Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: A Statistical Analysis Plan for a Prospective cohort study

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Purpose of the statistical analysis plan

The statistical analysis plan (SAP) is intended to bring the team together on the same page. The SAP adds another layer of specificity to the project; it was prepared prior to finalizing the data collection period but before reviewing data or conducting any analyses. The study was pre-registered at ClinicalTrials.gov (NCT02572700) and the study protocol published as open access.[1] The SAP was initiated after finalizing the protocol and published online (parkerinst.dk). Deviations from the pre-specified protocol are described in the SAP. The SAP contains a more technical and detailed elaboration of the principal features stated in the protocol including detailed procedures for executing the statistical analyses of the primary and secondary variables and other data, and the presentation of tables, figures and listings. Reporting of the study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [2]

Introduction

Pain is a cardinal symptom of inflammation and is considered the most influential disease manifestation in psoriatic arthritis (PsA) according to the patient's perspective.[3,4] In some patients, the usual relationship between pain and inflammatory activity abolish as widespread pain (WP) and tenderness starts to outlast the arthritic disease activity. Mounting allodynia and hyperalgesia develop in these patients and their experience of pain often gains neuropathic features such as burning, tingling, prickling, numbness.[5] This phenomenon is due to sensitization of the central (and peripheral) nervous system, where the normal pain processing cut out, resulting in exaggerated responses to afferent input and disturbed central pain modulation.[6-9], WP is a great challenge in patients with PsA since the level of inflammatory load can be obscure due to the complexity and variation of clinical manifestations. It can be difficult to determine if WP is caused by exaggerated pain processing or by unrecognized disease activity in e.g., tendons, less accessible joints, the spine, entheses and the skin. Unawareness of the origin and mechanisms of pain can lead to misinterpretation of disease activity (especially by composite scores) and erroneous treatment strategies. In research settings, structural and functional brain imaging and other advanced techniques[10,11] are useful for studying pain processing. However, no feasible gold standard exists for diagnosing central sensitization in clinical settings. The Widespread Pain Index (WPI)[12], the Tender Point Count (TPC)[13] and the PainDetect Questionnaire (PDQ)[14] represent candidate patient-reported instruments to assess features related to central sensitization such as pain distribution, widespread allodynia and neuropathic pain features. Ultrasonography (US) is a highly sensitive method to detect tissue inflammation and changes in

musculoskeletal structures.[15] Studies report that US is superior to clinical examination in detecting joint synovitis,[16,17] and enthesitis,[18] in PsA, and discrepancies between US and clinical (composite) disease activity measures have been reported.[19,20]
Based on these considerations, we set out to investigate if pain profiles and US pathology in PsA patients are of prognostic value in relation to treatment outcomes.

Data source

The current study will include prospectively collected data on patients with PsA treated in routine care who initiate a conventional synthetic- or biologic – disease modifying (cs/bDMARD) treatment due to active PsA.

Analysis objectives

Our overall scientific objective is to investigate pain profile in relation to arthritic US findings in patients with PsA, and to study the predictive value of pain profile and ultrasonographic scores on response to conventional synthetic or biologic disease modifying (cs/bDMARD) treatment.

Population

The study is designed as an exploratory, prospective observational study enrolling patients with PsA according to CASPAR criteria,[21] who initiate/switch b/csDMARDs in routine care due to active PsA. Patients complete an examination programme at baseline and after 4 months including interview, clinical, ultrasonic and para-clinical assessments as well as electronic questionnaires. The inclusion period was between 17th of September 2015 and 1st of June 2017. A flow chart (figure 1) depicts the eligibility and inclusion process.

Collected variables

Interview

Baseline

A physician (PH or CB) interviews patients regarding their PsA and psoriasis diagnoses, current and former medical treatments, demographic and lifestyle factors and known co-morbidities (physical and mental) according to the pre-specified protocol.[1] Variables of interest for are depicted in Table 1.

Follow-up

At follow-up the same physicians (PH or CB) register changes in medical treatments including reasons for withdrawal of cs/bDMARDs.

Patient reported outcome measures (PROMs)

Touchscreen questionnaires are used for completing PROMs at baseline (Table 1) and at follow-up.

The intensity of pain is assessed by a visual analogue scale (VAS) (0-100 mm). The WPI and PDQ are applied to assess the patient's pain profile; WPI[12] is applied to determines if the pain is widespread or not, and the PDQ[14,22] clarifies if nociceptive or neuropathic pain features are dominating. These measures are described in more details in a later section.

Four other disease related concepts are covered by PROMs (Table 1):
- Health related quality of life/disease impact is assessed by The Psoriatic Arthritis Impact of Disease (PsAID)[4] and the Dermatology Life Quality Index (DLQI).[23]
- Mental well-being/anxiety is assessed by Generalized anxiety disorder (GAD-10)[24] and the Medical Outcome Survey Short Form-36 mental health score (MOS SF-36 MH).[25]
-Spinal disease activity is reported by the Bath ankylosing spondylitis disease activity index (BASDAI).[26]
-Physical function is addressed by the Bath Ankylosing functional index (BASFI), the Health Assessment Questionnaire disability index (HAQ-DI)[27] and the MOS SF-36 physical function scale (SF-36 PF) and physical component summary (SF-36 PCS).[25]

At 4 months follow-up a transition score is completed indicating if patients perceive their condition as improved, worsened or unchanged.

