all the components of the PMR-AS to show effect in the same direction in case of remission or flare, as was the case in the BRIDGE-PMR study.

Weighing all the pros and cons and due to a lack of better alternative, using the PMR-AS as a primary outcome measure is in my opinion of added value in PMR trials. But I plea for describing each component as secondary outcomes in clinical trials. If the PMR-AS is widely adapted by clinical trials it would lead to increased homogeneity and comparability of clinical trials, to compensate for the mentioned caveats. The PMR-AS is easy to implement in clinical practice, it is not time-consuming and could also be used in usual care to facilitate monitoring of disease activity and treatment response. It might help the treating rheumatologist and patients setting concrete treatment goals in the management of PMR.

One-sided versus two-sided testing in randomized controlled superiority trials on drug efficacy

In the BRIDGE-PMR study, we deliberately chose one-sided instead of two-sided testing because our alternative hypothesis was that the efficacy of RTX could only be in one direction (more efficacious), but this was challenged by several reviewers. Arguments for single sided testing include firstly that we did not expect RTX to perform worse than the placebo group, as both groups received similar GC treatment and it is not to be expected that the group receiving GC-monotherapy would perform better than the RTX + GC treatment group.

However, in scientific research it is common and more accepted to use two-sided testing in research. With two-sided testing more accurate and less biased results can be obtained as two directions of the alternative hypothesis are assessed. This is especially the case when it is not possible to exclude the possibility that the experimental intervention performs worse than the reference or placebo treatment. Using either a one- or two-sided test has influence on the sample size under study, the interpretation and decision of regulatory authorities, and possibly the acceptance rate of a study by peer reviewed scientific journals.

In the scientific community opinions differ on whether one-sided testing should be used due to several reasons. It may be seen as a means to facilitate reporting marginal results as significant, and a significant result in the opposite direction may be missed, which could be harmful for patients. However, I do plead for more acceptance of one-sided testing, especially in those situations where it makes sense that there is only one possible direction in clinical trials. In contrast to two-sided testing, there is more power at the same significance (alpha) level leading to fewer type II errors. Also, trials are then more efficient, more ethical and less costly as it requires a smaller sample size of participants.

Everything considered, it was justified in my opinion to use one-sided testing in the BRIDGE-PMR study as this is a trial that tests the efficacy of an intervention that has not been evaluated before in other studies and compares RTX to placebo.
Generalizability of the results of the PMR patients under study

In epidemiology, inferences on (sub)populations are drawn by studying only a small sample of the target population. The extent to which it is possible to generalize the findings of research in this thesis to the total PMR population depends on the sample under study.

Concerning the PMR patients we studied, the generalizability may be limited as our population can be considered as patients in secondary or tertiary care. Whereas most PMR patients are treated by general practitioners, and a considerable amount of PMR patients are being treated by internists, patients in secondary care are referred from primary care for a reason, e.g. patients with a more atypical, severe or refractory PMR, or who develop more GC-related AE. The patients studied in this thesis may thus represent a different subset of PMR patients considering prognosis when compared to first line patients.

Several efforts can be made in order to increase generalizability of future research findings to the general PMR population. First, efforts should be made to stimulate collaborations between rheumatologists and internal medicine and primary care physicians. Second, the same classification criteria for PMR should be used in clinical trials. In 2012 the 2012 EULAR/ACR PMR classification criteria were developed. These have a high sensitivity but lower specificity as its ability to discriminate PMR from other inflammatory conditions such as RA, compared to the previous classification criteria for PMR (Chuang, Bird, Jones and Healy). This may lead to erroneously including RA patients in PMR studies. However, in this thesis this was mitigated by excluding patients who developed a clinical presentation of RA during follow-up, from the study. Compared to previous classification criteria, the 2012 EULAR/ACR PMR classification criteria require lower cut-off references for ESR and also include an elevated CRP. This increases the generalizability of the patients under study. This area becomes grayer when the question arises if patients with normal CRP and ESR at diagnosis should be eligible for interventional trials with GC-sparing agents. Previous research has shown that normal CRP and ESR at diagnosis is associated with shorter GC-treatment duration and therefore represent a more benign subgroup. Thus, the benefits of adding GC-sparing to this PMR subgroup might not outweigh the risks associated with DMARDs. The results of studies using classification criteria for PMR are therefore only generalizable for the subgroup of patients that have a worse prognosis.

