OPEN ACCESS

CLINICAL SCIENCE

Predictors for severe persisting pain in rheumatoid arthritis are associated with pain origin and appraisal of pain

Christoph Baerwald ,[1] Edgar Stemmler,[2] Sixten Gnüchtel,[2] Katharina Jeromin,[2] Björn Fritz,[2] Michael Bernateck,[3] Daniela Adolf,[4] Peter C Taylor ,[5] Ralf Baron[6]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/ard-2023-225414).

[1]Zentrum für Seltene Erkrankungen, University Hospital Leipzig, Leipzig, Germany
[2]AbbVie Deutschland GmbH & Co KG, Wiesbaden, Germany
[3]Center for Rheumatology & Pain-Medicine, Hannover, Germany
[4]StatConsult GmbH, Magdeburg, Germany
[5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Botnar Research Centre, Oxford, UK
[6]Department of Neurology, University Hospital Schleswig Holstein, Kiel, Germany

Correspondence to
Professor Christoph Baerwald; cbaerwald@outlook.de

Received 18 December 2023
Accepted 4 May 2024
Published Online First 30 May 2024

ABSTRACT

Objectives To determine the proportion of patients with rheumatoid arthritis (RA) with severe persisting pain and to identify predictive factors despite treatment-controlled disease activity.

Methods This prospective multicentre study included outpatients with RA scheduled for escalation of anti-inflammatory treatment due to active disease and severe pain (Disease Activity Score 28 (DAS28)>3.2 and Visual Analogue Scale (VAS)>50). At week 24, patients were stratified into reference group (DAS28 improvement>1.2 or DAS28≤3.2 and VAS pain score<50), non-responders (DAS28 improvement≤1.2 and DAS28>3.2, regardless of VAS pain score) and persisting pain group (DAS28 improvement>1.2 or DAS28≤3.2 and VAS pain score≥50). The former two subgroups ended the study at week 24. The latter continued until week 48. Demographic data, DAS28-C reactive protein, VAS for pain, painDETECT Questionnaire (PD-Q) to identify neuropathic pain (NeP) and the Pain Catastrophising Scale were assessed and tested for relation to persisting pain.

Results Of 567 patients, 337 (59.4%) were classified as reference group, 102 (18.0%) as non-responders and 128 (22.6%) as patients with persisting pain. 21 (8.8%) responders, 28 (35.0%) non-responders and 27 (26.5%) persisting pain patients tested positive for NeP at week 24. Pain catastrophising (p=0.002) and number of tender joints (p=0.004) were positively associated with persisting pain at week 24. Baseline PD-Q was not related to subsequent persisting pain.

Conclusions Persisting and non-nociceptive pain occur frequently in RA. Besides the potential involvement of NeP, pain catastrophising and a higher number of tender joints coincide with persisting pain.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pain is a cardinal symptom of inflammatory arthritis and represents a critical parameter for evaluating treatment success.
⇒ Persisting pain leads to considerable limitations in daily life and occurs in some patients with rheumatoid arthritis (RA) despite meaningful improvement of inflammatory disease activity.

WHAT THIS STUDY ADDS

⇒ Persisting and, in particular, neuropathic pain components are frequent in RA. Neuropathic pain is present more often in non-responders to disease-modifying anti-rheumatic drug treatment and patients with persisting pain despite controlled disease activity.
⇒ Pain catastrophising and the number of tender joints are independent predictors of persisting pain in patients with RA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As pain in RA represents a multifactorial process, screening for pain catastrophising and the number of tender joints could help to identify patients at risk for chronic pain and support pain phenotyping for suitable treatment. Neuropathic pain and other contributing factors should be adequately identified and treated in patients with persisting pain.

INTRODUCTION

Patients diagnosed with rheumatoid arthritis (RA) highlight pain as their most significant problem with the highest need for improvement.[1 2] According to the definition from the International Association for the Study of Pain, pain is an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.[3] Nociceptive pain in RA usually results from synovitis or structural joint damage due to bone loss induced by osteoclastogenesis, which is caused by pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-2 or IL-6.[4 5] It might be augmented by central sensitisation, that is, pain facilitation in the spinal cord. Furthermore, damage to nociceptive nerve endings in the affected joint might induce neuropathic pain (NeP) due to lesions or diseases affecting the somatosensory nervous system either peripherally or centrally.[6] In 2021, the framework for pain phenotyping was refined: besides nociceptive pain caused by inflammation and damage of tissues and NeP resulting from nerve damage, nociplastic pain was introduced as a third category.[7 8] It arises from altered nociception despite no clear evidence of disease or lesion of the somatosensory system, for example, in fibromyalgia. Given that NeP and nociplastic pain potentially involve the

Check for updates

To cite: Baerwald C, Stemmler E, Gnüchtel S, *et al*. *Ann Rheum Dis* 2024;**83**:1381–1388.

central nervous system, it is crucial to acknowledge that reliably distinguishing these non-nociceptive pain phenotypes is a task yet to be mastered. In the literature, the proportion of patients with RA identified to likely have NeP ranges from 5% to 17%; another roughly 20% is reported to possibly have NeP.[9–12] NeP, at the time of the start of this study, not being distinguished from nociplastic pain and pain catastrophising has already been shown to interfere with achieving remission in RA and early RA.[11 13–15] A result which fits well findings for depression and anxiety, which are frequently related to pain and have also been reported to hinder remission achievement.[16 17] Persisting pain as a potential consequence of any pain phenotype mentioned above is usually understood as current and prolonged pain resulting from various causes, including diseases or damage to musculoskeletal structures. Recent findings suggest that 59%–79% of patients with RA have persisting pain.[18] To enrich the knowledge on the occurrence of persisting pain in RA, the aims of the PAIN-CONTROL study were: (a) to determine the proportion of patients with RA having persisting pain and NeP, (b) to compare the clinical and patient-reported outcomes (PROs) of patients with persisting pain to reference patients responding to treatment and non-responders after 24 weeks of disease-modifying anti-rheumatic drug (DMARD) therapy and (c) to identify characteristics that may predict persisting pain.

