The Journal of Rheumatology 2023;xx:xxxx
doi:10.3899/jrheum.220500
First Release February 1 2023

The Journal of Rheumatology

Pain Mechanisms Associated With Disease Activity in Patients With Rheumatoid Arthritis Treated With Disease-Modifying Antirheumatic Drugs: A Regression Tree Analysis

Alyssa Wohlfahrt[1], Lutfiyya N. Muhammad[2], Jing Song[2], Dorothy D. Dunlop[2], Tuhina Neogi[3], Clifton O. Bingham III[4], Marcy B. Bolster[5], Wendy Marder[6], Daniel J. Clauw[6], and Yvonne C. Lee[2]

ABSTRACT. ***Objective.*** Although pain affects the assessment of disease activity in patients with rheumatoid arthritis (RA), pain is not always directly related to peripheral joint inflammation. Peripheral and central nervous system regulatory mechanisms also affect pain perception. We used regression tree methodology to identify mechanisms most predictive of disease activity after disease-modifying antirheumatic drug (DMARD) treatment.

Methods. Disease activity was evaluated using the Disease Activity Score in 28 joints (DAS28) in 176 patients with RA, before and after starting a DMARD. Quantitative sensory testing (QST), including pressure pain thresholds (PPTs), temporal summation, and conditioned pain modulation (CPM), were used to assess pain mechanisms. Regression tree methodology was used to determine the QST modalities most predictive of DAS28 after DMARD treatment.

Results. This analysis identified 4 groups defined by baseline DAS28 category and either knee PPT (a combined measure of peripheral and central nervous system dysregulation) or CPM (a measure of descending pain inhibition). Among patients starting with low/moderate disease activity, lower knee PPT (PPT ≤ 4.65 kgf) most strongly predicted higher posttreatment disease activity (group 1 mean DAS28 2.8 [SD 1.0] vs group 2 mean DAS28 3.5 [SD 1.0]). Among patients starting with high baseline disease activity, less efficient descending pain modulation (CPM ≤ 1.55) most strongly predicted higher posttreatment disease activity (group 3 mean DAS28 3.4 [SD 1.4] vs group 4 mean DAS28 4.6 [SD 1.1]).

Conclusion. These results highlight the importance of identifying and treating aberrant peripheral and central pain regulation in patients with RA starting or switching DMARD therapy.

Key Indexing Terms: disease-modifying antirheumatic drugs, inflammation, pain management, pain perception, pain thresholds, rheumatoid arthritis

Pain is a commonly cited symptom for patients with rheumatoid arthritis (RA). Disease-modifying antirheumatic drugs (DMARDs) reduce RA symptoms[1-3]; however, with treatment, some patients have no or only minimal improvement in pain.[3]

Although several studies have examined predictors of disease activity, few have been identified. Baseline disease activity, measured using the Disease Activity Score in 28 joints (DAS28) or Clinical Disease Activity Index (CDAI), is the most consistent predictor of future disease activity.[4-8] Other potential predictors of DMARD response have been reported, but associations have been weak and/or were not consistently replicated in independent cohorts.[9,10] Measuring disease activity through composite scores such as the DAS28 or CDAI may pose a barrier to identifying predictors of disease activity, as these scores are influenced by pain. Although pain is thought to reflect peripheral joint inflammation, pain can result from noninflammatory sources, such as dysregulated central nervous system (CNS) pain processing, which is unlikely to be treated effectively by

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the National Institutes of Health (R01-AR-064850, P30-AR-07257, K24 AR070892 to TN, and P30-AR072759 to COB).

[1]A. Wohlfahrt, MS, Tufts University School of Medicine, Boston, Massachusetts; [2]L.N. Muhammad, PhD, MPH, J. Song, MS, D.D. Dunlop, PhD, Y.C. Lee, MD, MMSc, Northwestern University, Chicago, Illinois; [3]T. Neogi, MD, PhD, Boston University School of Medicine, Boston, Massachusetts; [4]C.O. Bingham III, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland; [5]M.B. Bolster, MD, Massachusetts General Hospital, Boston, Massachusetts; [6]W. Marder, MD, MS, D.J. Clauw, MD, University of Michigan, Ann Arbor, Michigan, USA.

YCL owns stock or stock options in Cigna and has received research support from Pfizer. MBB has research grants from Corbus, Cumberland, Genentech, Amgen, AbbVie, Pfizer, and the Rheumatology Research Foundation. All other authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. Y.C. Lee, Northwestern University Feinberg School of Medicine, Medicine/Rheumatology, 18-093, 633 North St. Clair Street, Chicago, IL 60611, USA. Email: Yvonne.lee@northwestern.edu.