Societal impact and future directions

Knowledge valorization

Universities have three core tasks and these consist of a) teaching, b) scientific research, and the less well known task of c) societal services such as disseminating the knowledge to benefit society. Knowledge valorization, which essentially means translating scientific knowledge into economic and/or societal value, plays an important role in this third task of universities. The third task is less well known amongst scientific researchers and may consequently lead to inadequate utilization of scientific knowledge for societal benefit. This is problematic for several reasons. First, it leads to waste of scientific research which is often publicly funded. Second, it contributes to the knowledge paradox. This is what happens when research that could potentially contribute to innovation, health or economic benefits, is not implemented in society and thus society is not able to benefit from the scientific developments.

With my PhD project, mainly the second task of the university has been fulfilled. There are several measures that can be taken to increase the third task and to enhance the participation of researchers and policy makers of universities in knowledge participation. First, awareness of valorization should be enhanced. Awareness may be created by giving workshops on the valorization process and by increasing interactions between researchers, policy makers and people of the target group (PMR patients). Clearly defined goals can be set up in order to have a clear vision of the what, how, with whom and when. Support can be asked from the departments of valorization of the universities. The Department of Valorization of Radboud University Nijmegen the Netherlands for example helps to find funding from grants, gives support in grant application procedures, evaluation, patenting and commercialization of new technologies. Also within the research departments, agreements on valorization can be made.

Another means that could enhance valorization is applying for patents. This generally plays a limited role in the valorization process but could enhance knowledge valorization as further research could then be funded, and market access can be facilitated by the pharmaceutical company. If the positive results are indeed confirmed in further research, the treatment may become available for a broader group of patients from the target group, which is ultimately the goal of scientific research.

Other factors that play a pivotal role in knowledge valorization are dissemination of knowledge through conferences and scientific journals, open access, networking and creating partnerships with other scientific institutes and setting up valorization tracks. Concerning the research on PMR in The Sint Maartenskliniek, several partnerships have already been formed with the departments of rheumatology from Rijnstate Hospital in Arnhem, Maxima Medisch Centre in Eindhoven, and Gelre Hospital in Ede and Apeldoorn. Increasing partnership with other centers enables transfer of scientific knowledge and enhances the study inclusion rate. Another means by which universities can stimulate valorization are valorization tracks that focus on research that has a significant impact on society instead of mainly focusing on research performance surrogates and proxies like H-index, PhDs, amount of funding raised as is now the case with tenure tracks. Examples of measures of valorization success are the number of spin-offs, awarded patents, contracts with private or public partners, interviews on television or newspaper, and web publications.

Future directions of research in PMR

This dissertation raises several questions and perspectives for further research:

Are RTX and MTX indeed efficacious in PMR? And if so, which treatment strategy is best and will this change the landscape of PMR management?

So far, the efficacy of RTX has been proven in a small double blinded controlled proof of principle study and the efficacy of MTX, efficacy albeit modes, has been shown with MTX 10 mg / week in a small RCT. The results of both RTX (including retreatment strategy) and MTX (in a higher dose) should be confirmed in a larger phase III trial. At the moment, there is an ongoing trial of MTX versus placebo at the Sint Maartenskliniek and collaborating rheumatology centers (PMR MODE study), and funding is sought for a larger trial with RTX. A big challenge will be recruitment of sufficient PMR patients, stressing the importance of collaborations between centers. Momentarily only recently diagnosed PMR patients are eligible for this trial.
If one or both treatments are proven efficacious, it raises several further questions concerning the management of PMR. E.g., what treatment strategy will be best for PMR patients? Will mainly recently PMR patients profit the most from DMARD treatment in addition to (a short) glucocorticoid treatment? Will this lead to a shift of PMR treatment strategy from predominantly managed in primary care to secondary care? Will patients benefit most from a monotherapy or combination therapy of RTX / MTX with glucocorticoid, or even a combination of DMARD therapy of MTX + RTX as is often the case in RA?