METHODS

Patient sample

Patient enrolment started on 8 November 2016 (first patient, first visit) and was completed on 9 July 2021 (last patient, last visit). All participants were outpatients recruited from 50 study centres specialising in rheumatology across Germany. Patients were required to meet the following criteria for enrolment: (a) adult patients (≥18 years of age) with a previously signed informed consent regarding study participation and corresponding procedures, (b) confirmed diagnosis of RA according to the ACR/EULAR 2010 criteria, (c) active disease (Disease Activity Score 28 (DAS28)>3.2) plus swollen joint count (SJC)>3, normal C reactive protein (CRP) or CRP above the normal upper limits, and scheduled for escalation of anti-inflammatory treatment, (d) disease duration (RA)≤8 years, (e) patient-reported pain intensity score of ≥50 on a 0–100 Visual Analogue Scale (VAS) and (f) intellectual capacity to participate in study-related procedures and complete individual questionnaires. Patients with active disease, determined by a distinct inflammatory component and reporting considerable pain (≥50 on a 0–100 VAS), were deemed most suitable for analysing the impact of persisting pain on treatment outcomes following therapy escalation.

Study-related procedures

PAIN-CONTROL was a longitudinal study over 24 and 48 weeks, depending on treatment outcome at week 24, which determined the subgroup classifications as specified below. PAIN-CONTROL is registered in the German Clinical Trial Register (DRKS00010717). Study sites entered data via an electronic case report form with a unique subject ID code on a web-based encrypted platform. Patient questionnaires were transcribed by hand and stored on-site. Plausibility checks on defined limits and variable values were conducted using automated feasibility checks. At baseline, anti-inflammatory treatment initiation or escalation was given, while demographic data (eg, gender, age, disease duration and body mass index) and baseline laboratory values comprising autoantibodies to rheumatoid factor and anti-citrullinated peptide were collected. Clinical assessments included measurement of DAS28 using either C reactive protein (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR). Additionally, the following PROs were completed: the painDETECT Questionnaire (PD-Q) investigating symptoms of NeP, the Rheumatoid Arthritis Impact of Disease Questionnaire (RAID) assessing RA impact on daily life, the Patient Health Questionnaire 9 (PHQ-9) reflecting depressive symptoms, the Health-Assessment Questionnaire Disability-Index (HAQ-DI) measuring physical function, and the Pain Catastrophising Scale (PCS) evaluating the individual appraisal of pain.[19–23] The cut-offs used to evaluate the extent of NeP symptoms were ≤12 points (NeP negative), 13–18 points (inconclusive) and ≥19 points (NeP positive).[20] Clinical assessments and PROs were scheduled at each study visit, that is, baseline and weeks 12, 24 and 48. The anti-inflammatory treatment of study participants was adjustable at the treating physician's discretion regarding national treatment guidelines for RA.[24] Besides obligatory initiation or escalation of treatment, there were no study-related procedures or limitations regarding anti-rheumatic treatment, including medication to manage inflammatory pain. At week 24, patients were assigned to three subgroups based on their response to treatment (DAS28-ESR or DAS28-CRP) and reported pain level: patients with DAS28 improvement from baseline>1.2 or DAS28≤3.2 and VAS pain score<50 were considered the reference control group. Patients with DAS28 improvement from baseline≤1.2 and DAS28>3.2 were considered non-responders, regardless of the VAS pain score. Patients reporting a VAS pain score ≥50 and either a DAS28 improvement from baseline>1.2 or DAS28≤3.2 were considered the persisting pain group and were followed up to week 48. This classification was supposed to distinguish patients with a primary inflammatory disease component whose pain likely results from inflammation from patients with persisting pain despite reduced disease activity or patients not responding to escalation of treatment. For the reference group and non-responders, the study ended at week 24. Patients with persisting pain continued until week 48 and were recommended at week 24 to seek adjunctive pain treatment based on a shared decision between patient and physician.

Statistical data analysis

Descriptive information from data on interval and ratio levels is presented as arithmetic mean (SD), including CIs for specified outcomes of interest, while results for nominal data are presented using absolute and relative frequencies, n (%). Proportions are presented as relative frequencies only. For patient classification at week 24, treatment response was assessed either by DAS28-CRP or DAS28-ESR. For descriptive statistical analysis and variable selection, only DAS28-CRP values were used. Variable selection for multivariable regression modelling identifying baseline predictors of persisting pain comparing patients of the corresponding subgroup to individuals from the reference group at week 24 was conducted as follows: initial reduction of variables was obtained by factor analysis, selecting the variable with the highest factor loading from factors with eigenvalues >1 obtained by Varimax rotation. Subsequently, study directors (CB, PCT, RB) reviewed the top variables of each factor, whereas they could overrule the results in justifiable cases, for example, when factor loading of a total score was only slightly lower than the score's item. Second, a stepwise approach in multivariable logistic regression modelling (using a criterion of 15% as the significance level for inclusion and 20% as the significance level for remaining in the model in order to yield a higher power) using bootstrapping (bootstrap sample: B=500) was applied. Variables

included in the model in at least 60% of the bootstrapped models were selected for the final regression to identify factors for being assigned to the persisting pain subgroup (in comparison to the reference group). The results were transformed into individual risk scores and included in a nomogram, which, for convenience, can be used to estimate the outcome of an individual patient given baseline values directly. Data processing and analysis were performed using SAS V.9.4 (SAS Institute), and the nomogram was created using R V.4.2.0 (R Foundation, Vienna, Austria).[25 26] The study results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.[27]

Sample size determination

Given the exploratory nature of this study, the sample size was determined by the requirements for predictive modelling. We assumed patients with persisting pain to be the least common group compared with the reference group and non-responders. According to the literature, regression modelling requires at least 10 times the number of independent variables desired for regression modelling.[28] The maximum planned number was 12 independent variables as potential predictors, meaning that at least 120 patients would have to be classified as having persisting pain at week 24, whereas the maximum number of patients to include in the study was n=700. Therefore, recruitment was stopped after either 120 patients with persisting pain were identified or the total number of patients enrolled exceeded 700.

RESULTS

Patient sample characteristics

Patients with a previous RA diagnosis (n=567) were included in this per-protocol analysis. All patients were scheduled to initiate or escalate anti-inflammatory treatment due to increased disease activity (DAS28>3.2). The proportion of female patients in the total sample was 67.9%. On average, patients had a mean age (SD) of 57.6 (12.9) years and a disease duration of 2.5 (2.6) years. At week 24, given corresponding response to anti-inflammatory treatment, the majority of patients (337, 59.4%) were assigned to the reference group, while 102 (18.0%) patients were classified as non-responders and 128 (22.6%) patients fulfilled the criteria for persisting pain and were followed up to week 48. Patient recruitment was stopped after 120 patients with persisting pain were identified, whereas already included patients were allowed to finish the study, resulting in 128 patients in the respective subgroup (see figure 1 for study design). The baseline characteristics of the three subgroups did not reveal any differences regarding demographic background.