Accepted for publication December 6, 2022.

DMARDs.[11-13] In a recent analysis, we observed that those with more abnormalities in endogenous pain modulation were less likely to respond well to DMARD therapy, highlighting the importance of CNS pain regulation.[14]

The objective of this study was to explore the relationship between pain mechanisms and DAS28-measured disease activity with DMARD treatment. We used an agnostic approach employing regression tree methodology to determine which pain mechanisms best discriminated between patients with RA who had differing levels of DAS28 disease activity after initiation of a new DMARD.

METHODS

Study population. This is a secondary analysis of data from patients with RA in the Central Pain in Rheumatoid Arthritis (CPIRA) study.[15-17] CPIRA is a longitudinal study that recruited participants from 5 academic medical centers. Participants were required to meet American College of Rheumatology (ACR) 2010 criteria for RA.[18] All participants had active disease, defined by a rheumatologist, necessitating the start of a new DMARD. Reasons for exclusion included the following: starting hydroxychloroquine as the new DMARD, switching between DMARDs with the same mechanism of action, daily prednisone dose of ≥ 10 mg, regular use of opioids, severe Raynaud phenomenon, peripheral neuropathy, severe peripheral vascular disease, and/or diagnosis of another autoimmune disease. Participants taking medications affecting the CNS (eg, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants) were required to be on a stable dose for 3 months prior to enrollment. This analysis was restricted to participants with $DAS28_{baseline}$ ≥ 2.6 (active disease) who completed both baseline and follow-up study visits.[19] This study complied with the Declaration of Helsinki, and the institutional review boards at all participating sites approved the study (Boston University H-32334, Brigham and Women's Hospital 2013P000951, Johns Hopkins University NA_00085841, Northwestern University STU00206528, University of Michigan HUM00081289). Written informed consent was obtained from all participants.

Participant assessment. The baseline visit was within 1 month prior to starting a new DMARD, and the follow-up visit occurred approximately 3 months after DMARD initiation. All subjects underwent a physical examination, including swollen and tender joint counts (28 joints). Subjects and trained assessors provided global assessments of disease activity. Serologic status was determined by chart review. Blood was drawn for C-reactive protein (CRP), and DAS28-CRP(4) scores were calculated.[20] Additional details about the CPIRA study have been previously published.[17]

Quantitative sensory testing. Trained research coordinators assessed participants' pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM).

Pressure pain thresholds. PPTs were assessed as measures of pain sensitization. PPTs were measured at joint (bilateral wrists and knees) and nonjoint (bilateral trapezius muscles and thumbnails) sites in random order, using a Wagner Force 10 FDX Algometer (Wagner Instruments). The pressure reading (kgf) that elicited pain was recorded as the PPT, and the average of 3 trials for each site was reported. Lower PPTs were indicative of greater sensitization. PPTs at joint sites were considered combined measures of both peripheral nervous system (PNS) and CNS dysregulation, whereas PPTs at nonjoint sites were considered purely measures of CNS dysregulation.[15,21] These assumptions were based on results of a previous study showing that patients with RA (mean DAS28 2.7) had significantly lower PPTs at joint sites than healthy controls. They also had lower PPTs at nonjoint sites, but the magnitude of difference was smaller and not statistically significant.[22] The observation of enhanced pain sensitivity at joint sites, beyond what was observed at nonjoint sites, was suggestive of peripheral sensitization, even among patients with low disease activity.

Temporal summation. TS was assessed as a measure of CNS pain facilitation.[21,23] A series of weighted, wire-tipped probes were tapped against the skin at the dorsal wrist and mid-forearm. The probe eliciting a pain rating of 30 to 40 out of 100 was tapped against the skin 10 times as the subject rated the pain. TS was calculated as the difference between patient-reported pain at the 10th tap and the 1st tap. Larger differences were indicative of greater pain facilitation.[15,23,24]

Conditioned pain modulation. CPM was assessed as a measure of the descending endogenous pain pathways.[15,25] The PPT at the left trapezius was assessed. Participants were then instructed to immerse their right hand in a 7 °C water bath for 30 seconds. After 20 seconds, the PPT at the left trapezius was assessed while the participant's hand remained in the cold water.[26,27] CPM was calculated as the ratio of the PPT during cold water submersion to the PPT before cold water submersion. High values reflected efficient descending modulation of pain, whereas low values reflected inefficient descending pain inhibition.[15]