Do different subsets of PMR benefit from different treatments and can these different subsets be identified by immunological profiles?

Drugs may have different effects in different patients. In the BRIDGE-PMR study both recently diagnosed PMR patients (n=38) and relapsing PMR patients on a GC-dose of at least 7.5mg/day (n=9) were included in the study. Beforehand we did not have evidence that there could be any differences in treatment effect between these subgroups of PMR. Even though the power of the study is too small to assess heterogeneity of response, it would be interesting to assess in future studies whether any treatment differences exist in different subsets of PMR and if these subsets can be identified by different immunological and cytokine profiles. There is accumulating evidence that persistence of elevated monocyte and neutrophil counts in PMR and GCA contributes to a more relapse prone disease course. This change in leukocyte composition (myeloid shift) can sometimes be difficult to demonstrate in patients and therefore research has been conducted in order to identify biomarkers that are more easily identified in PMR (and GCA) patients. However, only few studies on biomarkers that are associated with clinical outcomes in PMR exist and more research is needed. Profiling may help avoiding over- and undertreatment with GC or DMARDs by identifying patients whom are likely to respond to a certain treatment. Also, identifying certain subgroups that may not benefit from a specific treatment avoids false negatives in studies. Regarding approval of a drug for certain subgroups by regulatory authorities, it should be emphasized that these subgroups should be identified prior to commencement of a trial. Post-hoc analysis such as performed in the BRIDGE-PMR study are unlikely to approve the treatment for subgroups because post-hoc testing allow for data mining and the risk for false positives, also known as “the risk of spurious correlation from multiple testing”. However, it does justify a new trial with proper identification of subgroups prior to study and study power to take into account multiple testing issues.

Is RTX efficacious in GCA?

One of the contributing factors of initiating the RTX in PMR trial in this thesis, albeit of low quality of evidence, was a case report of a GC-refractory GCA patient with concomitant PMR successfully treated with RTX. Both in PMR and GCA, a disturbed B-cell homeostasis was found in untreated patients, increased presence of auto-antibodies in sera was found, and an association between GCA severity and presence of mature B-cells in tertiary lymphoid organs in temporal artery biopsies. Recently, research has been published that found that circulating B-cells in GCA patients produce cytokines that skewed macrophages to a pro-inflammatory state. As PMR and GCA are related diseases, the question now arises whether RTX is efficacious in GCA. A glucocorticoid-sparing agent is an unmet need in GCA management. GCA is treated with much higher GC-doses (usually starting 60mg/day) and associated with even more morbidity and GC-related adverse events compared to PMR. As in PMR, in GCA there are limited GC-sparing DMARDs available. Currently, there is on ongoing trial in the United Kingdom (BIOVAS trial) that assesses different biologicals in refractory non-ANCA related vasculitis, amongst others rituximab in GCA. Especially if the confirmatory trial of RTX in PMR is positive, RTX efficacy in GCA should be high on the (inter) national research agenda.
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Chapter 8

Summary in Dutch
Nederlandse samenvatting
Deze thesis heeft als doel om enkele "unmet needs" van polymyalgia rheumatica (PMR) te bestuderen. Ondanks dat het een inflammatoire reumatische aandoening is, is er nog niet veel onderzoek naar gedaan wereldwijd. Het is geen dodelijke ziekte maar net als vele andere reumatische ziekten kan PMR leiden tot significante hinder en impact op het dagelijkse leven en functioneren van patiënten.

Er zijn meerdere uitdagingen bij PMR. Zo is de pathogenese nog niet helemaal opgehelderd, en is er weinig bekend over uitlokkende factoren bij PMR zoals voorafgaande infecties met ziekteverwekkers. Daarnaast is de diagnose niet altijd makkelijk te stellen gezien er geen gouden standaard bestaat voor het aantonen van de ziekte en de differentiaaldiagnose breed is. De ziekte presentatie is vaak heterogeen of atypisch, zoals normale ontstekingswaarden bij presentatie.

