

BMJ Open Can the painDETECT Questionnaire score and MRI help predict treatment outcome in rheumatoid arthritis: protocol for the Frederiksberg hospital's Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME-cohort) study

Signe Rifbjerg-Madsen,¹ Anton Wulf Christensen,¹ Mikael Boesen,^{1,2} Robin Christensen,¹ Bente Danneskiold-Samsøe,¹ Henning Bliddal,¹ Else Marie Bartels,¹ Henning Loch,³ Kirstine Amris^{1,3}

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For numbered affiliations see end of article.

Correspondence to

Dr Signe Rifbjerg-Madsen; signe.rifbjerg-madsen.02@regionh.dk

ABSTRACT

Introduction: Pain in rheumatoid arthritis (RA) is traditionally considered to be of inflammatory origin. Despite better control of inflammation, some patients still report pain as a significant concern, even when being in clinical remission. This suggests that RA may prompt central sensitisation—one aspect of chronic pain. In contrast, other patients report good treatment response, although imaging shows signs of inflammation, which could indicate a possible enhancement of descending pain inhibitory mechanisms.

When assessing disease activity in patients with central sensitisation, the commonly used disease activity scores (eg, DAS28-CRP (C reactive protein)) will yield constant high total scores due to high tender joint count and global health assessments, whereas MRI provides an isolated estimate of inflammation.

The objective of this study is, in patients with RA initiating anti-inflammatory treatment, to explore the prognostic value of a screening questionnaire for central sensitisation, hand inflammation assessed by conventional MRI, and the interaction between them regarding treatment outcome evaluated by clinical status (DAS28-CRP). For the purpose of further exploratory analyses, dynamic contrast-enhanced MRI (DCE-MRI) is performed.

Method and analysis: The painDETECT Questionnaire (PDQ), originally developed to screen for a neuropathic pain component, is applied to indicate the presence of central sensitisation. Adults diagnosed with RA are included when either (A) initiating disease-modifying antirheumatic drug treatment, or (B) initiating or switching to biological therapy.

We anticipate that 100 patients will be enrolled, tested and reassessed after 4 months of treatment.

Data collection includes: Clinical data, conventional MRI, DCE-MRI, blood samples and patient-reported outcomes.

Strengths and limitations of this study

- Frederiksberg hospital's Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME) is the first prospective cohort study in an rheumatoid arthritis (RA) population, which examines the prognostic value of the painDETECT score (ie, presence of central sensitisation) on treatment outcome.
- The FRAME study is adding new knowledge to the research fields within central sensitisation and dynamic contrast-enhanced (DCE-MRI) in RA.
- The FRAME study is limited by a heterogeneous RA population and 4 months of follow-up time.

Ethics and dissemination: This study aims at supporting rheumatologists to define strategies to reach optimal treatment outcomes in patients with RA based on chronic pain prognostics. The study has been approved by The Capital region of Denmark's Ethics Committee; identification number H-3-2013-049. The results will be published in international peer-reviewed journals.

INTRODUCTION

Rheumatoid arthritis (RA) is a condition characterised by synovial inflammation, joint destruction and pain. In spite of the increased focus on treat-to-target over the past 10 years,^{1–4} some patients with RA still report pain as a major concern.⁵ In a recent study, 12% of patients with RA in stable Disease Activity Score 28 C reactive protein (DAS28-CRP) remission for 1 year continued to report clinically significant pain.⁶ Other

studies have shown that RA leads to widespread pain and pain hypersensitivity in 10–20% of patients, and that these cases are associated with poorer treatment outcomes.^{7 8} This distinct pattern of persistent pain in some patients with RA has led researchers to hypothesise that synovial inflammation may prompt central sensitisation.⁹ In the presence of tissue inflammation, the responsiveness of peripheral and central neurons increases and elicits pain hypersensitivity with features of allodynia and hyperalgesia.^{10 11} This is a normal response reflecting neuroplasticity.¹² The question is whether central sensitisation may persist in subsets of patients and lead to chronic pain states in which pain is no longer coupled to ongoing synovial inflammation.