Statistical analysis. Since the objective of this study was to identify pain mechanisms most predictive of disease activity after DMARD treatment, we chose $DAS28_{follow\text{-}up}$ as the outcome. The DAS28 is a validated measure of disease activity commonly used in clinical practice: DAS28 scores ≥ 5.1 indicate high activity, scores from < 5.1 to ≥ 3.2 indicate moderate disease activity, scores < 3.2 to ≥ 2.6 indicate low disease activity, and scores < 2.6 indicate remission.[28] Specific components of the DAS28 (eg, swollen joint count [SJC], tender joint count [TJC], patient global assessment [PtGA], CRP) were not assessed as outcomes because these components have not been validated as individual measures of disease activity. Regression tree methodology was used to identify the baseline quantitative sensory testing (QST) measures with the strongest relationship to $DAS28_{follow\text{-}up}$, as well as the optimal threshold of the selected predictor. Selected predictors minimized regression tree criterion based on the mean squared error. The final tree was identified from cross-validation to prune within 1 standard prediction error of the minimum error.[29]

Potential predictors included the baseline QST measures and $DAS28_{baseline}$ category. Each QST measure was included individually, as well as aggregated with other QST measures that reflected similar pain concepts. Assessments were only combined if they had the same units of measurement. To obtain overall measures of pain sensitization, reflecting both peripheral and CNS dysregulation, we calculated 2 measures, the sum of PPT wrist + PPT knee, as well as the sum of all PPT measurements. To obtain an overall assessment of CNS dysregulation, we calculated the sum of PPT thumb + PPT trapezius. To obtain an overall assessment of CNS pain facilitation, we calculated the sum of TS forearm + TS wrist. $DAS28_{baseline}$ category was also included as a potential predictor because it is the only factor that consistently predicts future DAS28 disease activity.[4-8] Specifically, participants were categorized into the following clinically meaningful baseline DAS28 disease activity groups: low (2.6 ≤ $DAS28_{baseline}$ scores < 3.2), moderate (3.2 ≤ $DAS28_{baseline}$ scores < 5.1), and high ($DAS28_{baseline}$ scores ≥ 5.1).[28] The regression tree analysis software further grouped together individuals with low and moderate baseline DAS28 disease activity and kept those with high baseline DAS28 disease activity in their own group.

Sensitivity analyses evaluated the stability of the findings across age, sex, race, RA duration, BMI, and seropositive serology status. A total of 6 analyses were performed, with each factor entered in a regression tree analysis, including the QST measures and $DAS28_{baseline}$ category.

No power calculation was performed given the exploratory nature of this study. To our knowledge, no methods have been developed to support specific calculations, nor do standards regarding sample size or number of predictors exist. Descriptive statistics for demographics and characteristics of the study participants were computed using SAS version 9.4 (SAS

Institute). Regression tree analyses were conducted with Salford Predictive Modeler software, version 8.0 (Salford Systems).

RESULTS

Participant characteristics. One hundred seventy-six participants in the CPIRA study who met inclusion criteria were included. Most participants were female (84%). Mean age (SD) deviation was 55.2 (14.6) years (Table 1). Participants had RA, on average, for 10.9 (12.9) years, and most were seropositive (75%). Fifty-eight percent of participants were adding an additional DMARD to their treatment or switching to a different DMARD. Of those switching DMARDs (n = 51), 29% were previously on a tumor necrosis factor inhibitor (TNFi). Fourteen percent were previously on abatacept (ABA), and 10% were previously on methotrexate (MTX). Other less commonly used DMARDs included leflunomide (LEF: 8%), tocilizumab (TCZ; 8%), tofacitinib (TOF; 6%), and sulfasalazine (SSZ; 6%). Of all participants starting a DMARD (n = 176), 36% were starting MTX. Thirty percent were starting a TNFi, and 11% were starting ABA. Other less commonly started DMARDs included TCZ (7%), TOF (7%), rituximab (4%), LEF (3%), and SSZ (1%). Forty-five percent were taking glucocorticoids at baseline.

Table 1. Baseline characteristics.

	N = 176
Female sex	148 (84)
Age, yrs, mean (SD)	55.2 (14.6)
White race[a]	131 (75)
BMI[b], mean (SD)	28.9 (6.9)
RA disease duration[c], yrs, mean (SD)	10.9 (12.9)
Seropositive[d]	131 (75)
On DMARD therapy	102 (58)

Values are n (%) unless indicated otherwise. [a] n = 174. [b] BMI calculated as weight in kilograms divided by height in meters squared. [c] n = 173. [d] n = 175. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis.

