Dose reduction and discontinuation of prednisolone using structured treat-to-target taper in patients with polymyalgia rheumatica:

Protocol for an open label, parallel-group, multi-centre trial

1 Administrative information

1.1 Title

Dose reduction and discontinuation of prednisolone using structured treat-to-target taper in patients with polymyalgia rheumatica

1.2 Trial Registration

The trial will be registered at Clinicaltrials.gov. This protocol is structured according to the SPIRIT 2013 checklist.

1.3 Protocol Version

Version 1.2; 2022-11-08

1.4 Funding

The initiator of this study is MD, PhD Kresten Keller. Principal investigator Christoffer Søvsø Våben has received an introductory scholarship from Institute of Clinical Medicine, Aarhus University (65.000 DKR) to prepare this protocol and further prepare the study. Christoffer Søvsø Våben has received a scholarship from The Danish Rheuamtism Association (1.000.000 DKR) for VIP-salary for the two first years of the PhD project. Kresten Keller has received a grant from Independent Research Fond Denmark (2.000.000 DKR) covering the last year of PhD Salary as well as operating expenses.

There is a continuous search for funding. If funding is granted, an amendment to the protocol will be submitted to The Central Denmark Region Committee on Health Research Ethics. The financial contributors have no influence on design, conduct, and publication of the results.

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2 Introduction

2.1 Background and Rationale

Polymyalgia Rheumatica (PMR) is one of the most common inflammatory diseases of the elderly [1]. It is characterised by symmetrical pain in the proximal muscles, morning stiffness and raised inflammatory markers. Prednisolone remains a cornerstone in the treatment of PMR [2], even though it carries several significant adverse effects such as osteoporosis, diabetes and increased infection risk [3-5]. Methotrexate as a glucocorticoid sparing agent is rarely used because of limited evidence and potential side effects [6]. Therefore, prednisolone remains the standard drug of choice, and dose as well as treatment duration should be reduced as much as possible [7]. PMR is associated with giant cell arteritis (GCA), which is treated with a much higher prednisolone dosage than PMR [8]. Approximately 20% of PMR patients develop GCA during the course of their disease and some studies have shown that up to 1/3 of PMR patients have an undiagnosed GCA [1, 9, 10]. Since treatment regimens for GCA and PMR differ significantly in prednisolone dose and tapering, there is a rationale to screen PMR patients for GCA. Ultrasonography is a cheap, non-invasive and precise method to diagnose GCA [11, 12].

Danish National PMR guidelines as well as European League Against Rheumatism (EULAR) guidelines, suggests a starting dose of prednisolone from 12,5-25 mg daily and hereafter a gradually and individualised taper over approximately one year but these recommendations are not based on evidence. [13, 14]. Furthermore, the national guidelines states that PMR patients can be diagnosed and treated either by their general practitioner (GP) or a rheumatological department, but one is not recommended over the other [14]. Therefore, further research is necessary to determine where and how these patients are managed most successfully.

In other rheumatic diseases such as rheumatoid arthritis and axial spondyloarthritis, a treat-to-target approach has proven beneficial to control disease activity [15, 16]. Treat-to-target is characterized by setting a specific treatment goal corresponding to disease remission or low activity and then systematically trying to reach this goal. Leading experts have suggested that a treat-to-target strategy may be effective in PMR and proposed further studies in this field [17, 18]. Recently our research group published a retrospective study demonstrating that a systematic approach to prednisolone taper in PMR more effectively brings patients in prednisolone free remission, but the results must be confirmed in a prospective setting [19].

Perspectives

It is anticipated that this trial will improve the current treatment strategy for PMR patients. By using an evidence-based treat-to-target approach, patients will reach a faster prednisolone free remission, which results in less PMR related morbidity and less patients developing prednisolone adverse effects. By following PMR patients in a hospital setting, a larger proportion of GCA patients will be found. It is

expected that the rheumatological driven treat-to-target taper will overall be an improvement for PMR patients regarding symptom relief and quality of life and be a cheaper way to treat PMR patients in a long-term health-economic perspective.

2.2 Aim and Objective(s)

The overall aim of this study is to investigate benefits and harms associated with a systematic "treat-to-target" prednisolone taper strategy compared to usual care in newly diagnosed, treatment naïve patients with PMR.

Primary objective:

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the proportion of patients in prednisolone free remission after 52 weeks, in patients with PMR.

Key secondary objectives:

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in the patient-reported prednisolone dose from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the proportion of patients diagnosed with GCA during 52 weeks, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on number of relapses from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in the patient reported global VAS from baseline to week 52, in patients with PMR.