Clinical examination

Two experienced physicians (PH, CB), properly trained to undertake PsA assessments, perform a 66/68 swollen/tender joint count, a Psoriatic Area Severity Index (PASI score), a psoriatic nail evaluation, the SPARCC enthesitis score[28] and a TPC[13] at baseline and after 4 months on all patients. The clinicians are unaware of the results of the following US examinations. Each of these clinical variables will be reported at baseline (Table 1), while the scores obtained at follow-up will only be presented as part of outcome measures of interest.

Para-clinical assessments

Laboratory tests are taken and reviewed for every patient according to the protocol.[1] Only results on inflammation (C-reactive protein > or ≤ 10 mg/L) will be presented in the current study (Table 1). Radiographic assessment (x-ray) of hands and feet are taken at baseline and evaluated by a trained radiologist to determine if radiographic PsA pathology is present or not (Table 1).

Ultrasonic assessments

Ultrasonic (US) assessment is performed the same day as the clinical examination by one of two certified sonographers unaware of the clinical results. Grey-scale (GS) and colour Doppler (CD) US are performed for 26 joints (13 unilateral) and 12 entheses (6 unilateral) per patient using a General Electric Logiq E9 (Milwaukee, Wisconsin, USA) with a linear array matrix transducer (15 MHz frequency). All ultrasound examinations are done in longitudinal projections. Hands and feet joints are scanned from both the dorsal and plantar position, the knee scan includes medial and lateral projections, and the wrists are assessed by central, radial and ulnar scans. Images and clips are stored and will be scored by two US experts (KE, JG). For the purpose of calculating the interobserver reliability for GAUS, GSAUS, GCUS (measures explained in “Primary US variables/predictors" below), the two experts will score the same 10 patients on every US parameter as depicted in table 3s. Similarly, all scans on 10 patients will be scored twice by the same rater with a time interval of 10 days to calculate the intra-observer reliability. Before the reliability tests, five US examinations will be scored by the two experts together in order to achieve consensus.

Joints

The 26 joints include the metacarpo-phalangeal (MCP) 2-3 (dorsal and plantar), proximal interphalangeal (PIP) 2-3 (dorsal and plantar) and distal interphalangeal (DIP) 2-3 (dorsal and

plantar), the wrist (central/radial/ulnar and volar projection), the knees (medial and lateral), and metarso-phalangeal (MTP) 1-3 (dorsal), and DIP 2-3 (dorsal) of the toes. Each of the 46 projections will be semiquantitatively scored 0-3 for Grey-scale synovitis (GSS) and 0-3 for CD.[29,30]

The joint will also be assessed for erosions and osteophytes. Erosions are defined by a step-down contour defect visible in transversal and longitudinal planes (scored 0-3 with 0=no erosion, 1=erosion<2mm, 2=erosion>2mm, 3=large destruction of the joint). Osteophytes are defined by a step up contour semiquantitatively scored from 0-3 (0=no osteophyte, 1= small osteophyte, 2= medium osteophyte and 3=large and diffuse osteophytes).[31]
For GSS, CD activity, erosions and osteophytes, the score per projection will be used to calculate a total Joint (J)-GSS (range 0-138), a total (J)-CD (range 0-138), a total (J)-erosion score (range 0-138) and a total (J)-ostephytes score (range 0-138).

Tendons

Extensor and flexor tendons will be independently scored at the level of MCP, PIP, DIP and wrist joints (32 projections in total). The inspection of tendon pathology will be performed within 0-1.5 cm proximally and distally to the joint line having this centrally positioned on the screen. Structural changes as well as CD signals will be scored as present/absent (0/1). The GSS scores and CD scores of each tendon will be used to calculate a Total tendon (T)-GS score (range 0-32), and total (T)-CD score (range 0-32).

Entheses

12 entheses are scanned including the distal insertion of the triceps into the olecranon (TRI), the quadriceps insertion into the upper pole of the patella (QUA), the patellar tendon proximal and distal insertions (PATprox., PATdist.), the achilles tendon insertion on calcaneus (ACH), and the insertion of facia plantaris on the calcaneal bone (FAP). Scoring will be performed based on guidelines for the Madrid Sonographic Enthesitis Index (MASEI) instructions[32] and recommendations provided by Outcome Measures in Rheumatology (OMERACT).[33] Structural changes are rated as present/absent (0/1) based on fibrillary and hypoechoic pattern. Thickening is graded present/absent (0/1) by measuring the point at the maximal thickness on the bony insertion. Calcification/Enthesophytes are defined as calcifications at the entheses insertion into bone and graded (0-3) depending on the magnitude (no/small/moderate/large calcifications). CD signals within entheses will be scored from 0-3 and the Doppler signal must be less than 2mm from the insertion. In facia plantaris CD signal is not visualized as it is absorbed in the tissue of the

heel pad. Bursitis is assessed at the distal patellar tendon (infrapatellar bursitis) and the achilles tendon insertion (retrocalcaneal bursitis) and will be graded with 0/1 (absent/present).
Finally, total (E)-Structure (range 0-12), (E)-Thickening (range 0-12), (E)-Calcification (range 0-36), (E)-CD (range 0-33) and (E)-Bursitis (range 0-12) scores will be calculated.