Regression tree analysis. We identified 4 groups with differing levels of follow-up DAS28 disease activity (Figure 1). These groups were defined by $DAS28_{baseline}$ category and either knee PPT or CPM. Among patients starting with low/moderate baseline DAS28 disease activity, knee PPT > 4.65 kgf, indicative of less pain sensitization, most strongly predicted lower posttreatment DAS28 disease activity (group 1 $DAS28_{follow\text{-}up}$ mean [SD] 2.8 [1.0] vs group 2 $DAS28_{follow\text{-}up}$ 3.5 [1.0]). Among patients starting with high baseline DAS28 disease activity, CPM > 1.55 (indicative of efficient descending pain modulation) most strongly predicted lower posttreatment DAS28 disease activity (group 3 $DAS28_{follow\text{-}up}$ 3.4 [1.4] vs group 4 $DAS28_{follow\text{-}up}$ 4.6 [1.1]).

Group 1 (n = 67) had low/moderate baseline DAS28 disease activity and baseline knee PPTs > 4.65 kgf, consistent with low overall pain sensitization. This group also had the highest baseline PPTs and lowest baseline TS for all tested sites (Table 2). Mean (SD) baseline CPM was 1.37 (0.35), which was lower than mean baseline CPM levels for groups 2 and 3. This group also had the lowest levels of patient-reported pain intensity at baseline (Table 2). At follow-up, this group had the lowest DAS28 disease activity (mean $DAS28_{follow\text{-}up}$ 2.8 [1.0]), with 25% of this group meeting the established DAS28 definition of low disease activity ($2.6 \leq DAS28_{follow\text{-}up}$ scores < 3.2) and 48% meeting definition of remission ($DAS28_{follow\text{-}up} < 2.6$; Figure 2). PtGA decreased by 1.47 (2.28), TJC decreased by 3.04 (5.40), and SJC decreased by 1.60 (3.34).

Group 2 (n = 53) had low/moderate baseline DAS28 disease activity and baseline knee PPTs ≤ 4.65 kgf. This group had low baseline PPTs at all sites tested, consistent with pain sensitization due to PNS and CNS dysregulation (Table 2). These individuals also had high baseline TS, reflective of CNS pain facilitation. Baseline CPM was moderate (CPM 1.42 [SD 0.28]), indicating some induction of endogenous pain inhibition. Baseline patient-reported pain intensity was moderate. At follow-up, group 2 had moderate DAS28 disease activity (mean $DAS28_{follow\text{-}up}$ 3.5 [1.0]). PtGA decreased by 1.15

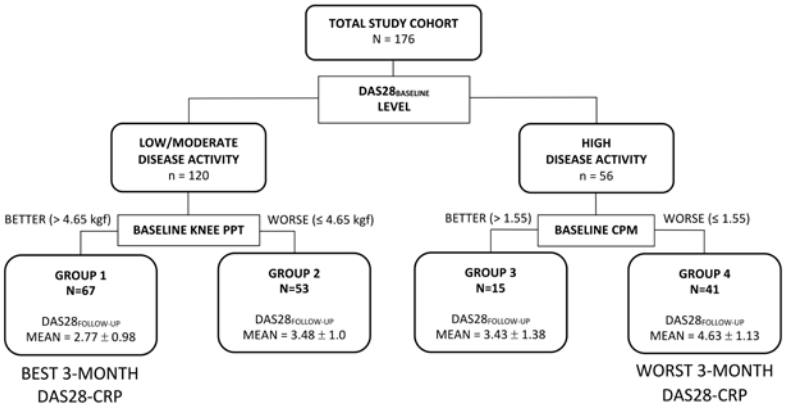

Figure 1. Regression tree of predictors of disease activity after DMARD treatment. $DAS28_{baseline}$ categories were defined based on the clinically defined categories of DAS28 score: low ($2.6 \leq DAS28_{baseline}$ scores < 3.2), moderate ($3.2 \leq DAS28_{baseline}$ scores < 5.1), and high ($DAS28_{baseline}$ scores ≥ 5.1).[28] The outcome of DAS28-CRP shown in the bottom row of boxes was assessed as a continuous variable. CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score in 28 joints.