Tot heden is de hoeksteen van de behandeling uit glucocorticoïden (GC) en wordt over het algemeen gedacht dat prednisolon een relatief veilige en effectieve behandeling is voor PMR, en dat de meeste patiënten binnen twee jaar wel genezen zijn. Echter, dit blijkt in de praktijk tegen te vallen gezien rond de 50% van de patiënten één of meer flare ontwikkelen tijdens het afbouwen van de GC. Hierdoor duurt de behandeling best lang en bereikt maar 33-50% van de PMR patiënten, die behandeld worden in het ziekenhuis, GC-vrije remissie twee jaar na start van de behandeling. Daarnaast duurt de GC-behandeling bij tot 40% van de PMR patiënten minstens vier jaar. Ondanks dat er maar een medium-hoge GC dosis wordt voorgeschreven treedt bij rond de 50% van de PMR patiënten GC-gerelateerde bijwerkingen op, met name na langdurige behandeling. Patiënten die langer dan twee jaar met GC worden behandeld hebben een grotere kans op bijwerkingen zoals gewichtstoename, osteoporose, fracturen, cataract, infecties, metabole en cardiovasculaire bijwerkingen. GC-sparende behandelalternatieven zijn daarom nodig om zodoende de GC-gerelateerde bijwerkingen te verminderen.

Tot heden zijn er weinig GC-sparende medicamenteuze opties en het lage aantal wetenschappelijk studies die zijn verricht zijn niet eenduidig of negatief wat betreft effectiviteit van GC-sparende middelen. Studies naar GC-sparende behandelingen staan daarom nog steeds hoog op de onderzoeksagenda van de EULAR/ACR.

Het doel van deze thesis was daarom om verschillende "unmet needs" van PMR aan te pakken. Enkele aan bod komende factoren zijn de atypische klinische presentatie, mogelijke uitlokkende factoren en het uitbreiden van GC-sparende behandel mogelijkheden.
Belangrijkste bevindingen

Hoofdstuk 2: Er is geen associatie gevonden tussen het ontstaan van PMR en infectieuze triggers.

De immunopathogenese van PMR is grotendeels onopgelost en waarschijnlijk multifactorieel.

Mogelijke factoren die bijdragen aan het ontstaan zijn genetische achtergrond, veroudering van het immuunsysteem en omgevingsfactoren. In ons onderzoek bestudeerden wij of omgevingsfactoren zoals infecties voorafgaand aan PMR zijn met het ontstaan van PMR. Eerdere onderzoeken beschrijven namelijk een seizoensgebonden patroon en associatie tussen het ontstaan van PMR / reuscelarteriïtis (RCA) na een voorafgaande infectie met Mycoplasma pneumoniae, Chlamydophila pneumoniae, Parvovirus B19 en parainfluenza virus type 1. Het wetenschappelijke bewijs laat tot dusver eigenlijk tegenstrijdige resultaten zien.

Daarom wordt in hoofdstuk 4 data van 448 patiënten geanalyseerd middels een chi-square goodness of fit test om te kijken of er sprake is van een seizoensgebonden patroon. Daarnaast werd data betreffende de incidentie van infectieziekten van het Rijksinstituut Volksgezondheid en milieu (RIVM) verkregen. Van deze data werden index digits uitgerekend en stond het getal 100 voor het gewogen gemiddelde van infecties op dat tijdpunt voor de jaren 2007 tot en met 2017.

Er werd een bimodaal seizoenspatroon gezien wat betreft de incidentie van aanvang PMR-symptomen echter de chi-square goodness of fit test was statistisch niet significant. Ook werd er geen relatie aangetoond tussen de incidentie van de PMR-symptomen en de incidentie van infecties met Mycoplasma pneumoniae, Chlamydophila pneumoniae, Parvovirus B19 en parainfluenza virus type 1. De resultaten van deze studie laten niet zien dat onderzochte verwekkers een trigger zijn voor het ontstaan van PMR. De voornaamste beperkingen van dit onderzoek zijn het retrospectieve karakter en het feit dat eerstelijns PMR patiënten niet onderzocht zijn.