Main variables of interest

Primary US variables/predictors

The main US variable of interest is defined as a global acute ultrasonic score (GAUS) reported as a binary variable GAUS = 0 or GAUS > 0. The GAUS (range 0-203) will be calculated as the sum of CD scores: (J)-CD (range 0-138) + (E)-CD (range 0-33) + (T)-CD score (range 0-32).

Secondary US variables/predictors

These will include measures of global subacute ultrasonic score (GSAUS) and the global chronic ultrasonic score (GCUS) as binary variables where the median value will be the cut-off defining patients with high versus low levels of GSAUS and GCUS pathology, respectively.
The GSAUS (range 0-204) will be calculated as the sum of Joint (J)-GSS (range 0-138) + (T)-GSS (range 0-32) + (E)-Structure (range 0-12) + (E)-Thickening (range 0-10) + (E)-Bursitis (range 0-12). It was decided not to include the thickness of the distal patella enthesis when calculating the GSAUS as explained in the “protocol deviations” section below.
The GCUS (range 0-312) will be calculated as the sum of (J)-erosion (range 0-138) + (J)-ostephytes score (range 0-138) + (E)-Calcification (range 0-36).

Primary pain profile variable/ predictor

Inspired by the revised 2016 diagnostic criteria for fibromyalgia[12], we will define a widespread pain profile as having pain in at least 4 of 5 predefined body regions (generalized pain criterion) in addition to having a WPI ≥4. The WPI consist of 19 body parts supported by an explanatory body diagram, and patients indicate the body areas in which they have experienced pain during the last week, resulting in a score between 0 and 19. Patients are carefully instructed not to consider joint pain when completing the WPI. All the WPI body parts except the jaw, chest and abdomen are listed within one of the 5 predefined body regions as described by Wolfe et al.[12]

Secondary pain profile variables/predictors

Augmented pain processing will also be explored in secondary analyses by the TPC, a swollen/tender joint ratio (SJ/TJ) and the PDQ score.

While a TPC ≥11 (in addition to chronic widespread pain) indicates fibromyalgia (FM) according to the old (1990) FM criteria[13], an Italian study[34] found a TPC≥8 to discriminate between FM and PsA (sensitivity 93% and specificity 82%). We will explore this cut-off as indicator of widespread, non-arthritic allodynia in the present study.

A low SJ/TJ ratio is an indicator of excessive tenderness relative to inflammatory joint activity. A SJ/TJ <0.5 has been associated with decreased chance of treatment response in rheumatoid arthritis (RA).[35] A SJ/TJ ratio <0.5 will be explored as an indicator of augmented pain processing in the present study, and the joint count will be based on a maximum of 66 joints (hips excluded).

The PDQ[14] was develop to identify neuropathic pain features in patients with low back pain. A PDQ score between 0-12 indicates pure nociceptive pain, while scores between19-38 represent neuropathic pain features and scores of 13-18 reflect unclear/mixed pain mechanisms. The PDQ has previously been applied to study pain mechanisms in rheumatic diseases[22,36] and acceptable measurement properties of PDQ in PsA has reported.[37] In the current study we will apply a binary categorization of PDQ scores to distinguish patients with a pure nociceptive (PDQ score ≤12) from those with a mixed/neuropathic pain profile (PDQ score ≥13).

Endpoints/Response measures

Response to treatment will primarily be evaluated according to a 20% improvement in American College of Rheumatology criteria (ACR20).[38] Secondary outcomes include achievement of Minimal Disease Activity (MDA),[39] DAPSA 50% response,[40]and the patient's own rating of improvement measured by the transition score. Exploratory outcome measures will include ΔDAS28-CRP and ΔDAPSA scores, as well as change in domains of the PsA core outcome set measures with the instruments depicted in table 4.[3]

Statistical methodology and analyses

Baseline characteristics

Baseline characteristics (including demographics, comorbidities, medication, clinical and ultrasonic characteristics, patient reported outcome measures and biomarkers) will be described presenting binary outcomes as numbers with corresponding percentages, continuous outcomes as means with corresponding standard deviations (SD), and ordinal outcomes (or continuous data that are not normally distributed) as medians with corresponding interquartile range (IQR). Chi-square

tests, independent t-test or Mann-Whitney U test will be used to examine statistically significant differences in baseline characteristics between patients with a WP profile compared to patients without a WP profile, as well as for comparisons of patients grouped according to the additional pain and ultrasonic profiles.

Interobserver and intraobserver reliability

The inter- and intra-rater reliability for GAUS, GSAUS, GCUS will be quantified using the intraclass correlation coefficient (ICC).[41] ICC ranges between 0 (no reliability) and 1 (perfect reliability). Values <0.40 will be interpreted as poor reliability, 0.40 to 0.59 as fair reliability, 0.60 to 0.74 as good reliability and 0.75-1.00 as excellent reliability.[42] The ICC will be of the type ICC(2,1), i.e. based on a two-way random effects model estimating agreement with single measures.[41,43]

Treatment persistency and reasons for withdrawal

The total number and percentage of patients who continued treatment from baseline to follow-up will be reported for each pain profile (WP versus no WP). Among patients who stopped treatment during the observation period, reasons for withdrawal will be reported as either 1) adverse events or 2) lack of efficacy.