In contrast to RA patients with chronic pain states who report constant high tender joint count, and high global health assessments and visual analog scale (VAS)_{pain} score, another subset of RA patients indicate good treatment effect on self-reports despite disease activity according to, for example, imaging.¹³ It could be speculated whether descending pain inhibitory mechanisms^{12 14} are predominant in this particular subset of patients with RA, or whether their low-pain reporting is a result of other cognitive pain-coping mechanisms.

In patients with central sensitisation, estimation of disease activity alone by application of DAS28-CRP might lead to misinterpretation. A high DAS28-CRP composite score may be inflated by higher tender joint count and patient-reported global health assessments, which in this case will remain refractory to effective anti-inflammatory therapy. MRI represents a more objective and sensitive method than DAS28-CRP to assess inflammation.¹⁵ The most commonly used MRI scoring system is the OMERACT RA MRI Scoring (RAMRIS) system based on postcontrast imaging acquisition.¹⁶ It includes synovitis and bone marrow oedema (BME) scores, which are reliable and responsive in detecting treatment changes. RAMRIS also includes an erosion score.¹⁷ Dynamic contrast-enhanced MRI (DCE-MRI) is an imaging technique where MRI sequences are acquired sequentially and rapidly prior to and during the infusion of a contrast agent. This technique correlates better with the histopathological findings of synovial inflammation than the conventional postcontrast MRI.^{18–22}

It is of value for the rheumatologist to be able to assess the presence of central sensitisation, especially when confronted with a patient with few clinical signs of inflammation. Possible central sensitisation needs to be taken into account when balancing expectations during shared decision-making with the patient prior to initiating medical therapy. In patients with persistent pain primarily caused by altered central pain processing, treatment strategies targeting underlying pain mechanisms are warranted.

With the painDETECT Questionnaire (PDQ), the rheumatologist may have an easily applicable and prognostic useful tool to judge the possible treatment outcome of anti-inflammatory treatment.

Rationale and hypothesis

The PDQ was developed and validated in 2006 for the purpose of establishing a screening tool to detect the likelihood of a neuropathic pain component being present in individual patients. A validated algorithm was developed to be able to calculate a score with a range from 0 to 38. A score ≥ 19 indicates that the presence of a neuropathic pain component is likely. A score ≤ 12 indicates that it is not therefore reflecting other pain mechanisms. A score of 13–18 is considered ambiguous.²³

Subsequent analyses of the somatosensory symptoms reported in the PDQ of 3057 patients with either diabetic neuropathy, representing prototypical neuropathic pain, or fibromyalgia, representing prototypical central sensitisation, revealed very similar somatosensory phenomena.²⁴ The PDQ score has also been shown to correlate with the tender point count and pressure-pain thresholds in a population with chronic widespread pain,²⁵ and to clinical manifestations of central sensitisation in a cohort of patients with osteoarthritis.²⁶ To the best of our knowledge, only one small study has shown PDQ data in relation to inflammatory joint disease. Their results suggest that back pain in ankylosing spondylitis is a mixed pain condition that includes a neuropathic pain component.²⁷

In our study, we consider conventional MRI to reflect objectivity when assessing joint inflammation. We interpret a total PDQ score ≥ 19 as a sign of central sensitisation, in most cases indicating that pain perception is no longer coupled to ongoing inflammatory activity. A total score ≤ 12 is interpreted by us as a sign of a nociceptive pain phenotype arising from local inflammation. We consider a score of 13–18 uncertain; a neuropathic pain component cannot be ruled out, but will not be included in our prediction model. Both patients with reversible central sensitisation, a normal phenomenon seen in some patients in relation to inflammation, and patients with irreversible central sensitisation¹² are expected to have a total PDQ score ≥ 19 . To be able to separate the two groups, we will take a possible interaction between the baseline total PDQ score ≥ 19 and synovitis load defined by the hand RAMRIS score into account.

We hypothesise that a total PDQ score ≥ 19 at baseline can predict a poorer clinical treatment response (DAS28-CRP, VAS_{pain}) when initiating anti-inflammatory treatment in patients with RA.