However, differences in 95% CIs regarding clinical characteristics and PROs were found between the reference group and patients with persisting pain regarding RAID, HAQ-DI, PCS and the Numerical Rating Scale for global disease activity, with the latter group showing higher baseline scores for these measures (online supplemental table 1). Similar results were obtained for DAS28-CRP and VAS pain, whereas the baseline 95% CI for patients with persisting pain was above the results of both reference patients and non-responders (DAS28-CRP: 95% $CI_{Reference}$=4.80 to 5.00, 95% $CI_{Non\text{-}Responders}$=4.71 to 5.09, 95% $CI_{Pers.Pain}$=5.13 to 5.47; VAS pain: 95% $CI_{Reference}$=66.9 to 69.7, 95% $CI_{Non\text{-}Responders}$=66.5 to 71.5, 95% $CI_{Pers.Pain}$=71.6 to 76.1). Escalation of RA treatment at baseline was characterised across all subgroups by an increase in conventional synthetic (cs), biological (b) or targeted-synthetic (ts) DMARD prescriptions (ΔcsDMARDs≥16.7%, ΔbDMARDs≥13.3%, ΔtsDMARDs≥2.9%) and glucocorticoids, (Δglucocorticoids≥23.2%). Glucocorticoids

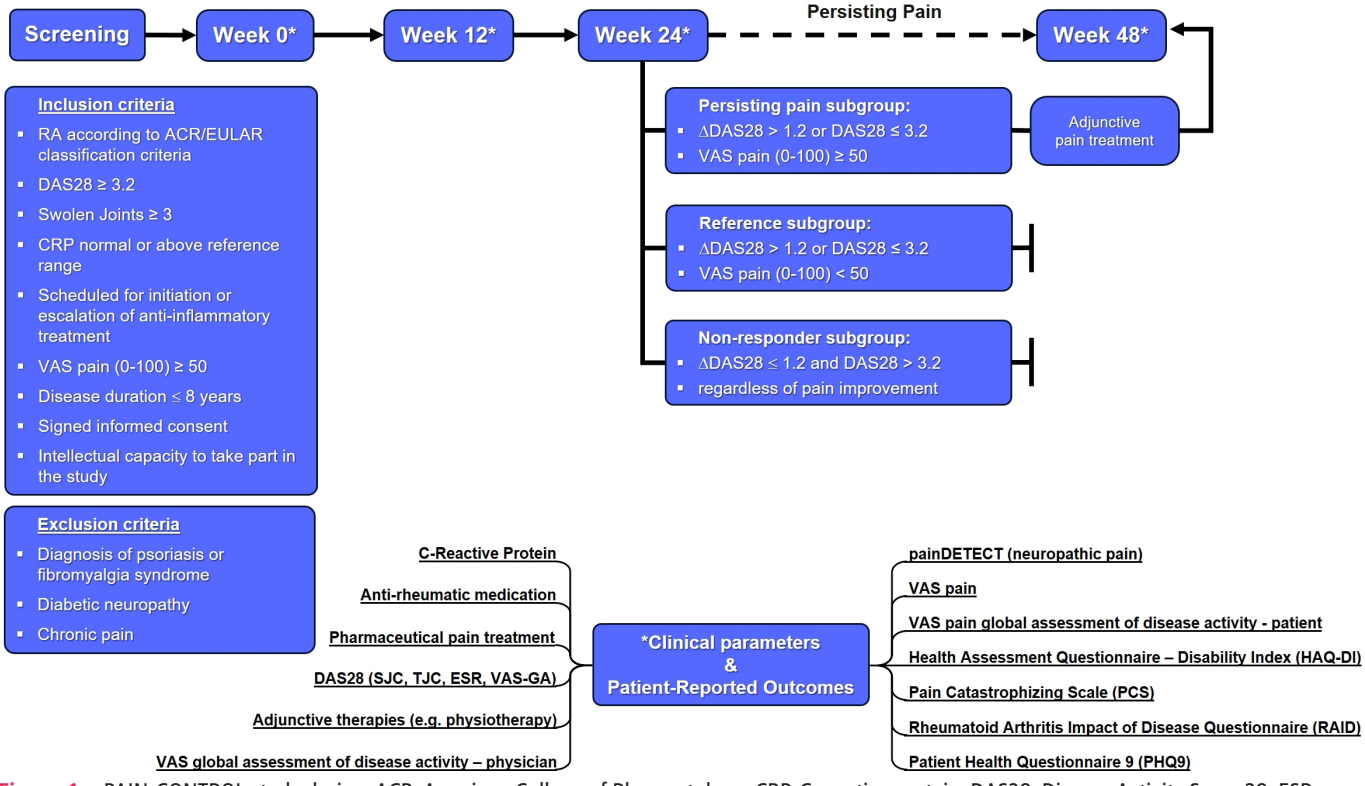

Figure 1 PAIN-CONTROL study design. ACR, American College of Rheumatology; CRP, C reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale; VAS-GA, Visual Analogue Scale - Global Assessment of Disease Activity.

Table 1 Patient characteristics according to the subgroup classification at week 24