Secondary objectives:

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in PMR-Activity Score (PMR-AS) from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the proportion of patients with an undiagnosed vasculitis verified by ultrasound at the 52-week visit, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in SF-36 MCS from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in SF-36 PCS from baseline to week 52, in patients with PMR
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in HAQ-DI from baseline to week 52, in patients with PMR.

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in PMR VAS from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in fatigue VAS from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in stiffness VAS from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in morning stiffness duration (min) from baseline to week 52, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on frequency of adverse effects and comorbidities related to prednisolone treatment after 13, 26, 39 and 52 weeks, in patients with PMR.

Other (exploratory) objectives:

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on 13 weeks sustained prednisolone free remission after 65 and 104 weeks, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the patient reported accumulated prednisolone dosage after 13, 26, 39, 52, 65, 78, 91 and 104 weeks, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on prednisolone dose at 13, 26, 39, 52, 65, 78, 91 and 104 weeks, only in GCA free PMR patients.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in PMR-AS from baseline to 104 weeks, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in SF-36 MCS and PCS, HAQ-DI, PMR VAS, fatigue VAS, stiffness VAS, global VAS and morning stiffness duration (min) from baseline to week 65, 78, 91 and 104, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on number of relapses after 65, 78, 91 and 104 weeks, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the proportion of patients diagnosed with GCA during 104 weeks (incidence), in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the proportion of patients with an undiagnosed GCA verified by ultrasound at the 104-week visit, in patients with PMR.
- To compare the effect of a treat-to-target taper strategy, relative to usual care, on changes in inflammatory and cardiovascular biochemical markers from baseline to 13, 26, 39, 52, 65, 78, 91 and 104 weeks, in patients with PMR.

- To compare the effect of a treat-to-target taper strategy, relative to usual care, on the frequency of adverse effects and comorbidities related to prednisolone treatment after 65, 78, 91 and 104 weeks, in patients with PMR.

Other information:

- The proportion of GCA patients at baseline

2.2.1 Hypotheses

- More patients will be in prednisolone free remission after one and two years in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- No difference will be seen in changes in PMR-AS after one and two years in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- No difference will be seen in outcomes related to patient reported outcome measures (SF-36 MCS and PCS, HAQ-DI, PMR VAS, fatigue VAS, stiffness VAS, global VAS and morning stiffness duration (min)) in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- The absolute dosage of prednisolone will decrease faster in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- The total accumulated prednisolone dose will be lower after one and two years in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- Fewer patients will have an undiagnosed GCA after one and two years when comparing a treat-to-target prednisolone taper with usual care.
- No difference is seen in the total number of GCA patients found with vascular ultrasound after one and two years when comparing a treat-to-target prednisolone taper to usual care.
- No difference is seen in inflammatory and cardiovascular biochemical markers after one and two years in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- Less adverse effects to prednisolone will occur in PMR patients receiving a treat-to-target prednisolone taper vs. usual care.
- Following a treat-to-target taper in a hospital setting will be a more cost-effective approach than treatment in general practise.

2.3 Trial Design

It is a 1-year open label randomised trial, with a planned 1-year extension. Study population is 120 patients with newly diagnosed treatment naïve PMR. Patients will be randomised to either structured treat-to-target

prednisolone taper in a hospital setting according to a standard tapering scheme, or to usual care by general practitioners. Treatment effect is evaluated every 3 months.

3 Methods

3.1 Participants, Interventions and Outcomes

3.1.1 Study Setting

The study is a multicentre study and patients will be included from rheumatological departments in the Central Denmark Region (Aarhus University Hospital, Silkeborg Regional Hospital, Horsens Regional Hospital, Randers Regional Hospital, and Gødstrup Regional Hospital), Southern Denmark Region (Esbjerg Regional Hospital, Vejle Regional Hospital) and Northern Denmark Region (Aalborg University Hospital, North Denmark Regional Hospital, Hjørring). The primary research group will be located at the Department of Rheumatology, Aarhus University Hospital.

3.1.2 Eligibility Criteria

Inclusion criteria

- Patients newly diagnosed with PMR according to the EULAR criteria for PMR [20].
- No sign of GCA on ultrasonography of the temporal and axillary arteries.
- Age over 50 years.
- Danish spoken and written language skills sufficient to fill out questionnaires.