Objectives

The objective of this study is to examine whether the PDQ score, the RAMRIS synovitis score, and the interaction between them are possible prognostic factors for treatment outcome, primarily assessed by a change in DAS28-CRP, in patients with RA initiating any anti-inflammatory treatment.

METHODS

Study design

The 'FRAME cohort' (Frederiksberg hospitals Rheumatoid Arthritis, pain assessment and Medical Evaluation) study is a closed cohort study with an expected inclusion period from 1 March 2013 to 1 September 2014, followed by 4 months of follow-up. Owing to administrative delays PDQ and conventional and DCE-MRI were not added to the examination program before 1 May 2013. Participants will have a baseline visit before initiation, or during the start of treatment, and one follow-up visit after approximately 4 months (figure 1), in order to evaluate the clinical treatment effect, in line with normal clinical practice in Denmark. All information is recorded and all examinations are carried out at a single centre. The examination programme is performed in 1 day with the order of assessment being the same each time.

Participants

Participants entering this study are recruited from three hospital sites: Frederiksberg Hospital, Gentofte Hospital

and Køge Hospital, and from private rheumatology clinics in the Copenhagen area. To be eligible, participants must be ≥ 18 years and diagnosed with RA according to the 1987 or 2010 ACR criteria^{28 29} and either (A) initiate treatment with any DMARD and have been without treatment 6 months prior to initiation (including newly diagnosed with RA) or (B) initiate or switch to biological treatment.

Potential participants are identified by SRM, AWC or site managers. The decision to initiate or change to biological treatment is taken collectively by senior rheumatologists at the department's biologics conference where representatives of the study are also present. Only SRM and AWC are screening potential participants for eligibility (figure 1), and informed consent is obtained prior to the baseline visit.

Exclusion criteria, treatment responsibility and the drop out procedure are thoroughly described elsewhere by the coauthor AWC.³⁰ The main exclusion criteria are: no consent, diagnosed condition with a risk of neuropathy (eg, diabetes), treatment with intramuscular or