	Reference group (N=337)	Non-responders (N=102)	Persisting pain (N=128)
Female, n (%)	233 (69.1)	65 (63.7)	87 (68.0)
ACPA positivity, n (%)	187 (55.5)	43 (42.2)	73 (57.0)
Age, years, mean (SD)	57.1 (13.2)	59.9 (12.0)	57.1 (13.0)
Disease duration, years, mean (SD)	2.5 (2.6)	2.7 (2.8)	2.5 (2.5)
DAS28-CRP, mean (SD)	4.9 (0.9)	4.9 (1.0)	5.3 (1.0)
PD-Q score	14.0 (6.8) | 287	15.5 (7.1) | 78	15.5 (6.5) | 111
PD-Q (NeP positive), n (%)	82 (28.6) | 287	32 (41.0) | 78	40 (36.0) | 111
RAID	5.8 (2.0) | 332	6.0 (1.9) | 100	6.6 (1.7) | 125
PHQ-9	7.3 (5.1) | 328	8.4 (5.4) | 98	7.9 (5.1) | 123
HAQ-DI	1.1 (0.7) | 333	1.2 (0.6) | 101	1.3 (0.6) | 125
PCS	19.7 (12.4) | 328	21.5 (12.3) | 96	24.1 (12.5) | 123
VAS pain (0–100), mean (SD)	68.3 (13.0)	69.0 (12.8)	73.8 (13.0)
NRS disease activity (0–10), mean (SD)	6.7 (1.5)	6.9 (1.4)	7.2 (1.4)
csDMARDs,[1] n (%)	143 (42.4)	50 (49.0)	63 (49.2)
csDMARDs,[2] n (%)	232 (70.3) | 330	67 (65.7)	83 (66.9) | 124
bDMARDs,[1] n (%)	41 (12.2)	15 (14.7)	19 (14.8)
bDMARDs,[2] n (%)	84 (25.5) | 330	36 (35.3)	37 (29.8) | 124
tsDMARDs,[1] n (%)	6 (1.8)	2 (2.0)	1 (0.8)
tsDMARDs,[2] n (%)	27 (8.2) | 330	5 (4.9)	9 (7.3) | 124
Glucocorticoids,[1] n (%)	130 (38.6)	49 (48.0)	62 (48.4)
Glucocorticoids,[2] n (%)	227 (68.8) | 330	73 (71.2)	94 (75.8) | 124
NSAIDs,[1] n (%)	141 (41.8)	42 (41.2)	46 (35.9)
NSAIDs,[2] n (%)	79 (23.9) | 330	28 (27.5)	24 (19.3) | 124
Coxibs,[1] n (%)	41 (12.2)	14 (13.7)	22 (17.2)
Coxibs,[2] n (%)	25 (7.6) | 330	8 (7.8)	11 (8.9) | 124
Opioids,[1] n (%)	7 (2.1)	4 (3.9)	6 (4.7)
Opioids,[2] n (%)	11 (3.3) | 330	4 (3.9)	6 (4.8) | 124
Antidepressants,[1] n (%)	8 (2.4)	4 (3.9)	7 (5.5)
Antidepressants,[2] n (%)	4 (1.2) | 330	1 (1.0)	4 (3.2) | 124
Adj. pain therapy,* n (%)	26 (7.9) | 330	15 (14.7)	23 (18.5) | 124

Table 1 presents the characteristics of the patients assigned to the respective subgroups at week 24. If data were missing, the number of patients with valid data is also presented. Given the escalation/initiation of anti-inflammatory treatment at baseline, this table presents frequencies for treatment categories until baseline[(1)] and the treatment prescribed at baseline[(2)].
*Adjunctive pain therapy includes any type of non-drug pain treatment documented from baseline but not until baseline.
ACPA, anti-citrullinated peptide antibodies; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire-Disability Index; NeP, neuropathic pain; NRS, Numerical Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PCS, Pain Catastrophising Scale; PD-Q, painDETECT Questionnaire; PHQ-9, Patient Health Questionnaire 9; RAID, Rheumatoid Arthritis Impact of Disease Questionnaire; tsDMARDs, targeted synthetic disease-modifying anti-rheumatic drugs; VAS, Visual Analogue Scale.

and csDMARDs were the most frequently prescribed anti-inflammatory treatment for therapy adjustment at baseline, followed by bDMARDs (see table 1). Interestingly, in contrast to increasing prescriptions for DMARDs and glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 inhibitors were prescribed less frequently. Non-pharmacological pain management from baseline was used by 26 (7.9%) patients of the reference group, 15 (14.7%) non-responders and 23 (18.5%) patients with persisting pain based on the subgroup classification at week 24. In the 72 patients discontinuing study participation, 38 (52.8%) declined or did not attend follow-up visits without any given reason, 20 (27.8%) wished to withdraw from the study and 7 (9.7%) were unable to attend follow-up visits due to other illnesses or comorbidities (figure 2).

Persisting pain and NeP

At week 24, the proportion of patients having a VAS pain score ≥50 despite a DAS28 improvement was 22.6%. Until week 24, the proportion of patients testing positive for NeP decreased steadily in the reference group (week 0: 28.6%, week 12: 12.7%, week 24: 8.8%) and declined slightly with a rebound between weeks 12 and 24 among non-responders (week 0: 41.0%, week 12: 19.7%, week 24: 35.0%). Patients with persisting pain exhibited a relatively constant proportion of NeP after an initial reduction (week 0: 36.0%, week 12: 21.8%, week 24: 26.5%, week 48: 21.8%) (figure 3A–C). Remarkably, in contrast to patients with persisting pain, non-responders had the highest proportion of NeP-positive findings at week 24. However, patients testing positive for NeP were found across all subgroups, and the overall proportion of patients reporting a VAS pain score ≥50 after 24 weeks of (escalated) DMARD treatment was still 69.6%. Furthermore, residual pain (ie, VAS scores ≥20 and <50) was common in all subgroups at the end of the study (reference subgroup: n=188 (55.8%), non-responders: n=26 (25.5%), persisting pain patients: n=42 (36.5%), table 2). 87 out of 128 patients with persisting pain at week 24 had valid PD-Q scores at week 48. Of these, 19 patients (21.8%) tested positive for NeP, of which 9 patients (47.4%) still reported persisting pain at week 48. 21 patients (24.2%) tested inconclusive for NeP, and 14 (29.8%) of these still reported persisting pain at week 48. 49 patients classified as having persisting pain at week 24 reported pain alleviation at week 48 and now fulfilled the criteria of the reference group.

DAS28 and symptom-specific PROs

Besides the PROs measuring pain, other outcomes of interest were also considered to provide a more detailed picture of the treatment effects in the specified subgroups. Among these measures, the DAS28, which also determined the subgroup classification, revealed that 192 (57.0%) patients in the reference group and 26 (20.3%) patients with persisting pain had a DAS28<2.6 after 24 weeks of DMARD therapy. By then, another 45 (13.4%) patients in the reference group and 33 (25.8%) persisting pain patients had a DAS28 between 2.6 and 3.2. At week 24, when the reference group and non-responders had reached the end of the study, mean DAS28-CRP values were 2.3 (0.8) (95% CI: 2.2 to 2.4) for the reference group, 4.7 (1.1) (95% CI: 4.5 to 4.9) for non-responders and 3.2 (1.2) (95% CI: 2.9 to 3.5) for patients in the persisting pain subgroup. Thus, as expected, average DAS28-CRP results were lowest for reference patients, followed by patients with persisting pain and non-responders. The same pattern of results was observed for the RAID, PHQ-9, HAQ-DI and PCS, whereas the CIs of the reference group were lowest and did not overlap for all four PROs (figure 3D–F, online supplemental table 2). Notably, less than 25% of non-responders and patients having persisting pain achieved a RAID acceptable symptom state, corresponding to