Exclusion criteria

- Peroral, intraarticular or intramuscular application of glucocorticoids within the last month.
- Previous prednisolone treatment for GCA/PMR.
- Unable to give consent.
- Symptoms of GCA (newly onset-headache, tenderness of the temporal artery, jaw claudication, vision disturbances).
- Active malignant cancers within the last 5 years (except basal cell carcinoma).
- Other inflammatory rheumatic diseases (eg. rheumatoid arthritis, polymyositis, spondyloarthritis, psoriatic arthritits, gout).
- Uncontrolled diseases (eg severe active asthma, cardiac disease with NYHA class IV)

3.1.3 Interventions

Both groups are diagnosed by a rheumatologist according to the inclusion and exclusion criteria. Hereafter treatment with prednisolone is started with 15 mg as a morning dose according to the standard starting dose

advised in national as well as EULAR guidelines [13, 14]. All patients will receive a thorough information about PMR and what symptoms to be aware of including GCA symptoms.

Usual Care

Patients randomized to "usual care" are dismissed from the hospital after the diagnosis and the prednisolone taper are subsequently performed by the patient's general practitioner. A letter is sent to the general practitioner informing that the patient is included in a scientific study, guidance for prednisolone tapering according to national guidelines, and where to find further information (See appendix 1).

Rereferral of patients if general practitioners need rheumatological assistance, is part of normal clinical practise. During this trial, patients rereferred to rheumatological assessment from general practice will receive a treatment similar to other patients seen in the outpatient clinic according to standard care but will not receive the structured treat-to-target taper.

Treat-to-target Prednisolone Taper

Patients randomized to the "Treat-to-target" group is prescribed with a systematic prednisolone taper according to the Table 1 below, which adhere to the Danish national guidelines[14]. The starting dose can be increased if remission is not reached initially. Preferably dosage should be increase to a maximum of 25 mg daily according to Danish and EULAR guidelines [13, 14]. If prednisolone dosage is increased, Table 2 below is followed until a daily dosage of 15 mg is reached. Hereafter Table 1 is followed.

Table 1

Treatment Week	Daily Prednisolone dosage
1-2	15.00 mg
3-4	12.50 mg
5-9	10.00 mg
10-14	10.00/7.50 mg
15-19	7.50 mg
20-24	7.50/5.00 mg
25-29	5.00 mg
30-34	5.00/2.50 mg
35-39	2.50 mg
40-44	2.50/0.00 mg
45	0.00 mg

Table 2

Treatment week after prednisolone increase	Daily prednisolone dose
1-2	25.00 mg
3-4	20.00 mg
5-6	15.00 mg

Table 1: Where two dosages is separated by an /, it refers to alternating dosages every other day.

Furthermore, as part of their out-patient monitoring and treat-to-target approach, this group of patients will be monitored with blood samples four weeks after the first visit and hereafter every 4th week (including HgbA1C, after 1 and 3 months), which adhere to clinical practice. A nurse will subsequently make a minimum of 5 phone consultations at approximately week 3-5, 11-16, 24-32, 38-42, 52, and hereafter minimum every 3 months where the focus will be on symptoms, medical compliance, medical adverse effects and results of the blood samples. When the patient reaches prednisolone free remission, a last phone consultation is planned 2-3 months after and if the patient is still in remission further consultations is not necessary according to clinical practice. The patient will still receive the study questionnaires and come to the two-year study visits.

The nurse will consult a rheumatologist if one of the following occurs:

- The patient reports cranial symptoms of GCA
- If a second relapse occurs
- If CRP is not normalized or the patient still has symptoms after the first month of treatment

If the patient is not in remission at the first phone consultation after 3-5 weeks or at the phone consultation one month after a relapse, additional phone consultations will be added monthly until the patient is deemed in remission and hereafter the above mentioned structure will be followed.

After consultation with a rheumatologist, it can be determined if the patient should proceed in the nurse-managed care or be transferred to doctor-managed care. On clinical indication the doctor can furthermore decide to change the tapering scheme for the patient and plan additional visits for the patient and repeat the vascular ultrasound if it is deemed necessary.

No widely accepted scoring system for PMR relapse exists [21]. In this study relapse is defined as the reappearance of signs and symptoms of PMR, accompanied by an increase in C-reactive protein level attributable to disease activity [22]. Between visits relapse is defined as symptoms leading to an increase in prednisolone dose determined by the treating physician. If relapse occur, prednisolone dosage will be increased to the previous level where symptoms were under control and tapering resume according to Table 1 from here.

This group of patients are also referred to a DXA and initiation of alendronate is recommended on clinical indication in all patients with a T-score of less than -1.0 at baseline or in case of low energy fractures in hip or spine. Treatment and further DXA scans are performed according to national guidelines [23].