Hoofdstuk 3: In ons cohort komen PMR patiënten voor met een atypische presentatie zoals lage ontstekingswaarden. In vergelijking met PMR patiënten met verhoogde ontstekingswaarden bij presentatie is dit een andere subset van PMR met een verschillende klinische presentatie bij diagnose en met een verschillend (gunstiger) beloop.

De bevindingen uit hoofdstuk 3 ondersteunen de hypothese dat er verschillende subsets van PMR bestaan, met een atypische presentatie zoals lage ontstekingswaarden bij diagnose. Het betreft een subset met een mildere klinische presentatie en beloop. De hypothese dat er verschillende subsets van PMR bestaan werd onderzocht middels het opzetten van een retrospectief cohort. In totaal werd data van 454 PMR patiënten (klinische diagnose) bestudeerd om te onderzoeken of patiënten met normale ontstekingswaarden a) “vroeg” in het ziekteproces zijn gediagnosticeerd, b) een verschillende subset van PMR zijn met verschillende klinische presentatie en prognose, c) verkeerd geclassificeerd werden als PMR. Het meeste bewijs vonden wij voor hypothese b, enig bewijs voor hypothese a, en onvoldoende bewijs voor hypothese c. Hypothese b wordt ondersteund door het feit dat de klinische karakteristieken van patiënten met normale ontstekingswaarden kwamen overeen met die van patiënten met verhoogde ontstekingswaarden, hetzij milder van aard. Op baseline hadden patiënten met normale ontstekingswaarden minder vaak anemie en perifere artritis in vergelijking met patiënten met verhoogde ontstekingswaarden. De prognose was ook beter aangezien bij patiënten met normale ontstekingswaarden minder vaak DMARDs werden voorgeschreven en zij ook eerder werden terug verwezen naar de eigen huisarts in GC-vrije remissie. Verder werd bij een deel van de patiënten met op baseline normale ontstekingswaarden, gedurende follow-up verhoogde ontstekingswaarden waargenomen ten tijde van een flaire. Dit pleit voor hypothese b, echter ook voor hypothese a. Deze patiënten kunnen dan mogelijk gezien worden als “vroeg in het ziekte proces te zijn gediagnosticeerd” aangezien de ontstekingswaarden pas later gedurende de ziekte stijgen. Verder bleek in de subgroep van patiënten met normale ontstekingswaarden, de patiënten die in de periode vóór het stellen van de diagnose normale ontstekingswaarden hadden, langer ziekte duur hadden in vergelijking met de patiënten die voor het stellen van de diagnose verhoogde ontstekingswaarden hadden. In vergelijking met patiënten die op baseline verhoogde ontstekingswaarden hadden, had de subgroep patiënten met normale ontstekingswaarden op baseline eveneens een langere duur van symptomen voordat de diagnose gesteld werd. Dit suggereert een vertraging in het stellen van de diagnose, waarschijnlijk ten gevolge van de atypische presentatie.

Er werd onvoldoende bewijs gevonden voor hypothese c. Een aanzienlijk aandeel patiënten die op baseline normale ontstekingswaarden hadden, ontwikkelden verhoogde ontstekingswaarden tijdens follow-up. In beide groepen werd dezelfde incidentie van reumatoïde gevonden tijdens follow-up. Echter, in onze studie werden alle patiënten die negen maanden na de index event een alternatieve diagnose ontwikkelden, buitengesloten van de studie. Door het design van onze studie is het niet mogelijk om hypothese c volledig onaanneemelijk te maken.

Beperkingen van deze studie zijn het retrospectieve karakter en meer objectieve uitkomstmaten zoals echo, MRI of PET-CT om eventuele bursitis / artritis van de schouders en heupen vast te stellen. Daarnaast is er waarschijnlijk ook sprake van index event bias, en is de generaliseerbaarheid mogelijk beperkt tot PMR-patiënten die behandeld worden in de tweede en derde lijn en niet de eerste lijn.

Sterke punten van deze studie zijn de redelijk grote aantallen patiënten met alleen de diagnose PMR en niet PMR / RCA zoals de meeste studies.