Primary analyses

The primary outcome is ACR20, coded as a binary variable. The co-primary predictors of interest are WP and GAUS, both coded as a binary variable. The primary analyses will be based on logistic regression models investigating if there is an association between ACR20 response and each of the primary predictors of interest (WP, GAUS). Furthermore, a test for interaction between GAUS and WP will be performed. Estimates will be reported from unadjusted and adjusted models, and the crude numbers of responders will be reported for each of the binary predictors. The adjusted models would ideally include all available factors that are expected to influence the result (hypothesis driven model), however, due to the relatively small sample size and risk of statistical overfitting, the models will only be adjusted for age (years) and gender (male/female). The design of the primary models is illustrated in Table 2.

Rationale for the selected confounders

Augmented pain processing seem to be more prominent in women compared to men[36,44], and it is possible that gender affects the odds of experiencing a treatment response[45-47], and hence may confound the relationship between WP pain profile (predictor) and response (outcome). Similarly, higher age may also by several pathways influence both the measures of the primary

predictors and the chance of achieving a treatment response. The primary model will not be adjusted by type of treatment received, due to risk of bias from indication for treatment.[48]

Secondary analyses

Secondary analyses will include repeating the logistic regression models using the secondary outcomes (MDA, DAPSA 50% and PR improvement) for the primary predictors (WP and GAUS, both binary), as well as repeating the logistic regression model with ACR20 as outcome for the secondary predictors of interest (binary measures of PDQ, TPC, SJ/TJ GSAUS and GCUS). The number of responders (and corresponding percentage) will be reported for every predictor (all categorical). Furthermore, change in the domains of the updated OMERACT core outcome set according to WP and GAUS profile will be analysed, and scatter diagrams will be applied to study the relationship between continuous measures of WPI and GAUS at baseline and the change in DAS28-CRP and in DAPSA during the treatment period.

Handling of multiplicity and other data conventions

In all analyses, p-values < 0.05 will be considered statistically significant. No correction for multiple testing will be done; instead the results will be interpreted with caution in the context multiplicity.

Missing data and analysis population

The main analysis population will be defined as those who fulfilled the inclusion criteria (i.e. the intention–to-treat population). For the outcomes (follow-up visit), missing data will be imputed by a non-responder assumption (i.e. baseline observation carried forward).

An as-observed population will be defined as those for whom data have been observed and no imputation will be carried out.

A per-protocol population will be defined as those who have complete data on the variables used for the analysis (i.e. the response variable and the predictor variables) and who adhered to the assigned treatment during the observation period.

Sensitivity analyses

A sensitivity analysis will be conducted to study the value of the primary pain and ultrasound predictors on ACR20 response including the per-protocol population and as-observed population.

Programming

The analyses will be conducted using the statistical program R (version 3.3.3).[49]

The program code for the primary analyses in the statistical program R:

```
#Logistic regression, ACR20 response, WP, univariate
M1<-glm(ACR_response ~ WP, family=binomial)
anova(M1, test="Chisq")
summary(M1)

#Logistic regression, ACR20 response, WP, adjusted for gender and age
M1<-glm(ACR_response ~ WP + Gender + Age, family=binomial)
M1<-glm(ACR_response ~ Gender + Age, family=binomial)
anova(M1,M0, test="Chisq")
summary(M1)

#Logistic regression, ACR20 response, GAUS, univariate
M1<-glm(ACR_response ~ GAUS, family=binomial)
anova(M1, test="Chisq")
summary(M1)

#Logistic regression, ACR20 response, GAUS, adjusted for gender and age
M1<-glm(ACR_response ~ GAUS + Gender + Age, family=binomial)
M1<-glm(ACR_response ~ Gender + Age, family=binomial)
anova(M1,M0, test="Chisq")
summary(M1)
```

Model performance

Discrimination, i.e. the model's ability to distinguish between the patients who will experience a response from those you will not, will be quantified with the measures sensitivity, specificity, and the concordance statistic, the *c*-index (i.e. the area under the receiver operating characteristic curve [ROC] in the case of binary outcomes)[50,51] The ROC curve is a plot of sensitivity (true positive rate) against one minus specificity (false positive rate) for consecutive cutoffs for the probability of experiencing a response.[52] The *c*-index is the probability, across all patients, that the model correctly predicts that one patient has a higher probability of experiencing a response compared to another patient, where 0.5 indicate predictions that are no better than chance.[50]

Protocol deviations

Some deviations from the original protocol were considered necessary for the current study in order to specify the statistical analyses and ensure feasibility and interpretability of the study results despite the exploratory approach.

Study design:

Protocol: The enrolment period will be from 17 September 2015 to 1 February 2017. Follow-up will be completed by 15 June 2017.
***SAP*:** The enrolment period was extended to 1st of June 2017.
Rationale: To increase the study population as enrolment was more difficult than first expected. Ethical approval was obtained for extending the enrolment period (no. 55414).

Clinical examination:

Protocol: An Assessment of Motor and Process Skills (AMPS test) will be performed by a calibrated occupational therapist who has attended a specialised training course in the standardised AMPS administration procedures.
SAP: The AMPS was only performed on the initial 30 patients included in the study, and AMPS results will not be part of the proposed manuscript. Instead these will be reported in a separate paper (later on).
Rationale: Many patients considered the examination programme too long. As AMPS was time-consuming and not a central part of the study objective we decided to eliminate this part in order to ensure compliance.