3.1.4 Outcomes

Primary Outcome

- Proportion of patients in prednisolone free remission 52 weeks from baseline

Key Secondary Outcomes

- Change in prednisolone dose from baseline to week 52
- Proportion of GCA patients diagnosed during the first 52 weeks
- Self-reported number of relapses during the first 52 weeks (assessed by increase in symptoms and an increase in prednisolone dosage)
- Change in patient-reported global VAS from baseline to week 52

Secondary Outcomes

- Change in PMR-AS from baseline to week 52
- Proportion of patients with an undiagnosed vasculitis assessed by ultrasound at week 52
- Changes in SF-36 MCS from baseline to week 52
- Changes in SF-36 PCS from baseline to week 52
- Changes in HAQ-DI from baseline to week 52
- Changes in patient reported PMR VAS from baseline to week 52
- Changes in patient reported fatigue VAS from baseline to week 52
- Changes in patient reported stiffness VAS from baseline to week 52

- Changes in patient reported duration of morning stiffness from baseline to week 52
- Proportion of patients where baseline DXA scan are performed during the first 3 months after baseline visit
- Proportion of patients where HgbA1C blood samples are taken during the first 52 weeks
- Frequency of patient reported adverse effects and comorbidities related to prednisolone treatment after 13, 26, 39 and 52 weeks
- Proportion of patients with patient reported infections during the first 52 weeks
- Changes in inflammatory and cardiovascular biochemical markers from baseline to week 52

Other (Exploratory) Outcomes

- Proportion of patients in 13 weeks sustained prednisolone free remission after 65 and 104 weeks
- Accumulated prednisolone dosage after 13, 26, 39, 52, 65, 78, 91 and 104 weeks
- Proportion of patients receiving prednisolone 65, 78, 91, and 104 weeks after diagnosis
- Changes in prednisolone dose from baseline to 104 weeks
- Changes in PMR-AS from baseline to 104 weeks
- Changes in PROMs from baseline to 65, 78, 91 and 104 weeks
- Self-reported number of relapses from baseline to week 104
- Percentage of GCA patients found during the 104 weeks (incidence)
- Percentage of GCA patients found with ultrasound at the 104 week visit
- Changes in inflammatory and cardiovascular biochemical markers from baseline to week 104
- Frequency of adverse effects and comorbidities related to prednisolone treatment after 65, 78, 91 and 104 weeks

Other information

- Proportion of GCA patients found at baseline

3.1.5 Participant timeline

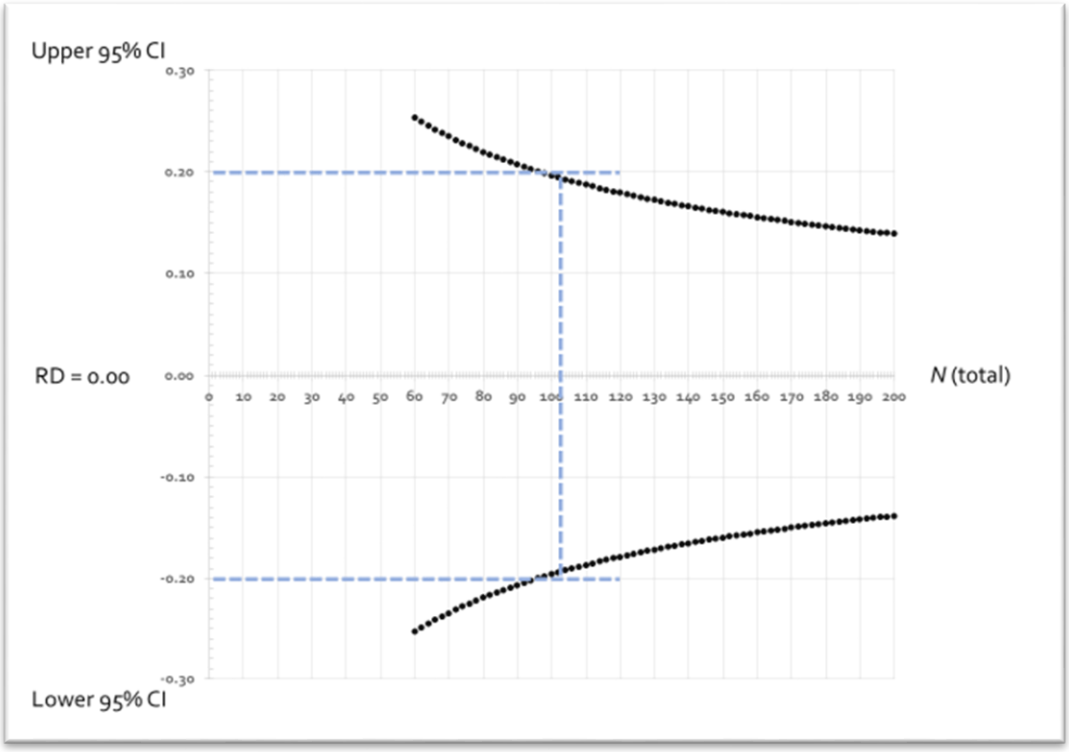
Table 3 below presents the study-timeline for all study visits. The group randomised to “Treat-to-target” will have additional telephone consultations and clinical blood samples as described in section 3.1.3. The group randomised to usual care will have additional consultations and clinical blood samples as decided by the general practitioner.