Table 2. QST measures and pain intensity at baseline for groups identified by regression tree analysis (N = 176).*

	Group 1 Low/Moderate Disease Activity (PPT Knee > 4.65), n = 67	Group 2 Low/Moderate Disease Activity (PPT Knee ≤ 4.65), n = 53	Group 3 High Disease Activity (CPM > 1.55), n = 15	Group 4 High Disease Activity (CPM ≤ 1.55), n = 41
QST Measures				
PPT knee	**7.54 (1.99)**	3.09 (1.05)	3.48 (2.70)	3.79 (1.87)
PPT wrist	**3.93 (1.37)**	2.04 (0.92)	1.93 (1.19)	2.29 (1.20)
PPT trapezius	**3.70 (1.39)**	1.99 (0.92)	1.94 (1.25)	2.25 (1.11)
PPT thumb	**4.62 (1.77)**	2.69 (1.37)	3.09 (1.75)	2.86 (1.18)
TS wrist	**11.31 (14.93)**	16.84 (14.01)	13.82 (12.34)	14.48 (16.19)
TS forearm	**9.11 (12.52)**	15.82 (15.84)	13.57 (12.69)	16.46 (14.72)
CPM	1.37 (0.35)	1.42 (0.28)	**1.97 (0.52)**	1.24 (0.18)
Patient-reported pain intensity,				
NRS (0-10)	**4.27 (1.97)**	5.75 (1.75)	6.21 (2.19)	6.73 (2.20)

Values are expressed as mean (SD). Best values are indicated in bold. * PPT knee: n = 175, TS wrist: n = 174, TS arm: n = 173, CPM: n = 173. CPM: conditioned pain modulation; NRS: numerical rating scale; QST: quantitative sensory testing; PPT: pressure pain threshold; TS: temporal summation.

(2.77), TJC decreased by 3.81 (5.20), and SJC decreased by 1.40 (3.62).

Group 3 (n = 15) had high baseline DAS28 disease activity and baseline CPM > 1.55. At baseline, this group had low PPTs at all sites, which may reflect pain sensitization due to PNS and CNS dysregulation (Table 2). Baseline TS was high, consistent with pain facilitation. As baseline CPM was used to define this group, all patients had high CPM ratios (mean CPM 1.97 [SD 0.52]), suggesting activation of endogenous pain inhibitory pathways. Baseline patient-reported pain intensity was moderate. At follow-up, group 3 had moderate DAS28 disease activity (mean $DAS28_{follow\text{-}up}$ 3.4 [1.4]), which corresponded to the greatest improvement in DAS28 of all 4 groups (Figure 2). This improvement was characterized by large decreases in PtGA (mean decrease of 2.49 [3.61]), TJC (mean decrease of 15.8 [9.02]), and SJC (mean decrease of 4.67 [4.42]).

Group 4 (n = 41) had high baseline DAS28 disease activity and baseline CPM ≤ 1.55. Baseline PPTs were low across all tested sites (Table 2), indicating pain sensitization due to PNS and CNS dysregulation. Baseline TS at the wrist (mean TS