Assessment of pain mechanisms:
Protocol: Characterization of pain profiles will be based on the following assessment tools:
The PainDETECT Questionnaire (PDQ), The Widespread Pain Index (WPI), The Swollen to Tender Joint Count Ratio (SJ/TJ) and the Tender Point Count (TPC).
SAP: When elaborating the SAP, the author group (including a rheumatologist with expertise in pain) achieved consensus on defining the primary variable of pain profile as the presence of widespread, non-arthritic pain interpreted as a WPI score ≥4 and presence of generalised pain (≥4/5 regions). The definitions of secondary measures of augmented pain processing by PDQ, TP and SJ/TJ still adhere to the protocol.

Rationale: Definitions of primary and secondary predictors were needed to clarify the study objective and specify the statistical analyses.

Imaging:

1)Protocol: Scoring of entheses/tendons will adhere to the Madrid Sonographic Enthesitis Index (MASEI) algorithm.

SAP: The scoring of entheses will not only rely on the MASEI algorithm but also include recommendations from the OMERACT expert group; due to assessment of Doppler and bursitis.[53] All knee scans were performed with the patient in supine position. In order to visualize maximal Doppler flow the knee was scanned in fully extended position, instead of 70^0 flexion as proposed in the MASEI publication.[54] This might have led to a systematic bias in measures of the distal patella enthesis thickness, as the ultrasonographers reported that a large proportion of patients had a pathological thickness (>4mm) of this site (according to the MASEI scoring) without any other characteristics of enthesitis or tendinopathy. It was therefore decided not to include this score in the total subacute ultrasound score. No error was suspected in the scoring of thickness of the proximal patella entheses.

Rationale: Based on current knowledge this was considered appropriate according to the two US experts (JGM, KE).

2)Protocol: The interobserver reliability of the two sonographers will be investigated by double scans of patient 6–35. US assessment will occur on the same day as the clinical examination.

SAP: The interobserver (KE vs JGM) reliability AND intraobserver (JGM) reliability will be tested. Only 10 patients will be used for these analyses.

Rationale: The reduced number of patients used for reliability testing does not adhere to gold standards but was chosen due to feasibility reasons.

Exploratory outcomes and response criteria:

Protocol: Response to treatment during the 4-month study period will be assessed by various outcome variables covering composite, clinician-reported and patient-reported measures (all depicted in Table 4 of the protocol).

SAP: The number of outcome measures is reduced and clear definitions of primary, secondary and exploratory outcome measures are provided. The newly endorsed 2016 revision of the PsA core domain set (by OMERACT) was taking into account when reporting outcomes.

Rationale: Based on statistical advises this was done to ensure clarity and interpretability of study results and to minimize the risk of mass significance.

Descriptive statistics and main analyses:

Protocol: Baseline variables will be described for all participants and in relevant subgroups (eg, according to treatment, pain profile or US activity).

SAP: Baseline data will be presented for patients according to their pain profile and US activity but not according to treatment.

Rationale: To ensure a clear presentation in accordance with the study objective and since subgrouping according to both treatment arm and pain profile was restricted by the study size.

Manuscript outline (tables, figures and supplementaries)