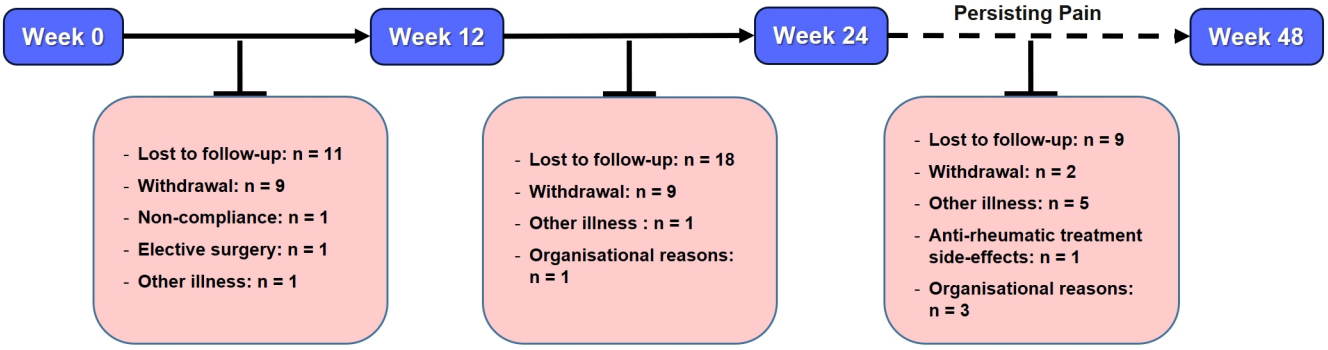

Figure 2 Patient-derived reasons for study discontinuation.

a RAID-score ≤2, whereas 43.8% of patients in the reference group achieved this symptom state.[29] Moreover, 25% of non-responders had a PHQ-9 score ≥10, which is equal to moderate symptoms of depression or worse.[21]

Prediction of group classification at week 24 using baseline characteristics

13 baseline variables (online supplemental table 3) and their pairwise interactions were selected for stepwise regression. Overall, 421 patients from the reference and persisting pain subgroups had complete data on the variables to be evaluated and were included in bootstrapped regression modelling. Baseline tender joint count (TJC) (84.0%), pain catastrophising behaviour (81.0%), adjunctive pharmacological pain medication (eg, opioids, antidepressants, anticonvulsants; 73.6%) and DMARDs (68.2%) were included in ≥60% of the bootstrapped models and thus chosen as independent variables for the final regression. Modelling the group affiliation at week 24 (persisting pain subgroup vs reference subgroup) by the previously chosen variables resulted in a significant model fit (Likelihood ratio test: $p<0.001$) with a reduction of the Akaike information criterion (AIC) from 530.5 (Intercept only) to 512.3 for the model with intercept and covariates. In this final model, the PCS ($p=0.002$) and the TJC ($p=0.004$) showed the strongest relation to the group affiliation at week 24 with 95% CI for ORs above 1. In detail, an increase of one point in the PCS score corresponded to a 2.8% higher probability of being assigned to the persisting pain subgroup (95% CI: 1.0% to 4.6%). Similarly, each other tender joint raised the probability of being classified with persisting pain by 4.7% (95% CI: 1.5% to 8.1%). The use of DMARDs up to baseline ($p=0.06$) and adjunctive pharmacological medication ($p=0.135$) also fulfilled the previously specified selection criteria and were included in the nomogram (figure 4), although their ORs' 95% CI included 1, corresponding to a p value >0.05.

DISCUSSION

To our knowledge, this is the first prospective real-world study in patients presenting with clinically active RA and RA-related pain, which shows that both persisting pain and NeP are common in patients with RA—despite an escalation of DMARD treatment