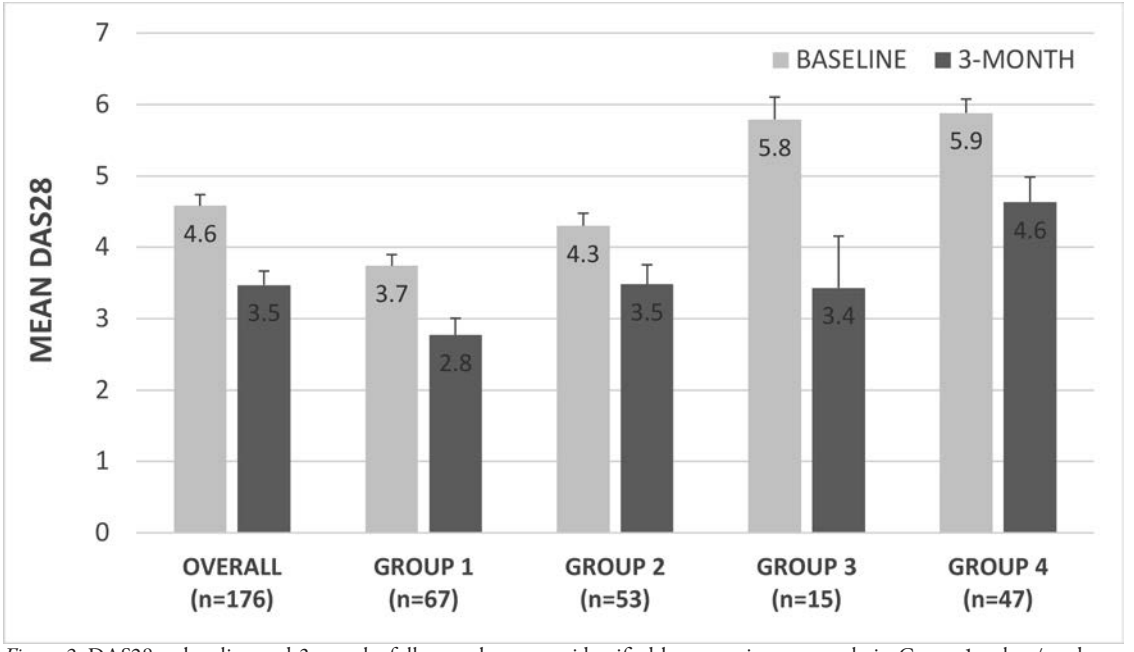

Figure 2. DAS28 at baseline and 3-months follow-up by groups identified by regression tree analysis. Group 1 = low/moderate $DAS28_{baseline}$ (DAS28 < 5.1) with baseline knee PPT > 4.65. Group 2 = low/moderate $DAS28_{baseline}$ (DAS28 < 5.1) with baseline knee PPT ≤ 4.65. Group 3 = high $DAS28_{baseline}$ (DAS28 ≥ 5.1) with baseline CPM > 1.55. Group 4 = high $DAS28_{baseline}$ (DAS28 ≥ 5.1) with baseline CPM ≤ 1.55. CPM: conditioned pain modulation; DAS28: Disease Activity Score in 28 joints; PPT: pressure pain threshold.

14.48 [16.19]) and forearm (mean TS 16.46 [SD 14.72]) were high, indicating high levels of pain facilitation. Low baseline CPM (mean CPM 1.24 [0.18]) was indicative of inefficient pain inhibition. This group had the highest levels of patient-reported pain intensity at baseline. At follow-up, group 4 had the highest mean DAS28 disease activity (mean $DAS28_{follow\text{-}up}$ 4.6 [1.1]). Although disease activity improved with DMARD treatment (Figure 2), improvement was less than seen in group 3, despite similar baseline DAS28 scores. PtGA decreased by 1.51 (2.35), TJC decreased by 5.54 (7.23), and SJC decreased by 5.63 (7.68).

All sensitivity analyses produced the same tree except for the BMI analysis, which produced an abbreviated tree.

DISCUSSION

We applied exploratory regression tree methodology to examine the relationship between baseline pain mechanisms and DAS28 following DMARD treatment. This paper is impactful and novel because the data pointed toward knee PPT being an important predictive factor among patients starting with low/moderate disease activity, which was not something that we had previously hypothesized or reported. In addition, we found that among patients with high baseline DAS28 disease activity, low CPM—an indicator of inefficient descending pain modulation—was the strongest predictor of higher $DAS28_{follow\text{-}up}$.

The observation that a lower knee PPT predicts higher $DAS28_{follow\text{-}up}$ highlights the effect of pain sensitivity on treatment response. Knee PPT was a more influential predictor of $DAS28_{follow\text{-}up}$ than thumbnail or trapezius PPT, both of which are considered purely measures of CNS pain regulation. Although knee PPT is classically considered a measure of peripheral sensitization in patients with joint disease, it likely captures both peripheral and central processes because CNS regulatory mechanisms affect pain sensitivity in a widespread distribution. These results suggest that peripheral sensitization provides an added contribution to the prediction of $DAS28_{follow\text{-}up}$, beyond what is provided by measures of CNS pain regulation alone.

Peripheral sensitization may be linked to future disease activity via multiple pathways. First, peripheral sensitization may be an early step toward dysregulated CNS pain processing and, ultimately, chronic pain. During peripheral sensitization, an increase in chemical mediators and neuronal remodeling leads to increased signaling to the spinal cord. This increase in nociceptor afferent input results in expansion of neuronal networks, which may lead to central sensitization.[30,31] Second, peripheral sensitization may serve as a proxy for more severe inflammatory disease, which is less responsive to DMARDs, or other peripheral pain conditions (eg, other joint disease such as osteoarthritis), which are not treated by DMARDs. For example, in a study of 1111 participants in the Multicenter Osteoarthritis Study (MOST), synovitis and effusion were associated with peripheral sensitization in participants with or at risk for knee OA.[32] Others have similarly found associations between PPTs at the knee and severity of pain in patients with OA.[33,34]