Appendix 1: Statistical analysis plan

Figure 1: Flow chart

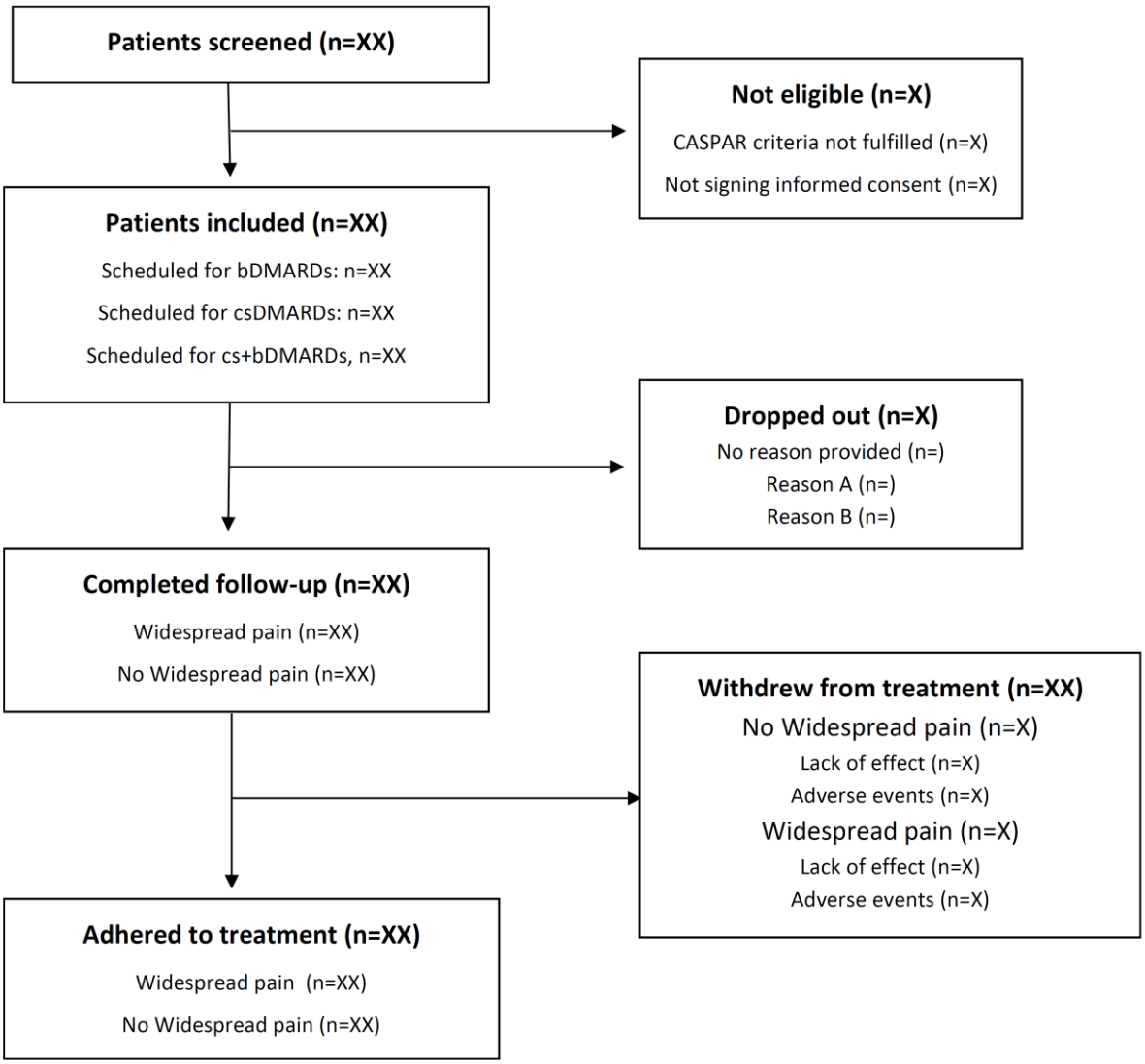

Table 1: Baseline characteristics according to pain profile

Demographics and disease characteristics	Total (n=)	WP+ (n=)	WP – (n=)	Difference (95%CI)	P-value
Age, years					
Female, n (%)					
PsA duration, months					
PsA symptom duration, months					
Psoriasis duration, months					
Spinal involvement, n (%)					
Higher educational level[1], n (%)					
Smoking (current), n (%)					
Alcohol daily use, n (%)					
Body mass index, kg/m^2					
Medication					
csDMARD naïve, n (%)					
bDMARD naïve, n (%)					
Scheduled for csDMARD, n (%)					
Scheduled for bDMARD, n (%)					
Scheduled for cs+bDMARD, n (%)					
NSAIDs daily use, n (%)					
Mild analgetics daily use, n (%)					
Opiods daily use, n (%)					
Clinical and composite measures					
VAS physician (0-100)					
Swollen joint count (0-66)					
Tender joint count (0-68)					
SJ/TJ ratio <0.5, n (%)					
SPARCC enthesitis (0-16)					
DAS28CRP score (0-10)					
DAPSA score (0-164)					
Tender point count (0-18)					
PASI (if BSA >1) (0-72)					
Nail psoriasis, n (%)					
Dactylitis (0-20)					
Patient reported outcome measures					
VAS global (0-100)					
VAS Pain (0-100)					
PDQ score (-1 -38)					
MOS SF-36 MCS (0-100)					

MOS SF-36 PCS (0-100)

PsAID-12 (0-10)

DLQI (0-30)

NRS Fatigue (0-100)

GAD-10 (0-50)

BASFI (0-10)

BASDAI (0-10)

HAQ-DI (0-3)

Paraclinic assessments

Radiographic PsA, n (%)

CRP level, mg/L

Ultrasonography

GAUS (0-203)

GSAUS (0-204)

GCUS (0-312)

Data are presented as mean (SD) unless otherwise stated. WP+, Widepread pain profile defined by a WPI≥4 and generalized pain. [1]Higher educational= University degree or similar. PsA, psoriatic arthritis; csDMARD, conventional synthetic disease modifying drugs; bDMARD, biologic disease modifying drugs; NsAID, Non-steroidal anti-inflammatory drugs; VAS, Visual Analogue Scale; SJ/TJ, swollen joints/tender joints; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; DAS28, Disease Activity Score with 28 joints and crp; DAPSA, Disease activity Index for psoriatic arthritis; PASI, Psoriatic Area Severity Index; PDQ, PainDETECT Questionnaire; MOS SF-36 MCS; Medical Outcomes Study Short Form 36 Mental Component Summary; MOS SF-36 PCS; Medical Outcomes Study Short Form 36 Physical Component Summary; PsAID, Psoriatic Arthritis Impact of Disease score; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; GAD-10, Generalised Anxiety Disorder; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ-DI, Health Assessment Questionnaire disability index; CRP, C-reactive Protein; GAUS, global acute ultrasound score; GSAUS, global subacute ultrasound score; GCUS, global chronic ultrasound score.