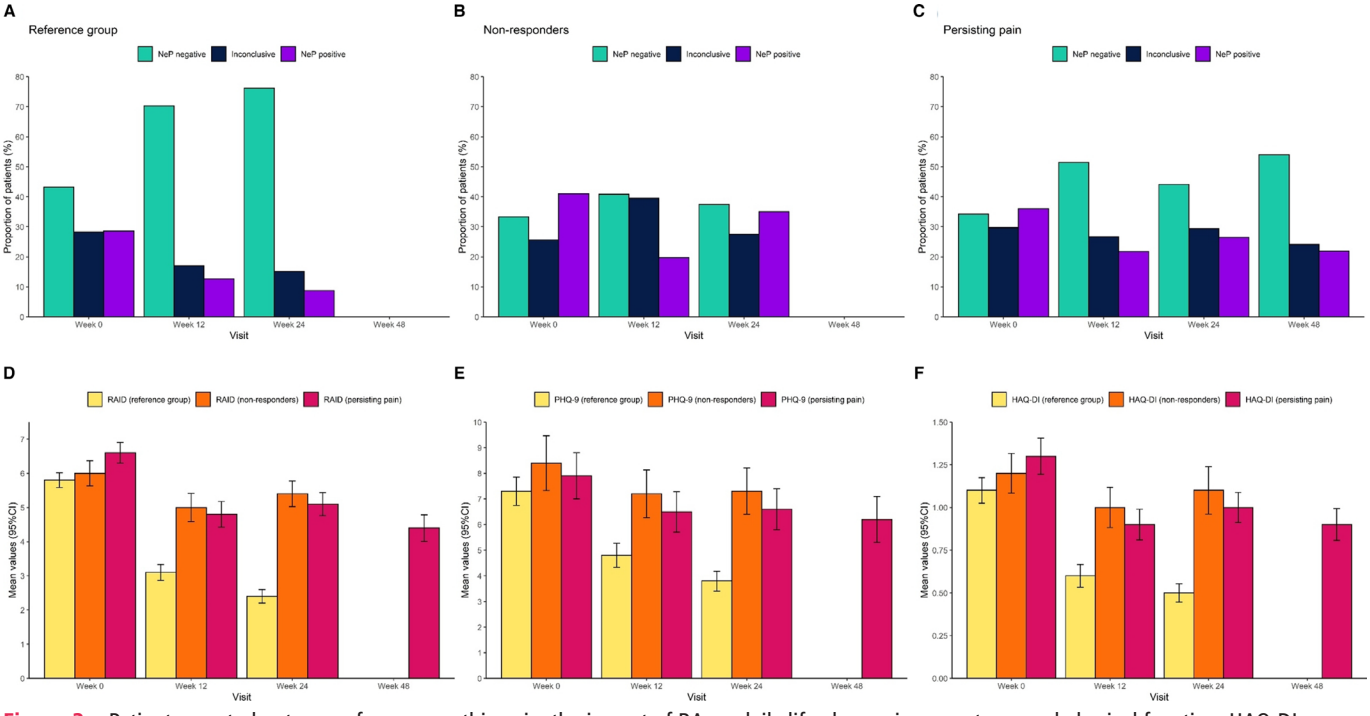

Figure 3 Patient-reported outcomes for neuropathic pain, the impact of RA on daily life, depressive symptoms and physical function. HAQ-DI, Health-Assessment Questionnaire Disability-Index; NeP, neuropathic pain; PHQ-9, Patient Health Questionnaire 9; RA, rheumatoid arthritis; RAID, Rheumatoid Arthritis Impact of Disease Questionnaire.

Table 2 Pain severity on a 0–100 Visual Analogue Scale at week 24 and week 48

		Reference group (N=337)	Non-responders (N=102)	Persisting pain (N=128)
Week 24	VAS<20, n (%)	149 (44.2)	5 (4.9)	0 (0)
	20≤VAS<50, n (%)	188 (55.8)	26 (25.5)	0 (0)
	VAS≥50, n (%)	0 (0)	71 (69.6)	128 (100)
		Reference group (study ended at week 24)	**Non-responders (study ended at week 24)**	**Persisting pain (N=115)**
Week 48	VAS<20, n (%)	–	–	15 (13.0)
	20≤VAS<50, n (%)	–	–	42 (36.5)
	VAS≥50, n (%)	–	–	58 (50.4)

Table 2 reflects the patient-reported VAS pain categories for the study subgroups at weeks 24 and 48 (patients with persisting pain only). Patients with a VAS pain score ≥50 and DAS28 improvement (>1.2) or low disease activity (≤3.2) were assigned to the persisting pain subgroup at week 24.
DAS28, Disease Activity Score 28; VAS, Visual Analogue Scale.

including subsequent standard of care therapy. After 24 weeks of DMARD treatment, 128 of 567 patients (22.6%) still scored ≥50 on the VAS pain despite improving DAS28 by ≥1.2 or attaining low disease activity. Pain of persisting nature despite remission or low disease activity has been reported in previous literature, whereas the choice of the remission criterion may play an essential role.[30 31] A recent study also demonstrated that NeP and comorbidities might hinder patients with RA from achieving Boolean remission.[11] These findings suggest that persisting pain and NeP do not necessarily prevent patients from responding to anti-inflammatory therapy but that these factors may diminish the likelihood of achieving and maintaining remission by impacting the patient global assessment (PtGA). Although patients and therapists differ in their perceptions of relevant treatment outcomes, pain is the strongest predictor for failure to achieve PtGA<1 and, therefore, for not achieving original Boolean remission criteria.[32 33] For this reason, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) have recently recommended revised Boolean 2.0 criteria for remission in RA by employing a higher threshold for PtGA of 2/10.[34] Our results suggest that persisting pain and NeP represent two different trajectories of RA, with 8.8% of the patients in the reference group scoring positive for NeP at week 24, compared with 35.0% in the non-responder group and 26.5% in the persisting pain group. Thus, NeP seems present irrespective of successful inflammatory suppression or persisting pain. This outcome is likely to reflect the underlying mechanisms of NeP, including damage to the peripheral nociceptors in joints, leading to peripheral sensitisation in combination with secondary central sensitisation related to nerve damage.[6 35] It remains to be investigated whether lesions or diseases affecting the nervous system are more frequent in non-responders and patients with persisting pain than in patients responding to anti-inflammatory treatment. In clinical practice, the symptoms and causes of persisting pain and NeP are not easily distinguishable and, in a worst-case scenario, may remain undetected by standard RA assessments.[36] The independence of NeP and persisting pain was further confirmed in our study using alternative regression