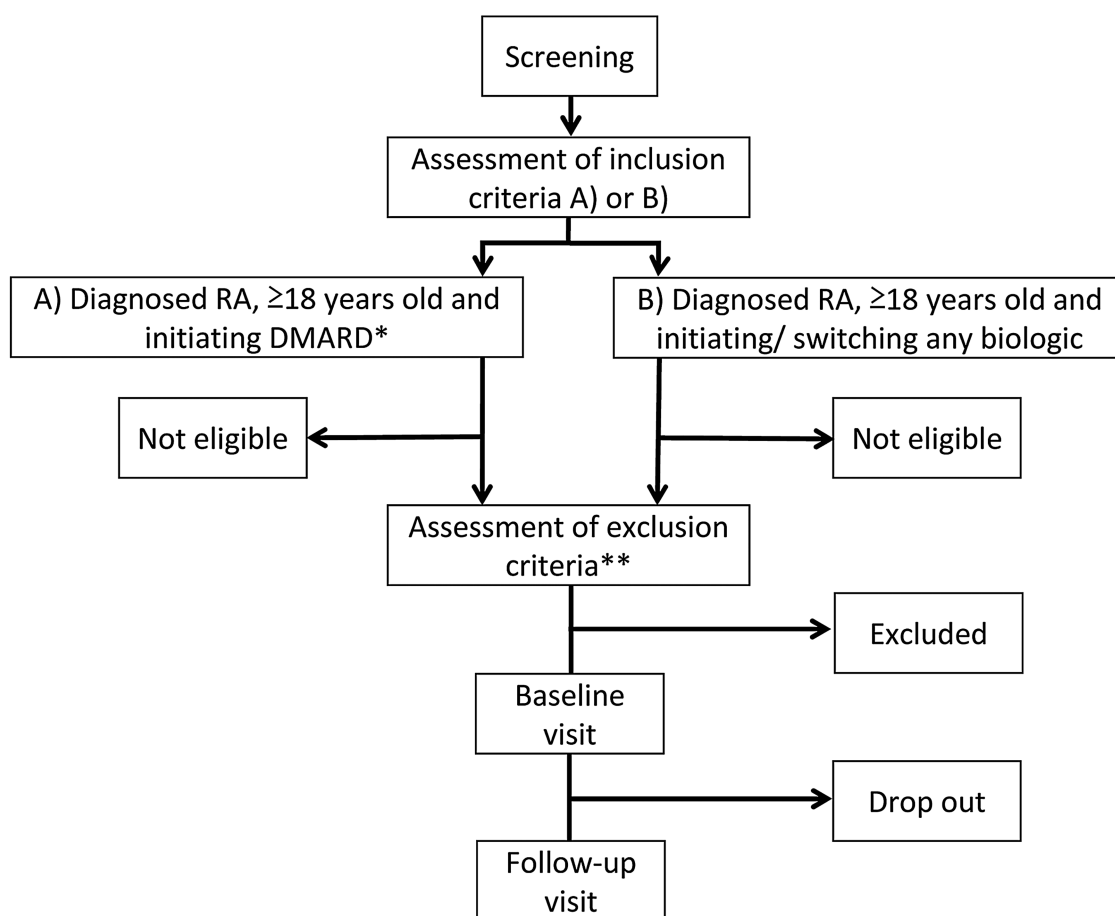


Figure 1 Overview of participant flow. * Either DMARD naïve or untreated with DMARD ≥ 6 months. **Exclusion criteria, 1. No consent 2. Pregnancy 3. Do not understand Danish 4. Other known inflammatory rheumatic diseases 5. Diagnosed with a condition with risk of neuropathic pain 6. Claudicatio intermittence 7. Intra-articular or intramuscular corticosteroids given < 3 weeks 8. Treatment with oral corticosteroids at doses equivalent to more than 10 mg prednisolone/day < 3 weeks 9. Inability to suspend usage of central acting analgesics 1 week prior to examination 10. Inability to suspend usage of mild analgesics 24 h prior to examination 11. For (A) treatment with DMARD > 3 weeks 12. For (B) treatment with any biological > 1 week 13. Contraindications for MRI. RA, rheumatoid arthritis.

Table 1 Summary of measures to be collected

		Baseline	4 months
Demographics			
Sex (male/female),		X	–
Age (years)		X	–
Disease duration (months)		X	–
Height (cm)		X	–
Weight (kg)		X	X
Medication			
MTX dose (mg/week)		X	X
Other current DMARD therapy (yes/no)		X	X
No. of previous biologics used (if any)		X	–
Name of current biological agent		X	–
Number of treatment weeks since baseline		–	X
Dose of oral prednisolone at assessment week (mg/week)		X	X
Dose of oral prednisolone 1 week prior to assessment week (mg/week)		X	X
Dose of oral prednisolone 2 weeks prior to assessment week (mg/week)		X	X
Intra-articular glucocorticoid injections in the previous 3 months (no.)		X	X
Intramuscular glucocorticoid injection in the previous 3 months (mg)		X	X
Consumption of analgesics*		X	X
Clinical examination			
Blood pressure (mm Hg)		X	X
46 swollen joint count		X	X
46 tender joint count		X	X
Swollen joint count/tender joint count ratio		X	X
Manual tender point examination		X	X
DAS28-CRP		X	X
Patient-reported outcomes			
PDQ		X	X
HAQ†		X	X
SF-36		X	X
GAD-10		X	X
MDI		X	X
VAS _{fatigue}		X	X
Transition questionnaire		–	X
Ultrasound Doppler activity			
Semi-quantitative scoring system (Doppler score)		X	X
Quantitative scoring system (colour fraction)		X	X
MRI			
RAMRIS		X	X
DCE-MRI analysed by DYNAMIKA (http://www.imageanalysis.uk.org)		X	X
CPA measurements			
Pain threshold		X	X
Pain tolerance		X	X
VAS _{pain} limit		X	X
Temporal summation		X	X
Blood samples		mL blood	
Glass 1‡	CRP, ALAT, alkaline phosphatase, creatinine, estimated GFR, sodium, potassium	4.0	X
Glass 2‡	Haemoglobin, erythrocyte volume fraction MCHC, MCV, leucocytes, differential count, thrombocytes,	4.0	X
Glass 3	IgM-RF, anti-CCP	4.0	X

*Registered by self-report as weak or strong analgesics rated in four categories (never, <1 per week, 1–3 times per week, 4–7 times per week). †VAS_{pain}, VAS global health included.