Table 2: Prognostic value of US pathology and widespread pain profile on ACR20 response (ITT population)

			Simple logistic regression		Multivariable, adjusted for age and gender	
Predictors	n	n response (%)	OR (95%CI)	P-value	OR (95%CI)	P-value
Primary						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GSAUS >0			[Reference level]		[Reference level]	
Secondary						
Pain profile						
PDQ						
<13						
≥13			[Reference level]		[Reference level]	
TPC						
<8						
≥8			[Reference level]		[Reference level]	
SJ/TJ						
<0.5			[Reference level]		[Reference level]	
≥0.5						
US profile						
GSAUS						
<median*						
≥median*			[Reference level]		[Reference level]	
GCUS						
<median†						
≥median†			[Reference level]		[Reference level]	

GAUS, Global Acute Ultrasonic Score; GSAUS, Global Subacute Ultrasonic Score; GCUS, Global Chronic Ultrasonic Score; WP; widespread pain; PDQ, PainDetect questionnaire score; TPC, Tender Point Count; SJ/TJ, Swollen joints/Tender joints. *Median value =(to be defined), †Median value = (to be defined).

Table 3: Prognostic value of US and widespread pain profile on secondary outcomes

			Simple logistic regression		Multivariable, adjusted for age and gender	
Predictors	n	n response (%)	OR (95%CI)	P-value	OR (95%CI)	P-value
MDA						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GAUS >0			[Reference level]		[Reference level]	
DAPSA 50%						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GAUS >0			[Reference level]		[Reference level]	
PR-improvement						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GAUS >0			[Reference level]		[Reference level]	

GAUS, Global Acute Ultrasonic Score; WP; widespread pain; MDA, Minimal disease activity; DAPSA, Disease Activity Index for Psoriatic arthritis; PR-improvement; Patient reported improvement.

Figure 2: Scatter diagrams: Association between change in DAPSA and DAS28-CRP and baseline WPI and GAUS scores

a) WPI score vs ΔDAPSA
b) WPI score vs ΔDAS28
c) GAUS vs ΔDAPSA
d) GAUS vs ΔDAS28

Table 4: Change in the OMERACT PsA core set domains* from baseline to follow-up (ITT population)

PsA Core domains	All patients	WP-	WP+	Difference (95% CI)	P-value	GAUS=0	GAUS>0	Difference (95% CI)	P-value
MSK disease activity									
Δ SJC									
Δ TJC									
Δ SPARCC									
Δ BASDAI									
Skin disease									
Δ PASI									
Pain									
Δ VAS pain									
Δ SF-36 BP									
Physical Function									
Δ SF-36 PF									
Δ HAQ									
Δ BASFI									
HRQol									
Δ DLQI									
Δ PsAID									
Patient Global									
Δ Patient Global VAS									
Fatigue									
Δ NRS Fatigue									
Δ SF-36 VT									
Systemic inflammation									
Δ CRP									

*OMERACT PsA core domains set as updated and endorsed in 2016[3]

WP, Widespread pain; GAUS, Global Acute Ultrasonic score; CI, Confidence intervals; MSK, Musculoskeletal; SJC, swollen joint count; TJC, tender joint count; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; PASI, Psoriatic Area Severity Index; VAS, visual analogue scale; SF-36 BP, Medical Outcomes Study Short Form 36 Bodily Pain; PF; Physical Function; HAQ-DI, Health Assessment Questionnaire Disability Index; BASFI, Bath Ankylosing Spondylitis Functional Index; DLQI, DLQI, Dermatology Life Quality Index; PsAID, Psoriatic Arthritis Impact of Disease score; NRS, Numeric rating scale; VT; Vitality SFCRP, c-reactive protein.

Table 1s: Baseline characteristics according to ultrasound characteristics

Demographics and disease characteristics	n	GAUS > 0 (n=)	GAUS = 0 (n=)	Difference (95%CI)	P-value	n	GSAUS ≥ median (n=)	GSAUS < median (n=)	Difference (95%CI)	P-value	n	GCUS ≥ median (n=)	GCUS < median (n=)	Difference (95%CI)	P-value
Age, years															
Female, n (%)															
PsA duration, months															
PsA symptom duration, months															
Psoriasis duration, months															
Spinal involvement, n (%)															
Higher educational level[1], n (%)															
Smoking (current), n (%)															
Alcohol daily use, n (%)															
Body mass index, kg/m^2															
Medication															
csDMARD naïve, n (%)															
bDMARD naïve, n (%)															
Scheduled for csDMARD, n (%)															
Scheduled for bDMARD, n (%)															
Scheduled for cs+bDMARD, n (%)															
NSAIDs daily use, n (%)															
Mild analgetics daily use, n (%)															
Opiods daily use, n (%)															
Clinical and composite measures															
VAS physician (0-100)															
Swollen joint count (0-66)															
Tender joint count (0-68)															
SJ/TJ ratio <0.5, n (%)															

SPARCC enthesitis (0-16)

DAS28CRP score (0-10)

DAPSA score (0-164)

Tender point count (0-18)

PASI (if BSA >1) (0-72)

Nail psoriasis, n (%)

Dactylitis (0-20)

Patient reported outcome measures

VAS global (0-100)

VAS Pain (0-100)

PDQ score (-1 -38)

MOS SF-36 MCS (0-100)

MOS SF-36 PCS (0-100)

PsAID-12 (0-10)

DLQI (0-30)

NRS Fatigue (0-100)

GAD-10 (0-50)

BASFI (0-10)

BASDAI (0-10)

HAQ-DI (0-3)

Paraclinic assessments

Radiographic PsA, n (%)