Table 3, Participant timeline

	Inclusion	Ramdomisation	Questionnaire + Blood samples	Questionnaire + Blood samples	Questionnaire + Blood samples	1 year visit	Questionnaire + Blood samples	Questionnaire + Blood samples	Questionnaire + Blood samples	Termination Visit
Months	0	0-2 weeks	3	6	9	12	15	18	21	24
Informed consent	X									
PMR diagnosis	X									
Randomisation		X								
Sex	X									
Height and weight	X					X				X
Comorbidity	X		X	X	X	X	X	X	X	X
Medicine (incl Prednisolone information)	X		X	X	X	X	X	X	X	X
PROMs	X		X	X	X	X	X	X	X	X
PMR Symptoms	X		X	X	X	X	X	X	X	X
PMR Activity Score	X					X				X
Adverse effects to prednisolone	X		X	X	X	X	X	X	X	X
Physical examination	X					X				X
Blood sample, biobank	X		X	X	X	X	X	X	X	X
Vascular US	X					X				X

3.1.6 Sample size and power considerations

One retrospective study have been conducted in this field, where the control group comprised usual care in a hospital setting [19]. Assuming a 30% points difference (between proportions), an alpha of 0.05, and a good statistical power of 90%, a sample size calculation based on the *guestimated* proportions of patients successfully withdrawn from prednisolone and also in remission after one year (80% vs 50%), yields 52 patients in each group. Since this estimation is highly uncertain, we will aim for inclusion and randomisation (1:1) of 120 participants (approximately 60 patients in each group).



Interpretation of an apparent null finding: A 2-sided 95% confidence interval excluding differences greater than 20%points between the group proportions will be interpreted as indicating the absence of a clinically meaningful difference. As indicated in the figure, we would have a reasonable precision (±20%points) around the null (RD=0.00), with 102 participants in the sample (i.e., approximately 51 per group).

3.1.7 Recruitment

Patients will be recruited from all departments of rheumatology in the Central Denmark Region (Aarhus University Hospital, Silkeborg Regional Hospital, Horsens Regional Hospital, Randers Regional Hospital, Gødstrup Regional Hospital) as well as Esbjerg Regional Hospital, Vejle Regional Hospital, North Denmark Regional Hospital, Hjørring and Aalborg University Hospital. Both patients seen at the outpatient clinic and hospitalized patients can be recruited. If one of the above-mentioned departments find eligible patients, but not have the resources for inclusion at that time, the patient can be referred to one of the other collaborating departments for inclusion after patient consent. Participant enrolment is expected to take 24 months.

3.2 Assignment of Interventions

3.2.1 Allocation Sequence generation

Participants will be randomly assigned to either “Usual care” or “Treat-to-target” with a 1:1 allocation as per a computer-generated randomisation schedule stratified by site, using permuted blocks of random sizes between 2-6. The block sizes will not be disclosed, to improve the allocation concealment.

3.2.2 Allocation concealment mechanism

Randomisation will be set via the “Randomisation module” in Research Electronic Data Capture (REDCap) [24]. Allocation concealment will be ensured, as the service will not release the randomisation code until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

3.2.3 Implementation

All patients who give consent for participation and who fulfil the inclusion criteria will be randomized. Randomization will be implemented at the first visit after all initial information and examination has occurred. Randomization will be assigned by the attending physician at the study site via access to REDCap Randomization Module.

3.2.4 Blinding

This is an open-label study without blinding.

3.3 Data collection, management and analysis

3.3.1 Data collection methods

Demographics

At baseline information regarding sex, age, weight, height, other medication, comorbidity, previous history of shoulder and hip related pain, alcohol and tobacco consumption is obtained.