‡Will not be repeated if already taken within the past week.

ALAT, alanine aminotransferase; anti-CCP, anticitrullinated protein antibodies; CPA, computerised cuff pressure algometry; CRP, C reactive protein; DAS28-CRP, Disease Activity Score 28 C reactive protein; DCE-MRI, dynamic contrast-enhanced MRI; GAD-10, generalised anxiety disorder 10 items; GFR, glomerular filtration rate; HAQ, Health Assessment Questionnaire; IgM-RF, immunoglobulin-M rheumatoid factor; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MDI, Major Depression Inventory; MTX, methotrexate; PDQ, painDETECT Questionnaire; RAMRIS, RA MRI Scoring system; SF-36, Short form 36 items health survey; VAS, visual analogue scale.

intra-articular glucocorticoids given within 3 weeks or an oral daily dose of prednisolone above 10 mg, and contraindications for MRI. Finally, treatment with a DMARD or biologics must not have been initiated more than 3 weeks or 1 week, respectively, prior to the baseline visit.

Variables and outcome measures

Participants undergo an examination programme extracting the variables shown in [table 1](#). The primary outcome is a change in DAS28-CRP. Secondary outcome variables are VAS_{pain} and the RAMRIS synovitis and BME score of wrist and metacarpophalangeal (MCP) joints. When accounting for inflammation load, the RAMRIS synovitis score is primarily chosen. On an exploratory basis, change in disease activity detected by DCE-MRI will be analysed.

As described elsewhere, the response according to the European League Against Rheumatism (EULAR) response criteria, transition questionnaire score, and changes in the following variables will also be explored: DAS28-CRP subcomponents, number of tender points assessed by a manual tender point examination, Health Assessment Questionnaire (HAQ) total score, Major Depression Inventory (MDI) score, generalised anxiety disorder 10 items (GAD-10) score, Short Form 36 items (SF-36) mental and physical composite scores, VAS_{fatigue} and CRP.³⁰

Clinical examination and blood samples

A 46-joint count (44 joint index with the addition of the temporomandibular joints) *ad modum* EULAR and a manual tender point examination according to the guidelines in the 1990-American College of Rheumatology (ACR)-criteria for fibromyalgia are performed by a trained healthcare professional.³¹ As specified in [table 1](#), medication variables are recorded and blood pressure is measured. Blood samples are taken by a trained laboratory technician and treated according to set procedures.

Patient demographics and patient-reported outcomes

The PDQ has been translated into 19 different languages, including Danish. It is composed of questions regarding pain intensity (three numeric rating scales, pain course pattern, a pain drawing reflecting pain radiation, and seven questions addressing somatosensory phenomena which the patient rates on a six-category Likert scale (never—very strongly). A score ranging between 0 and 38, based on the patient's answers in the questionnaire, is calculated. For diagnostic purposes, a validated algorithm has been developed. A painDETECT score ≥ 19 indicates that a neuropathic pain component is likely, a score of 13–18 is considered uncertain, and a score ≤ 12 indicates that a neuropathic pain component is unlikely; resulting in three categories of patient pain characteristics. The PDQ is applicable to touch screen devices.^{32 33}

For a comprehensive description and overview of the single questions (items) in the questionnaire, we refer to the original article by Freynhagen *et al.*²³ The

questionnaire can be acquired from <http://www.pfizerpatientreportedoutcomes.com>.