CRP level, mg/L

Data are presented as mean (SD) unless otherwise stated. GAUS, Global Acute Ultrasound Score; GSAUS, Global Subacute Ultrasound Score; GCUS, Global Chronic Ultrasound Score. [1]Higher educational level refers to University degree (or similar), PsA, psoriatic arthritis; csDMARD, conventional synthetic disease modifying drugs; bDMARD, biologic disease modifying drugs; NsAID, Non-steroidal anti-inflammatory drugs; GCS, glucocorticoids; VAS, Visual Analogue Scale; SJ/TJ, swollen joints/tender joints; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; DAS28, Disease Activity Score using 28 joint and crp; DAPSA, Disease activity Index for psoriatic arthritis; PASI, Psoriatic Area Severity; PDQ, PainDETECT Questionnaire; MOS SF-36 MCS; Medical Outcomes Study Short Form 36 Mental Component Summary; MOS SF-36 PCS; Medical Outcomes Study Short Form 36 Physical Component Summary; PsAID, Psoriatic Arthritis Impact of Disease score; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; GAD-10, Generalized Anxiety Disorder; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ-DI, Health Assessment Questionnaire disability index; CRP, C-reactive Protein.

Table 2s: Baseline characteristics according to pain profile

Demographics and disease characteristics	n	PDQ < 13	PDQ ≥ 13	Difference (95%CI)	P-value	n	TPC < 8	TPC ≥ 8	Difference (95%CI)	P-value	n	SJ/TJ < 0.5	SJ/TJ ≥ 0.5	Difference (95%CI)	P-value
Age, years															
Female, n (%)															
PsA duration, months															
PsA symptom duration, months															
Psoriasis duration, months															
Spinal involvement, n (%)															
Higher educational level[1], n (%)															
Smoking (current), n (%)															
Alcohol daily use, n (%)															
Body mass index, kg/m^2															
Medication															
csDMARD naïve, n (%)															
bDMARD naïve, n (%)															
Scheduled for csDMARD, n (%)															
Scheduled for bDMARD, n (%)															
Scheduled for cs+bDMARD, n (%)															
NSAIDs daily use, n (%)															
Mild analgetics daily use, n (%)															
Opiods daily use, n (%)															
Clinical and composite measures															
VAS physician (0-100)															
Swollen joint count (0-66)															
Tender joint count (0-68)															
SJ/TJ ratio <0.5, n (%)											-	-	-	-	-
SPARCC enthesitis (0-16)															

DAS28CRP score (0-10)										
DAPSA score (0-164)										
Tender point count (0-18)						-	-	-	-	-
PASI (if BSA >1) (0-72)										
Nail psoriasis, n (%)										
Dactylitis (0-20)										
Patient reported outcome measures										
VAS global (0-100)										
VAS Pain (0-100)	-	-	-	-	-					
PDQ score (-1 -38)										
MOS SF-36 MCS (0-100)										
MOS SF-36 PCS (0-100)										
PsAID-12 (0-10)										
DLQI (0-30)										
NRS Fatigue (0-100)										
GAD-10 (0-50)										
BASFI (0-10)										
BASDAI (0-10)										
HAQ-DI (0-3)										
Paraclinic assessments										
Radiographic PsA, n (%)										
CRP level, mg/L										
Ultrasonography										
GAUS score										
GSAUS score										
GCUS score										

Data are presented as mean (SD) unless otherwise stated. [1]Higher educational level= University degree or similar. PDQ, PainDETECT Questionnaire; TPC, tender point count; SJ/TJ, swollen/tender joints; PsA, psoriatic arthritis; cs/bDMARD, conventional synthetic/biologic disease modifying drugs; NsAID, Non-steroidal anti-inflammatory drugs; VAS, Visual Analogue Scale; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; DAS28-CRP, Disease Activity Score, DAPSA, Disease activity Index for psoriatic arthritis; PASI, Psoriatic Area Severity; MOS SF-36 MCS/PCS Medical Outcomes Study Short Form 36 Mental/Physical Component Summary; PsAID, Psoriatic Arthritis Impact of Disease score; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; GAD-10, Generalized Anxiety Disorder; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ-DI, Health Assessment Questionnaire disability index; CRP, C-reactive Protein; GAUS, global acute ultrasound score; GSAUS, global subacute ultrasound score; GCUS, global chronic ultrasound score.

Table 4s: Predictive value of US pathology and widespread pain profile on ACR20 response for the per protocol population (n=XX)

			Simple logistic regression		Multivariable, adjusted for age and gender	
Predictors	n	n response (%)	OR (95%CI)	P-value	OR (95%CI)	P-value
Primary						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GSAUS >0			[Reference level]		[Reference level]	

GAUS, Global Acute Ultrasonic Score; WP; widespread pain, CI, confidence intervals

Table 5s: Predictive value of US pathology and widespread pain profile on ACR20 response using the 'as observed' population (n=XX)

			Simple logistic regression		Multivariable, adjusted for age and gender	
Predictors	n	n response (%)	OR (95%CI)	P-value	OR (95%CI)	P-value
Primary						
Pain profile						
WP+			[Reference level]		[Reference level]	
WP-						
US profile						
GAUS =0						
GSAUS >0			[Reference level]		[Reference level]	

GAUS, Global Acute Ultrasonic Score; WP; widespread pain, CI, confidence intervals

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