Physical examination

Physical examination including ability to raise arms, swollen and tender peripheral joints and hip mobility will be performed at baseline and after one and two years.

EULAR criteria for PMR and criteria for remission

At baseline EULAR criteria for PMR are recorded [20]. In addition, the PMR activity score is recorded at baseline and after one and two years [25]. Since no validated remission criteria for PMR exists, in this study, remission is defined as absence of PMR activity evaluated by the doctor based on symptoms and clinical

examination combined with a CRP level below 8.0 mg/l at the one- and two-year visit (exceptions can be made if an elevated CRP level is assessed to be explained by an ongoing infection at the sample time). Sustained prednisolone free remission at 65 months is assessed in patients who were in remission at the 1 year visit. If these patients have not been in contact with the hospital nor their general practitioner with relapse of symptoms and prednisolone has not been resumed according to questionnaires, sustained remission is assumed.

Vascular ultrasonography

Vascular ultrasound is accessed at baseline and after one and two years. A high-end ultrasound scanner with a linear probe is used. The right and left common superficial temporal artery, its parietal and frontal branch, and axillary artery are evaluated. Vasculitis is defined as a hypo-echoic wall swelling in both longitudinal and transverse view and in cranial arteries vasculitis is confirmed by compression sign [26]. The one- and two-year visit will either be performed at the inclusion study site or by the principal investigator at Aarhus University Hospital.

Patient reported outcome measures/Questionnaires

Every 3 months a questionnaire will be send electronically via REDCap, patients not able to fill out an online questionnaire will receive a phone questionnaire carried out by the principal investigator or a doctor/nurse/secretary assigned by the principal investigator. This questionnaire (See Appendix 2) will include:

- Current prednisolone dose
- Weekly prednisolone dosages since last questionnaire
- Weight
- New medications
- Adverse effects to prednisolone
- Duration of morning stiffness (minutes)
- PMR related symptoms including patient reported relapse
- Global-VAS, PMR-VAS, fatigue VAS, stiffness VAS
- SF-36
- HAQ-DI
- EQ-5D-5L

Patients who fail to report back on the questionnaires within two weeks, will receive a phone call by the principal investigator/project nurse/secretary/doctor.

Prednisolone dosage information

The patient will weekly fill in the current prednisolone dose in a standard scheme. In relation to the questionnaires the patients will then report the weekly doses for the last 3 months.

DXA

DXA scan is performed according to usual clinical practice.

Blood samples

Routine samples

Differential diagnostic evaluation at baseline: Creatine kinase, p-25-hydroxy vitamin D2+D3, Thyroid-stimulating hormone, ca^{2+}, M-component, kappa and lambda chains, immunoglobulin A, G and M, rheumatoid factor, anti citrullinated protein antibody, alkaline phosphatase, HgbA1C.

Biochemical routine tests performed at baseline for both groups and hereafter every 4 weeks for the group receiving a structured taper: CRP, ESR, creatinine, alanine aminotransferase, platelet count, haemoglobin, white blood cells, absolute neutrophil count, absolute lymphocyte count.

Research samples

The blood samples are collected by the Danish Reuma Biobank (DRB) under the regional Bio-and Genome Bank Denmark (RBGB). Immediately after sampling, blood samples are sent to the nearest biochemical department with a collaboration agreement with DRB for processing. Afterwards the samples are handled, registered and stored in DRB. Material will be reserved for this project. Material for analysis in the project is then provided by DRB to the project's research biobank.

A research biobank for blood samples will be established for the project, with an expected start on the 1st of March 2022 and an expected expire on the 31st of December 2028 at study termination. The following will be evaluated: C-reactive protein, HgbA1c, Multiplex immunoassay for cardiovascular and inflammatory biomarkers (Olink, Upsala, Sweden). A total of 300 ml is collected throughout the study. Excess material from the research biobank is transferred to a biobank for future research at study termination. The material in the biobank for future research is stored until 31st of December 2040. At that time point the material is either destroyed or anonymised. The biobank for future research is registered in the Danish Central Region internal list of research projects. The research biobank and the biobank for future research both conforms to The Danish law concerning patient confidentiality (Databeskyttelsesloven) and the General Data Protection Regulation (Databeskyttelsesforordningen).

Practical feasibility

This project is planned to start in March 2022. Inclusion of subjects will begin when written permissions have been granted. The inclusion period is expected to last 24 months. The project is expected to end in January 2029.