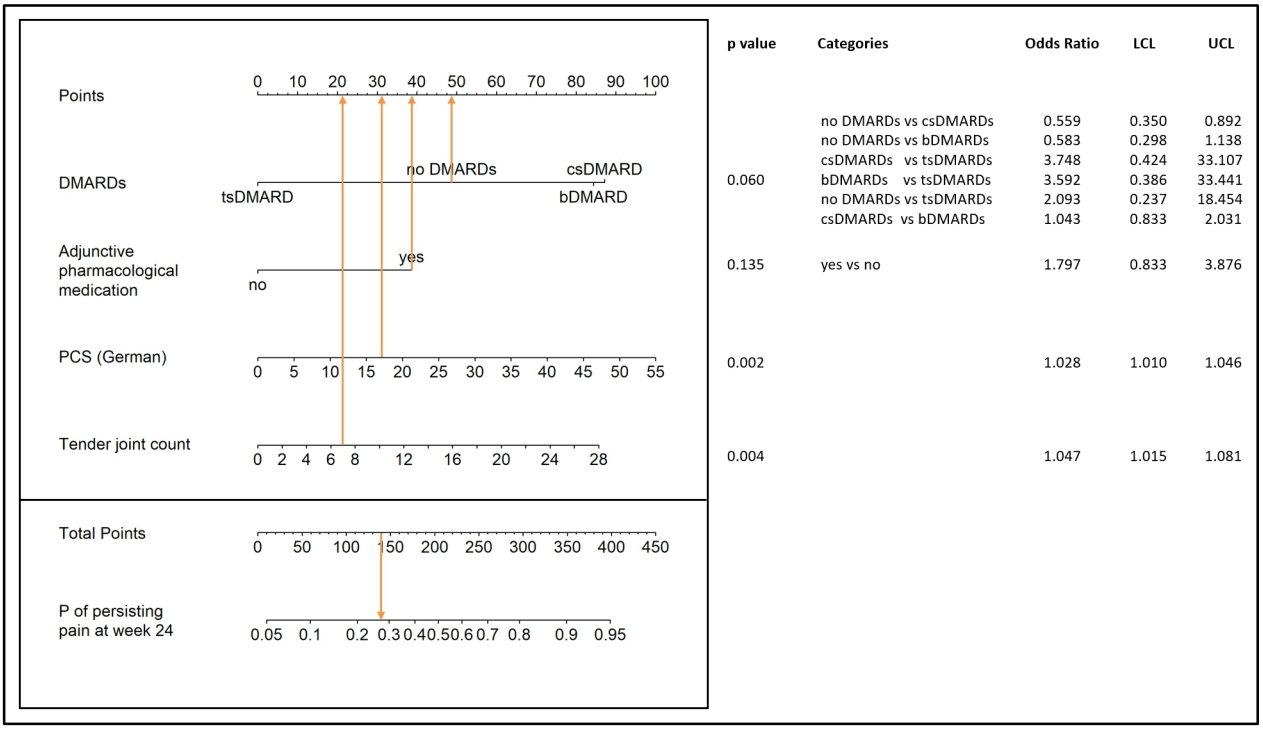

Figure 4 Nomogram for persisting pain-related variables identified by stepwise regression and final multivariable regression. bDMARD, biologic disease-modifying anti-rheumatic drugs; csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs; PCS, Pain Catastrophising Scale; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drugs.

analysis, demonstrating that baseline PD-Q was not related to persisting pain at week 24 (data not shown).

Importantly, our results showed that the baseline number of tender joints (TJC28) and pain catastrophising are independently related to the persisting pain classification at week 24. Pain catastrophising, a construct focusing on the individual appraisal of pain perception, is much less commonly assessed in RA routine assessments than the TJC28. Compared with non-catastrophisers, pain catastrophisers have more difficulty controlling and suppressing pain-related thoughts.[37] Pain catastrophising has also been shown to be linked to certain aspects of personality, whereas the discussion about state (situational) or trait (constant) characteristics of pain catastrophising is still ongoing.[38 39] However, recent findings suggest that JAKi may positively affect pain-related outcomes in patients with active RA, including catastrophising thoughts when pain results from extra-synovial mechanisms.[37 40 41] Interestingly, the proportion of pain catastrophisers seems similar across rheumatic diseases, whereas PCS scores ≥4 were reported to be particularly related to PROs focusing on the biological domain.[42] The way patients appraise their health condition – including pain or tender joints—and how they react to feelings resulting from this evaluation process may explain the association of pain and depression in rheumatic diseases.[43–45] According to our findings, non-responders who also had the highest proportion of NeP-positive findings at week 24 seem particularly prone to depressive symptomatology (25% reported moderate symptoms of depression or worse), supporting the pain-depression relation frequently reported. Our results are consistent with previous prospective observational studies reporting similar prevalence rates for depression.[46 47] Importantly, our results also highlight that improving persisting pain after 24 weeks of DMARD treatment is still possible. The use of adjunctive pharmacological therapy, glucocorticoids or NSAIDs may explain this finding only to a minor degree, given that the number of prescriptions for these therapies did not increase between weeks 24 and 48. Thus, it may be hypothesised that late treatment effects of DMARD therapy account for this finding. Concerning potential limitations, 72 patients discontinued their participation in the study. This finding may be attributed to the study conduct overlapping with the SARS-CoV-2 pandemic, resulting in missed or postponed appointments. Moreover, 20 patients withdrew from the study since they no longer wished to complete the study-related questionnaires. However, the total number of patients withdrawing was still acceptable compared with the analysis population (11.7% of 567 patients). Although the sample size was estimated assuming that patients with persisting pain would comprise the smallest subgroup, non-responders were. However, given that only four variables were included in the regression at the final step of the analysis, the ratio of patients to independent variables in the model can be assumed to return valid results. As a limitation of the study design, the extent to which non-responders represent a persistent inflammatory or rather persisting pain phenotype cannot be answered satisfactorily, given that such categories may not be mutually exclusive. This also extends to measuring NeP using the PD-Q which has not been designed to distinguish NeP from nociplastic pain, a novel pain phenotype introduced when this study had started. Thus, although patients with primary fibromyalgia and other interfering comorbidities were not eligible to participate in the study, it is possible that patients testing PD-Q positive had nociplastic pain instead of NeP or a combination of both, for example, in cases of secondary fibromyalgia. Hence, the development of diagnostic tools for reliable and valid pain phenotyping according to the new framework remains a crucial task and requires large longitudinal data samples. Moreover, the generalisability of our findings may be limited by the selection of the DAS28 and VAS pain criteria for response/improvement, whereas directional changes stay the same irrespective of applying the DAS28-ESR in case of DAS28-CRP absence. Thus, it remains debatable whether results would be different if remission criteria (eg, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Boolean) had been chosen to define the reference group. With this observational study including real-world data, various therapy combinations could have led to our findings. For the future research schedule, investigating the response of the mentioned pain phenotypes to available (adjunctive) treatments remains of high priority. In the analysis presented, the proportion of patients with persisting pain receiving adjunctive pain treatment between weeks 24 and 48 was too small for statistical analysis. From the findings of our study, it is evident that persisting pain and NeP (as well as potential nociplastic pain) are frequently found in patients with RA undergoing standard-of-care treatment. As a consequence, for clinical practice, if pain-relevant comorbidities have been excluded and patients consistently score on the upper half of a pain VAS, present with a large number of tender joints, or do not respond to DMARD therapy, NeP and nociplastic pain should be considered as explanation to this finding. PROs such as the RAID or the PD-Q may help facilitate patient-physician communication when the response to anti-inflammatory treatment does not extend to patient-reported symptom domains. Thus, these tools may be considered as a starting point for further diagnostic procedures and planning of tailored treatment following underlying pain mechanisms.

Acknowledgements The authors would like to thank all participants, study sites and investigators who participated in this clinical trial. CB has served as consultant to AbbVie and has received research funding and speaker fees from AbbVie. ES, SG, KJ and BF are AbbVie employees and may own AbbVie stock or options. MB has served as consultant to AbbVie and has received speaker fees from AbbVie. PCT has served as consultant to AbbVie and has received speaker fees from AbbVie. RB has served as consultant to AbbVie and has received speaker fees from AbbVie. DA is an employee of StatConsult GmbH and led statistical analyses, which was funded by AbbVie. Baseline data of the study were presented at the Annual Congress of the European Alliance of Associations for Rheumatology (EULAR), 1–4 June 2022, Copenhagen, Denmark.

Contributors CB, ES, DA and RB contributed to the conception and design of the study. SG, KJ and BF contributed to the acquisition of data. CB, ES, MB, DA, PCT and RB contributed to the analysis and interpretation of data. ES serves as the guarantor of the study. All authors contributed to drafting the article or revising it critically for important intellectual content. All authors gave final approval of the version to be submitted.