Hoofdstuk 4-5. In de dagelijkse reumatologische praktijk van de Sint Maartenskliniek wordt MTX zelden voorgeschreven aan PMR patiënten in de periode 2008-2017. De exacte rol, doses en effectiviteit van MTX in PMR is nog onduidelijk en meer onderzoek is nodig om hier meer duidelijkheid over te verkrijgen.

Er is nog veel onduidelijkheid over de exacte rol van MTX bij PMR. Dit komt omdat eerdere MTX studies wisselende resultaten laten zien qua effectiviteit, er verschillende (lage) doses MTX gebruikt werden, of weinig studiepatiënten hadden waardoor de studies een mogelijk effect niet konden aantonen. Er is weinig data over de effectiviteit van MTX in de dagelijkse reumatologische praktijk.
In hoofdstuk 4 wordt daarom het gebruik en de effectiviteit van MTX beschreven in PMR patiënten behandeld in de dagelijkse reumatoïde praktijk behandeld werden. Hiervoor wordt het eerder genoemde cohort PMR patiënten gebruikt als in hoofdstuk 2 en 3. Uit dit cohort werden in totaal 240 patiënten geselecteerd: 39 patiënten behandeld met MTX (interventiegroep) en 201 patiënten niet behandeld met MTX (controlegroep). Patiënten kwamen in aanmerking voor de controlegroep op het moment van de eerste flare (index event) en zij MTX-naïef waren. De eerste flare werd gekozen als index event omdat volgens de internationale PMR richtlijnen dan in aanmerking komen voor start MTX. De voornaamste uitkomstmaten waren het aantal flares per jaar (analyse middels Poisson regressie), dagelijkse GC dosis (gewogen gemiddelde, analyse middels lineaire regressie en gecorrigeerd voor tijdsduur behandeling) en de flare incidentie ratio van enkel de MTX groep (vóór versus na start MTX).

Na het index event was de jaarlijkse incidentie rate ratio van flares in de MTX versus controlegroep 0.80 (95%-CI 0.45 tot 1.42). In de MTX groep was de jaarlijkse flare rate 1.22 vóór en 0.43 ná start van MTX, resulterend in een flare incidentie ratio van 0.35 (95%-CI 0.23 tot 0.52). De gewogen dagelijkse GC dosis was hoger in de MTX versus controlegroep (ratio 1.37; 95%-CI 1.04 tot 1.80).

Concluderend betekent dit dat deze resultaten geen duidelijk effect van MTX op de flare rate tussen de groepen laten zien, en de gewogen dagelijkse GC dosis was juist hoger in de MTX groep. Echter, er is een kanttekening hierbij: Na het flare event lijkt de flare rate binnen de MTX groep zelf. Dit sugereert mogelijk toegeneemt van effectiviteit van MTX. In ons cohort wordt MTX aan een lage proportie patiënten voorgeschreven: 9% (39 van de 454).

Alleen één eerdere studie beschrijft het gebruik van MTX in de dagelijkse reumatoïde klinische praktijk; hierbij wordt MTX aan 19% van de PMR patiënten voorgeschreven. Meerdere factoren kunnen meespelen in het lage voorschrijfdraad van MTX in PMR patiënten van de Sint Maartenskliniek. Ten eerste werden de patiënten die deelnamen aan deze studie behandeld in de jaren 2008 tot en met 2017. Echter, de nieuwste richtlijnen over de behandeling van PMR verschenen pas in 2015. Ten tweede wijst het voorschrijfdrag van MTX mogelijk ook naar de twijfel die speelt bij reumatoïden over de exacte rol en effectiviteit van MTX in PMR. Ten derde had de controlegroep PMR patiënten een lagere prednisolon dosis op de index event. Mogelijk speelt hierbij de overweging dat de risico’s van MTX dan niet opwegen tegen de voordelen van MTX gezien er bij lagere prednisolon doses in het algemeen minder vaak bijwerkingen optreden.