3.3.2 Data Management

Before informed consent, information from the patient journal concerning symptoms, blood tests, inclusion criteria, and exclusion criteria can be passed from a person designated by the investigator. The information will be passed to an investigator in order to determine if the patient may be suitable for the study. After informed consent from the patient, information about demographic, comorbidities, medication, and results from the routine blood samples (incl. HgbA1C) and DXA scan is retrieved from the electronic patient journal (EPJ). Information about medications will also be retrieved from "Fælles Medicin Kort" (FMK). Informed consent gives the investigators, sponsor and representatives of the sponsor direct access to retrieve information in the patient journal etc., including the electronic patient journal, for the purpose of managing information regarding the patients general health data, which is necessary as part of completing the project as well as monitoring, including self-monitoring, quality control and general study monitoring in which they are obligated to perform. The study conforms to The Danish law concerning patient confidentiality (Databeskyttelsesloven) and the General Data Protection Regulation (Databeskyttelsesforordningen). All of the data mentioned above are considered source data. All information is documented in REDCap.

3.3.3 Statistical methods

All 95% confidence intervals and *P* values will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyse the key secondary outcomes in a prioritised order (i.e. "gatekeeping procedure"): The analyses of the key secondary outcomes will be performed in sequence until one of the analyses fails to show the statistically significant difference, or until all analyses have been completed at a statistical significance level of 0.05. The key secondary statistical tests will be reported with P values for hypothesis tests and claims of statistical significance. P-values (two sided) less than 0.05 will be considered statistically significant.

The primary analyses will be based on the Intention to Treat (ITT) population. The ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence). Accordingly, participants allocated to a treatment group (taper vs usual care) should be followed up, assessed and analysed as members of that group, irrespective of their adherence to the planned course of treatment (i.e., independent of withdrawals and cross-over phenomena).

The statistical objectives of a repeated measures design are to make inferences about the expected values of the observations, that is, about the means of the populations from which participants are sampled. This objective is achieved by taking into account treatment group and time effects in the model (Group×Time). Data will be analysed, with the particular outcome variable (Y_i) at baseline level ($Y_{0,i}$) as a covariate, using a

multilevel repeated measures mixed-effects model with participants as the random effects factor based on a restricted maximum likelihood (REML) model, while other covariates are handled as fixed effect factors.

Missing Data and the Repeated Measurements Using Mixed Models: As stated above, our primary analyses will be based on the ITT population, including all randomised participants with available data at baseline. Missing data will be handled indirectly and statistically modelled using repeated-measures linear mixed models (see below). These models will be valid if data are '*Missing at Random*' (MAR), where "*Any systematic difference between the missing values and the observed values can be explained by differences in observed data*" [27].Contrasts between groups will be estimated based on repeated-measures analysis of covariance applied in mixed effects linear models (i.e., at 52 weeks from baseline).

For continuous outcomes (e.g., Y_i score) will be the response (dependent) variable, and the baseline value (one for each participant), treatment group (two levels), and time will be included as covariates, as well as the interaction between treatment group and time; Patient ID will be handled as a random effects variable. As the study design was based on a stratified randomization technique, we will also adjust for the three stratification variables. This statistical model holds all between-group comparisons at all assessment points up to 52 weeks from baseline (including baseline) and allows for evaluation of the average effect, as well as the trajectory over time from baseline to the 52-week follow-up.

Categorical outcomes for dichotomous endpoints will be analysed with use of logistic regression with the same fixed effect factors and covariates as the respective analysis of continuous endpoints. Since Odds Ratios (ORs) for outcomes of common incidence either over- or under-estimate the corresponding risk estimate, we will convert all the calculated OR values and 95% confidence intervals into approximate Risk Ratios (RR) in the text. This approach will also allow us to calculate numbers-needed-to-treat (NNTs) and numbers-needed-to-harm (NNHs) for efficacy and safety outcomes by dividing 1 by the risk difference that can guide clinicians in their decision making.

3.3 Monitoring

3.3.1 Data monitoring

If questionnaires are left unreported by the study participants a reminder will be send via REDCap to the principal investigator who will then facilitate contact to the participants by phone to ensure all questionnaires are reported.

3.3.2 Harms

Harms are stated below in section 4.1

4 Ethics and dissemination

4.1 Research ethics approval

The study conforms to the Danish law concerning patient confidentiality (Databeskyttelsesloven) and the General Data Protection Regulation (Databeskyttelsesforordningen). Approval will be provided from the Central Denmark Region Committee on Health Research Ethics and the project registered in the Danish Central Region internal list of research projects before the recruitment of research subjects. Furthermore the study will be registered at ClinicalTrials.gov.