A detailed description of patient demographics and all other patient reported outcomes has been published elsewhere by the coauthor AWC.³⁰

Conventional and DCE-MRI

The most painful hand, as reported by the patient, is chosen for conventional and DCE-MRI examination. In case of no difference, the dominant hand is chosen. The examination is carried out in a 3 T Siemens Verio MR scanner with the patient supine and the target hand along the side of the body (3 T Verio), using a semiflex 15-channel body coil and the following protocol: gradient echo scout (GRE) (slice thickness (ST) 6 mm, field of view (FOV) 400×400 mm, time to echo (TE) 3.69 ms, repetition time (TR) 7.8 ms, scan time 17 s), coronal T1-weighted (T1W) turbo spin echo (TSE) (ST 1.5 mm, FOV 250×250 mm, matrix resolution 0.3×0.3×1.5 mm, TE 25 ms, TR 832 ms, scan time 4 min 28 s), coronal short-tau inversion recovery (STIR) (ST 2.5 mm, FOV 180×180 mm, matrix resolution 0.9×0.8×2.5 mm, TI 220 ms, TE 32 ms, TR 4500 ms, scan time 2 min 48 s), axial STIR covering the wrist and MCP joints (ST 5 mm ST, FOV 180×180 mm, matrix resolution 0.6×0.6×5 mm, TI 220 ms, TE 32 ms, TR 4500 ms, scan time 2 min 30 s), gradient echo three-dimensional (3D) T1W volumetric interpolated breath-hold examination (VIBE) (ST 0.9 mm, FOV 250×250 mm, matrix resolution 0.9×0.9×0.9 mm, Flip angle (FA) 10°, TE 6 ms, TR 13.5 ms, scan time 2 min 35 s). Simultaneously with the intravenous injection of 0.1 mL/kg body weight gadolinium contrast (Dotarem, Guerbert United, <http://www.guerbet.co.uk>) using a power injector (2 mL per second), a sequential coronal DCE-MRI gradient echo T1W (VIBE) sequence will be performed in 18 3 mm slices every 9 s, with 30 repetitions using the following parameters: TE 1.86, TR 5.51 FA 15°, matrix resolution 256×256, total scan time 4 min 40 s) covering the whole hand. Following the DCE-MRI sequence, the 3D T1W VIBE sequence will be repeated. Total imaging time will be approximately 30–35 min.

Image evaluation

Conventional coronal and axial STIR and 3D coronal T1W gradient-echo VIBE (GRE VIBE) precontrast and postcontrast images will be used for RAMRIS scoring. Three positions in the wrist and MCP joints 2–5 will be assessed according to the OMERACT RAMRIS recommendation and will be scored for synovitis (0–3) and bone oedema (0–3) with a total RAMRIS score of 0–21.^{16 34 35} The RAMRIS score has to alter by more than 1 unit to be considered a change. All images will be assessed blinded and paired by the same senior radiologist (MB).

Analysing the DCE-MRI data

The sequential coronal T1W GRE DCE-MRI images will be analysed using the software DYNAMIKA (<http://www>.

imageanalysis.uk.org),³⁶ applying previously published, standard methods.^{37–39}

Sample size considerations and statistical analyses

This study is designed as an exploratory study. It is anticipated that 100 participants are likely to be included during a period of 1 year and 4 months with an even distribution of patients with primarily newly diagnosed RA initiating disease modifying antirheumatic drug (DMARD) treatment and patients with established disease initiating or switching biological treatment (ie, all patients are included in the FRAME-cohort study protocol that has already been published).³⁰ Anticipating a common SD of 1.5 and the correlation between the pre-scores and postscores being $r=0.3$ for a paired *t* test with a two-sided significance level of 0.05, a sample size of 100 pairs has a power of 80% (0.797) to detect a mean change of 0.5 DAS28-CRP units. This we consider to be a conservative estimate.^{40–44} We will use SAS software (V.9.3; SAS Institute Inc., Cary, North Carolina, USA) in all analyses; the PROC UNIVARIATE statement will be used to summarise the data, and the PROC CORR (Spearman) statement will be used for the correlation analyses. When evaluating the data distributions of the continuous outcomes, we will use visual inspections of the studentised residuals to suggest whether the assumption of normality is reasonable. We will conduct the primary analyses based on the ‘full analysis set’ in agreement with the intention-to-treat principle; that is, all participants who enter the study, even if some withdraw during the study period, will be analysed. Any missing data at follow-up will be imputed with a non-responder assumption—using the baseline observations carried forward technique. We consider *p* values less than 0.05 to be statistically significant.