Our study also identified inefficient CPM as a predictor of higher RA DAS28 following treatment initiation among those with high baseline DAS28. This finding is similar to results from previous analyses using data from the same cohort but a different analytical approach (hypothesis testing with prespecified predictors).[14] The important distinction is that this study, using a data-driven approach, found that baseline DAS28 was an effect modifier of the relationship between CPM and future disease activity. CPM was not as important of a predictor among patients with low to moderate baseline DAS28. The role of baseline DAS28 as an effect modifier is consistent with a pathway in which joint inflammation may serve as a conditioning stimulus, activating the descending inhibitory pain mechanisms before participants even place their hands in the cold water bath. Thus, the observed response to the experimental conditioning stimulus (ie, cold water) may reflect additional descending pain inhibition capacity in the setting of an already activated system. These findings suggest that, for patients with chronic pain conditions (eg, RA), there may be greater value in assessing and understanding the capacity for additional activation of the descending pain modulatory pathways at times of stress (eg, high disease activity), rather than assessing and understanding the magnitude of CPM when the system is less stressed (eg, low disease activity).

The efficiency of the descending pain modulatory pathways is largely thought to be innate. Small studies have suggested that genetic polymorphisms in the serotonin transporter (*SLC6A4*) and mu opioid receptor (*OPRM1*) genes may be associated with the efficiency of CPM.[35,36] Patients with impairments in descending pain modulation may benefit from medications that alter these pathways. For example, the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine, and the combination SNRI and opioid agent, tapentadol, improved CPM in patients with diabetic neuropathy and inefficient pain modulation.[25,37,38]

Strengths of this study include the use of regression tree analysis to explore multidimensional subgroups and the use of well-accepted QST modalities and protocols to assess different types of pain dysregulation. In particular, we would like to emphasize the strengths that enable the current analyses to provide important information above and beyond our previous analyses showing associations between CPM and treatment response.[14] First, whereas our previous analysis was hypothesis-driven, here we used a data-driven approach to identify the most important predictors of disease activity. As a result, we were not constrained by preconceived ideas of what should be associated with future disease activity, enabling us to identify, for the first time, that QST measures have differing predictive value depending on baseline disease activity. Second, the use of regression tree methodology allowed us to identify specific cutpoints for the QST measures that best differentiated participants who have lower vs higher disease activity after 3 months of DMARD treatment. These results move the field forward by (1) emphasizing the need to incorporate baseline disease activity as an effect modifier of the relationship between pain regulatory mechanisms and future disease activity, and (2) providing a sense for the QST thresholds that yield the most value for predicting future disease activity.

Limitations of this study include the generalizability of the results given the relatively homogeneous study population (ie, White women with long disease duration). Since this was an

established disease population, some participants may also have joint damage, in addition to inflammation, contributing to pain. These results have not yet been replicated in a separate cohort, and future studies are needed to validate these findings in similar and more diverse cohorts. Additionally, we did not ask specifically about CNS drugs or DMARD usage prior to 6 weeks before study baseline. Other limitations were the absence of a control group who did not initiate DMARD therapy and the small size of group 3. Additionally, all QST measures are psychophysical measures, which are, at best, indirect measures of actual pain mechanisms. While we believe that knee PPT is a reasonable proxy for PNS and CNS dysregulation, it certainly may reflect other processes. In addition, although thumbnail was considered a nonjoint site, the measurement of PPT at the thumbnail could have been contaminated by joint inflammation, as it is close to the interphalangeal joint, which may be affected by RA.

In conclusion, as we move toward a precision-medicine based approach to managing complex, multifaceted outcomes (eg, pain), it is becoming increasingly critical to phenotype patients in a comprehensive manner. In this study, we demonstrated that measures of pain processing, evaluated by QST, are predictive of disease activity following initiation of DMARD treatment. Specifically, low knee PPT, indicative of pain sensitization due to both PNS and CNS dysregulation, was most predictive of DAS28 in response to DMARD treatment in patients with low or moderate pretreatment disease activity. In contrast, low CPM was most predictive of DAS28 after DMARD treatment in individuals with high pretreatment disease activity. These results indicate that, in the research setting, QST can identify specific pain pathways associated with poor treatment outcomes. Although QST would be challenging to implement in a busy clinical practice, these results are still impactful because they provide proof-of-concept that PNS and CNS dysregulation affect treatment outcomes. In addition, they highlight the need for a research agenda that includes the development of rigorous and reproducible biomarkers that can be used in the clinical setting to identify pain pathways in patients with systemic autoimmune conditions such as RA.