Prednisolone treatment

The treatment with prednisolone and the tapering strategy is in both groups prescribed in accordance to standard clinical practice described in national and EULAR guidelines [13, 14]. Both of the tapering strategies (hospital managed vs. general practitioner managed) is within what is currently offered at Danish hospitals.

DXA scan and osteoporosis prophylaxis

DXA are conducted in accordance with normal clinical practice. Vitamin D and Calcium are administered in accordance to standard clinical practise. If DXA scans reveals osteopenia or osteoporosis, alendronate treatment will be administered according to standard clinical practise.

Blood samples

Blood samples from the baseline visit as well as the 4th weekly blood samples in the "Treat-to-target prednisolone taper" group are conducted in accordance with normal clinical practise. The same applies to the blood samples conducted from general practitioners in the "usual care" group.

Both groups will have blood samples conducted every 3 months for the study biobank. Obtaining these samples can be associated with minimal pain as well as minimal risk of infection.

Ultrasound

Ultrasound is often used as part of the diagnostic workup for both PMR and GCA but is usually not performed in all patients. In this study it is assessed a benefit that all patients undergo ultrasound examination, because of the more thorough examination. The examination lasts approximately 30 minutes. No known harms are associated with this examination.

Based on the above, it is assessed that the risk of participating in the study is very limited. Both groups receive treatment according to normal clinical practice as well as following the current national guidelines. Yet the two approaches have never been compared and it is in the opinion of the investigators that this study will contribute to improve the clinical practice in this field in the future and any potential risks or side effects

are offset by the expected benefits of carrying out the study, which is therefore considered ethical and relevant.

Protocol amendments

All modifications to the protocol are reported to The Central Denmark Region Committee on Health Research Ethics and the Danish Central Region internal list of research projects.

4.2 Consent or assent

If the patient decline to participate it will not affect the further treatment of the patient. Information about the trial is given at an already scheduled appointment in the outpatient clinic or hospital ward. All information is provided by an investigator or by a person designated by the investigator. Patients who are interested in participating in the trial will be invited to a meeting with an investigator. Here, the patient will receive full oral and written information in uninterrupted surroundings and have the opportunity to ask questions. The patients are informed of their right to bring a friend or relative to the conversation beforehand and will at the meeting be offered 24 hours to consider their decision unless they do not want time to consider. The informed consent form is signed and dated by both the trial subject and the investigator. The participant receives a signed copy of the informed consent form and the original is kept in the participant's case record form. The patient may, at any time and without giving a reason, withdraw his or her consent. Withdrawal of consent will not affect the further treatment of the patient. The informed consent grants the investigator and relevant control authorities direct access to relevant health information during conduct of the study and for control purposes.

4.3 Confidentiality

All data including patient information is recorded in Research Electronic Data Capture (REDCap). The law on the processing of personal data is followed. Patients' informed written consent is collected before participation in the study. Patient information is protected in accordance with the Danish law concerning the processing of personal data. Approval must be provided by the Danish Central Region internal list of research projects. The research biobank conforms to the Danish law concerning patient confidentiality (Databeskyttelsesloven) and the General Data Protection Regulation (Databeskyttelsesforordningen).

4.3 Declaration of interests

Financial contributors do not influence the study implementation or publication of results. There is a continuous search for funding from other funds. If such funding is granted, an amendment to the protocol will be submitted to The Central Denmark Region Committee on Health Research Ethics.

The funds have no influence on study design, data handling, analyses, or presentation of data. The project manager has no financial association with the funds. No investigators have any conflicts of interest. Patients included in the trial will not be honored for participation.

The project was initiated on the initiative of the research group of this protocol.

4.4 Access to data

All source data will be accessible for Inspection by the Danish Health and Medicine Authority. Patient data and informed consent forms will be stored for 18 years and then destroyed, fully anonymized, or submitted to the State Archives. The Data protection regulation and the Data Protection Act are complied with at all times.

4.5 Ancillary and post-trial care

The Patient Compensation Association covers patients who against all expectations, should be injured in the study.

4.7 Dissemination policy

Positive, negative, and inconclusive results will be published in high-ranking international peer-reviewed journals. The reporting of results will adhere to the CONSORT guidelines for RCT studies [28]. MD Christoffer Søvsø Våben will be the first author on all publications. MD, PhD Kresten Keller will be senior author. Ellen-Margrethe Hauge and Robin Christensen will be co-authors. Furthermore, each trial centre will be assigned 1 co-authorship per paper per 10 patients who completes the trial. Authorship for other co-authors is awarded according to the Vancouver guidelines for authorship. This protocol will be published on ClinicalTrials.gov.

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