The descriptive statistics and data reporting will be parallel to what have been described elsewhere by AWC³⁰ and will be reported according to the “Enhancing the QUALity and Transparency Of health Research” (EQUATOR) network⁴⁵ and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.⁴⁶

To study the prognostic value of the PDQ score in relation to changes in DAS28-CRP, a multivariable regression model will be used to be able to, at the same time, account for inflammation defined by the baseline RAMRIS synovitis (ie, the ‘crude model’). The model will be handled using the analysis of covariance fitted in SAS using PROC GLM. Finally, the crude model will be adjusted for the following confounders: age (years), sex (male/female), disease duration (months), disease activity, group (A vs B), anti-citrullinated protein antibodies positive (yes/no) and concomitant prednisolone (ie, the ‘adjusted model’).

DISCUSSION

This study will contribute to the understanding of the role of central pain mechanisms in RA by determining

the prognostic value of the PDQ score on clinical and MRI outcomes following treatment initiation with any DMARD or biologics (including switch).

We primarily aim to describe the relationship between central sensitisation and treatment outcome. However, with the planned study design, we will also be able to describe a possible subgroup of patients with reported low tender joint count, and low global health assessment and VAS_{pain} score, but having inflammatory activity on MRI.

Furthermore, the study will contribute to the field within DCE-MRI by producing knowledge concerning detectable change in the inflammation load in a heterogeneous RA population as seen in daily rheumatological care, thus having a potential of generalisable interpretation. Knowledge about the presence of central sensitisation as an underlying pain mechanism may be useful for rheumatologists when treating patients with few obvious signs of inflammation and a high DAS28-CRP score primarily derived from patient reported information, such as high tender joint count and/or persistent pain. The PDQ is composed of 13 questions and takes about 5 min to fill in, which makes it a usable tool in daily clinical practice, potentially giving the rheumatologist a quick screening opportunity which will contribute independently of other measures to the overall clinical assessment of the patient.

Awareness of the possible reduced treatment effect of anti-inflammatory therapy in this group of patients is important, not only for the individual patient who can avoid potentially serious side effects, but also from a health economic perspective, since treatment with biologics is very costly. Finally, this study can help to set focus on the fact that clinical pain management in patients with RA may benefit from a shift from symptom-based approaches to an approach targeting underlying pain mechanisms.

This study design has certain possible limitations: when assessing disease activity by carrying out MRI of only one hand, there is a risk of underestimating the inflammation load in those patients with a non-typical presentation of RA. In these patients, the correct relationship between the PDQ score and inflammation may not be reflected. In the FRAME-cohort study, the patients also undergo ultrasound examination and a 46 swollen/tender joint count. This will give an indication of how many patients present with a non-typical RA disease pattern.

We aim to recruit 100 participants who are to initiate either DMARD or to initiate or switch biologics with an even distribution between the two groups. This implies that we will include a heterogeneous study population including (1) newly diagnosed patients who initiate their first DMARD, (2) patients with established arthritis who have paused DMARD therapy for at least 6 months and who are about to (re)initiate DMARD treatment, (3) patients with established arthritis who have failed conventional DMARD therapy and who are about to initiate with their first biological agent, and (4) patients with established arthritis who have failed treatment with

a previous biological agent and who are about to switch to another biological agent. Including these groups will give rise to overall heterogeneity, thereby reducing the statistical power in the subsequent analyses. However, we consider a mean change of 0.5 DAS28-CRP units (expected SD of 1.5) to be a conservative estimate,^{40–44} moreover, including diverse RA groups will add to the external validity of the study.

ETHICS AND DISSEMINATION

This study, including the amendments 38760, 41204 and 42070, has been approved by The Capital region of Denmark's Ethics Committee with the identification number H-3-2013-049. It is carried out in accordance with the Helsinki Declaration. Signed informed consent is obtained from all participants.

We aim to disseminate the results of the study through publication in international peer-reviewed journals and at international conferences.

Author affiliations

¹Department of Rheumatology, The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

²Department of Radiology, Frederiksberg Hospital, Copenhagen University Hospital, Bispebjerg & Frederiksberg, Copenhagen, Denmark

³Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

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Competing interests None.

Ethics approval Approved by The Capital region of Denmark's Ethics Committee.

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Data sharing statement No additional data are available.

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