De voornaamste limitatie van dit cohort is echter het retrospectieve karakter waardoor de patiëntengroepen niet zijn gerandomiseerd. Hierdoor spelen residuele confounding en confounding door (contra-) indicatie voor MTX ondanks correctie voor bepaalde variabelen waarschijnlijk een grote rol. De toegevoegde waarde van deze studie aan het wetenschappelijk bewijs voor de effectiviteit van MTX blijft beperkt.

Om de hypothese te beantwoorden dat MTX effectief is in PMR zou een grote dubbelblinde gerandomiseerde studie opgezet dienen te worden, met hoger gedoseerde MTX (25 mg /week) zoals dat gebruikelijk wordt voorgeschreven in andere inflammatoire aandoeningen zoals bijvoorbeeld reumatoïde artritis.

Hoofdstuk 6. Rituximab (RTX) is een veilig en mogelijk effectief prednison sparende behandeling in PMR. In vergelijking met de placebogroep, bereiken significant meer PMR patiënten zowel GC-vrije remissie als een lage dosis prednison (15 mg / dag) 21 weken na RTX in combinatie met een versneld GC-afbouwschema.

In hoofdstuk 5 wordt de effectiviteit van RTX beschreven in een 21-week lange dubbelblinde placebo-gecontroleerde trial met 47 PMR patiënten die voldoen aan de 2012 EULAR / ACR criteria voor PMR. In totaal werden 38 recent gediagnosteerde PMR patiënten en 9 relapsing PMR patiënten geïncludeerd (relapse op prednisolon dosis ≥7.5 mg / dag). Patiënten werden in een 1:1 ratio gerandomiseerd voor ofwel de RTX groep (1 x 1000 mg; n=23), ofwel de placebogroep (RTX x 0 mg; n=24), in combinatie met een GC-schema van 17 weken.

Meer patiënten in de RTX versus placebo groep bereikten de primaire uitkomstmaat: GC-vrije remissie (PMR-AS <10) op week 21: 48% (12/23) versus 21% (5/24), absolut risk verschil 27% (éénzijdige 95%-CI 4%), relatief risico 2.3 (éénzijdige 95%-CI 1.1, p=0.049).

Wat betreft de secundaire uitkomstmaten, bereikten meer patiënten in de RTX versus placebo groep een lage GC-dosis (GC ≤5 mg / dag): 100% (23/23) versus 54% (13/24), absolut risico verschil 46% (éénzijdige 95%-CI 20%), relatief risico 1.8 (éénzijdige 95%-CI 1.3), p=0.001, en bereikten patiënten in de RTX versus placebo groep een grotere mediane (IQR) afname van ochtendstiffheid in minuten: -60 (-120 tot -5) versus -20 minuten (-60 tot 0), absolut verschil 40, éénzijdige p=0.02. Daarnaast was er een grotere afname van de PMR-AS in de RTX versus placebo groep (gewogen gemiddelde (SD): -13.8 (2.9) versus -3.8 (3.6), absolut verschil -10 (éénzijdige 95%-CI 2.2, p=0.02). In de RTX groep treden meer infusie gerelateerde bijwerkingen op: 0 versus 3, rate ratio 3.47 (éénzijdige 95%-CI 1.3). Wat betreft de overige secundaire uitkomstmaten werden geen statistisch significante verschillen waargenomen.

Post-hoc analyses toonden aan dat de ziekte fase tot effectmodificatie leidt: de effectiviteit van RTX werd met name in recent gediagnosteerde PMR patiënten gezien en niet in de relapse PMR patiënten. In de recent gediagnosteerde PMR patiënten werd GC-vrije remissie (PMR-AS <10) in de RTX versus placebo groep bereikt in: 58% (11/19) versus 21% (4/19), absolut risico verschil 37% (éénzijdige 95%-CI 10% relatief risico 2.8 (éénzijdige 95%-CI 1.3): p=0.02. Wat betreft de secundaire uitkomstmaat GC ≤5 mg / dag werd ook hier een groter verschil in effectiviteit gezien in de recent gediagnosteerde patiënten (RTX versus placebo): 100% (19/19) versus 47% (9/19), absolut risico verschil 53% (éénzijdige 95%-CI 29%, relatief risico 2.1 (éénzijdige 95%-CI 1), p=0.001. In de relapsing PMR patiënten werden geen statistisch significante verschillen gezien in deze uitkomstmaten.