REFERENCES

1. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Sao Paulo Med J 2010;128:309-10.
2. Abbasi M, Mousavi MJ, Jamalzehi S, et al. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol 2019;234:10018-31.
3. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet 2001;358:903-11.
4. Morel J, Combe B. How to predict prognosis in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:137-46.
5. Smolen JS, van Vollenhoven RF, Florentinus S, Chen S, Suboticki JL, Kavanaugh A. Predictors of disease activity and structural progression after treatment with adalimumab plus methotrexate or continued methotrexate monotherapy in patients with early rheumatoid arthritis and suboptimal response to methotrexate. Ann Rheum Dis 2018;77:1566-72.
6. Teitsma XM, Jacobs JWG, Welsing PMJ, et al. Inadequate response to treat-to-target methotrexate therapy in patients with new-onset rheumatoid arthritis: development and validation of clinical predictors. Ann Rheum Dis 2018;77:1261-7.
7. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
8. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66:732-9.
9. Conigliaro P, Triggianese P, De Martino E, et al. Challenges in the treatment of rheumatoid arthritis. Autoimmun Rev 2019;18:706-13.
10. Lequerré T, Rottenberg P, Derambure C, Cosette P, Vittecoq O. Predictors of treatment response in rheumatoid arthritis. Joint Bone Spine 2019;86:151-8.
11. Bas DB, Su J, Wigerblad G, Svensson CI. Pain in rheumatoid arthritis: models and mechanisms. Pain Manag 2016;6:265-84.
12. Zhang A, Lee YC. Mechanisms for Joint Pain in Rheumatoid Arthritis (RA): from Cytokines to Central Sensitization. Curr Osteoporos Rep 2018;16:603-10.
13. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:581-92.
14. Heisler AC, Song J, Muhammad LN, et al. Association of dysregulated central pain processing and response to disease-modifying anti-rheumatic drug therapy in rheumatoid arthritis. Arthritis Rheumatol 2020;72:2017-24.
15. Lee YC, Bingham CO, Edwards RR, et al. Association between pain sensitization and disease activity in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Care Res 2018; 70:197-204.
16. Heisler AC, Song J, Dunlop DD, et al. Association of Pain Centralization and Patient-Reported Pain in Active Rheumatoid Arthritis. Arthritis Care Res 2020;72:1122-9.
17. Wohlfahrt A, Bingham CO 3rd, Marder W, et al. Responsiveness of patient-reported outcomes measurement information system measures in rheumatoid arthritis patients starting or switching a disease-modifying antirheumatic drug. Arthritis Care Res 2019;71:521-9.
18. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
19. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res 2012;64:640-7.
20. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017;3:e000382.
21. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6:599-606.
22. Lee YC, Lu B, Edwards RR, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthritis Rheum 2013;65:59-68.
23. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152 (3 Suppl):S2-15.
24. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77-88.
25. Yarnitsky D. Role of endogenous pain modulation in chronic pain

mechanisms and treatment. Pain 2015;156 Suppl 1:S24-31.
26. Edwards RR, Kronfli T, Haythornthwaite JA, Smith MT, McGuire L, Page GG. Association of catastrophizing with interleukin-6 responses to acute pain. Pain 2008;140:135-44.
27. King CD, Goodin B, Kindler LL, et al. Reduction of conditioned pain modulation in humans by naltrexone: an exploratory study of the effects of pain catastrophizing. J Behav Med 2013;36:315-27.
28. van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 2000;59 Suppl 1:i28-31.
29. Breiman L, Friedman J, Stone CJ, Olshen RA. Classification and regression trees. Boca Raton, FL: Chapman & Hall/CRC, 1984.
30. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895-926.
31. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. Ann Neurol 2013;74:630-6.
32. Neogi T, Guermazi A, Roemer F, et al. Association of joint inflammation with pain sensitization in knee osteoarthritis: The Multicenter Osteoarthritis Study. Arthritis Rheumatol 2016; 68:654-61.
33. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum 2013;65:363-72.
34. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149:573-81.
35. Olesen AE, Nielsen LM, Feddersen S, et al. Association between genetic polymorphisms and pain sensitivity in patients with hip osteoarthritis. Pain Pract 2018;18:587-96.
36. Lindstedt F, Berrebi J, Greayer E, et al. Conditioned pain modulation is associated with common polymorphisms in the serotonin transporter gene. PLoS One 2011;6:e18252.
37. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain 2012;153:1193-8.
38. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth 2014; 113:148-56.