Concluderend is er middels deze proef of concept studie effectiviteit van RTX aangetoond in PMR patiënten. Tot heden betreffen deze uitkomstmaten slechts de effectiviteit van RTX op korte termijn. Een langere termijn studie zou kunnen bevestigen of RTX ook op langere termijn (bijvoorbeeld één jaar na RTX) effectief is. Daarnaast is het belangrijk om de resultaten van deze proef of concept studie te bevestigen in een grotere fase III dubbelblinde placebo-gecontroleerde trial.
List of publications
List of publications

Publications related to this thesis


* Both authors contributed equally to this work.

Publications unrelated to this thesis


Conference abstracts


Marsman D, Den Broeder N, Van den Hoogen F, den Broeder AA, van der Maas A. Polymyalgia rheumatica: not only winter, but summer is coming too. Poster tour NVR 2019, Papendal the Netherlands; poster presentation ACR 2019, Atlanta.


Research grants

A double blind randomized placebo controlled trial to assess the effect of concomitant early high dose methotrexate versus placebo in patients with newly diagnosed polymyalgia rheumatica. ReumaNederland 2018
### PhD portfolio

#### Courses related to PhD

**2018**
- Biometrics, Radboudumc, Nijmegen
- Grant writing and presenting for funding committees, Radboudumc, Nijmegen
- Effective writing strategies, Radboudumc, Nijmegen

**2017**
- Scientific writing, Radboudumc, Nijmegen
- Management voor promovendi, Radboudumc, Nijmegen

**2016**
- BROK

#### Courses related to epidemiology

**2020**
- Reproductive Epidemiology and Toxicology- MED-BMS 66, Radboudumc, Nijmegen
- Applied medical research and society - MED-BMS81, Radboudumc, Nijmegen
- Missing data: consequenties en oplossingen. Epidem V8, VU, Amsterdam
- Causal inference ESP 48, NIHES, Erasmus MC, Rotterdam
- Health economics -ESP25, NIHES, Erasmus MC, Rotterdam
- K74 Multilevel analyse Epidem, VU, Amsterdam

**2019**
- Clinical trials MED-BMS48, Radboudumc, Nijmegen
- Systematic reviews and meta-analyses MED-BMS18, Radboudumc, Nijmegen
- Design and analysis of experiments -MED-BMS14, Radboudumc, Nijmegen

**2018**
- Epidemiologisch onderzoek: opzet en interpretatie; EPIDEM, V10, VU, Amsterdam
- Prediction models in health science - MED-BMS59, Radboudumc, Nijmegen
- Logistic regression, NIHES, Erasmus MC, Rotterdam

#### Other

**2020**
- Junior refereren, Department of Health Evidence, Radboudumc

**2019**
- Junior refereren systematic reviews, Department of Health Evidence, Radboudumc
- Journal club, Department of Health Evidence, Radboudumc

**2018**
- Junior refereren Measurement in medicine, Department of Health Evidence, Radboudumc
- Journal club, Department of Health Evidence, Radboudumc
Curriculum vitae


Zij verrichtte verschillende werkzaamheden als site en co-investigator voor de studies Ascore, UAA, Fact, STAPRA en Sanofi. In 2019 startte ze met de opleiding tot epidemioloog, en in januari 2021 met haar opleiding tot reumatoloog aan het Radboudumc, te beginnen met de vooropleiding in het Sint Antoniusziekenhuis (opleiders dr. Annelies van Ede en dr. Paul de Jong).
Dankwoord
Dankwoord

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Theses Sint Maartenskliniek


Research data management

Location
The data described in this thesis are stored at the departments of rheumatology and research of the Sint Maartenskliniek.

Access
Data, syntax and protocols may be obtained on request from the departments of rheumatology and / or research of the Sint Maartenskliniek.

Interoperable
Data is documented in English according to the FAIR principles.

Reusable
All data and syntax used in this thesis are accurately documented and can be reused for additional research and analysis.