Funding AbbVie funded this trial and participated in the trial design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review and approval of this publication. No honoraria or payments were made for authorship. Statistical analysis support was provided by StatConsult GmbH, which was funded by AbbVie. Medical writing support was provided by Dr Matthias Englbrecht, which was funded by AbbVie.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethics committee of the Medical Faculty of the Christian-Albrechts-University, Kiel, Germany (ID: D497/16). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the USA and Europe and after acceptance

of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select 'Home'.

ORCID iDs
Christoph Baerwald http://orcid.org/0000-0002-1406-3024
Peter C Taylor http://orcid.org/0000-0001-7766-6167

REFERENCES

1 Taylor PC. Pain in the joints and beyond; the challenge of rheumatoid arthritis. *Lancet Rheumatol* 2023;5:e351–60.
2 Mehta P, Taylor PC. Pain in rheumatoid arthritis: could JAK inhibition be the answer *Mediterr J Rheumatol* 2020;31:112–9.
3 Raja SN, Carr DB, Cohen M, *et al*. The revised IASP definition of pain: concepts, challenges, and compromises. *Pain* 2020;161:1976–82.
4 Walsh DA, McWilliams DF. Pain in rheumatoid arthritis. *Curr Pain Headache Rep* 2012;16:509–17.
5 Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol* 2012;8:656–64.
6 Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010;9:807–19.
7 Kosek E, Clauw D, Nijs J, *et al*. Chronic Nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain* 2021;162:2629–34.
8 Nijs J, Lahousse A, Kapreli E, *et al*. Nociplastic pain criteria or recognition of central sensitization? Pain phenotyping in the past. *J Clin Med* 2021;10:3203.
9 Koop SMW, ten Klooster PM, Vonkeman HE, *et al*. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. *Arthritis Res Ther* 2015;17:237.
10 Ahmed S, Magan T, Vargas M, *et al*. Use of the painDETECT tool in rheumatoid arthritis suggests neuropathic and sensitization components in pain reporting. *J Pain Res* 2014;7:579–88.
11 Salaffi F, Di Carlo M, Carotti M, *et al*. The effect of neuropathic pain symptoms on remission in patients with early rheumatoid arthritis. *Curr Rheumatol Rev* 2019;15:154–61.
12 Rifbjerg-Madsen S, Christensen AW, Boesen M, *et al*. The course of pain hypersensitivity according to painDETECT in patients with rheumatoid arthritis initiating treatment: results from the prospective FRAME-cohort study. *Arthritis Res Ther* 2018;20:105.
13 Ten Klooster PM, de Graaf N, Vonkeman HE. Association between pain phenotype and disease activity in rheumatoid arthritis patients: a non-Interventional, longitudinal cohort study. *Arthritis Res Ther* 2019;21:257.
14 Salaffi F, Gerardi MC, Atzeni F, *et al*. The influence of Fibromyalgia on achieving remission in patients with long-standing rheumatoid arthritis. *Rheumatol Int* 2017;37:2035–42.
15 Yoshida T, Hashimoto M, Horiguchi G, *et al*. Pain catastrophizing hinders disease activity score 28 - erythrocyte sedimentation rate remission of rheumatoid arthritis in patients with normal C-reactive protein levels. *Int J Rheum Dis* 2021;24:1520–9.
16 Michelsen B, Kristianslund EK, Sexton J, *et al*. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2017;76:1906–10.
17 Manning-Bennett AT, Hopkins AM, Sorich MJ, *et al*. The Association of depression and anxiety with treatment outcomes in patients with rheumatoid arthritis – a pooled analysis of five randomised controlled trials. *Ther Adv Musculoskelet Dis* 2022;14:1759720X221111613.
18 McWilliams DF, Dawson O, Young A, *et al*. Discrete trajectories of resolving and persistent pain in people with rheumatoid arthritis despite undergoing treatment for inflammation: results from three UK cohorts. *J Pain* 2019;20:716–27.
19 Gossec L, Paternotte S, Aanerud GJ, *et al*. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. *Ann Rheum Dis* 2011;70:935–42.
20 Freynhagen R, Baron R, Gockel U, *et al*. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22:1911–20.
21 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
22 Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789–93.
23 Sullivan MJL, Bishop SR, Pivik J. The pain Catastrophizing scale: development and validation. *Psychological Assessment* 1995;7:524–32.
24 Fiehn C, Holle J, Iking-Konert C, *et al*. S2E-leitlinie: therapie der rheumatoiden arthritis mit krankheitsmodifizierenden medikamenten. *Z Rheumatol* 2018;77:35–53.
25 SAS Institute. SAS® version 9.4.
26 Team RC. R: a language and environment for statistical computing. 2014. Available: http://www.R-project.org
27 Elm E von, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
28 Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. 1st edn. New York, NY: Springer, 2001.
29 Dougados M, Brault Y, Logeart I, *et al*. Defining cut-off values for disease activity States and improvement scores for patient-reported outcomes: the example of the rheumatoid arthritis impact of disease (RAID). *Arthritis Res Ther* 2012;14:R129.
30 Lee YC, Cui J, Lu B, *et al*. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther* 2011;13:R83.
31 Yoshida K, Matsui K, Nakano H, *et al*. Response to "pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study *Arthritis Res Ther* 2011;13:405.
32 Studenic P, Radner H, Smolen JS, *et al*. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012;64:2814–23.
33 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012;71:1702–5.
34 Studenic P, Aletaha D, de Wit M, *et al*. American college of rheumatology/ EULAR remission criteria for rheumatoid arthritis: 2022 revision. *Ann Rheum Dis* 2023;82:74–80.
35 Campbell JN, Meyer RA. Mechanisms of neuropathic pain. *Neuron* 2006;52:77–92.
36 Mathias K, Amarnani A, Pal N, *et al*. Chronic pain in patients with rheumatoid arthritis. *Curr Pain Headache Rep* 2021;25:59.
37 Salaffi F, Carotti M, Farah S, *et al*. Early response to JAK inhibitors on central sensitization and pain Catastrophizing in patients with active rheumatoid arthritis. *Inflammopharmacology* 2022;30:1119–28.
38 Sansone RA, Watts DA, Wiederman MW. Pain and pain catastrophizing among internal medicine outpatients with borderline personality symptomatology: a cross-sectional self-report survey. *Prim Care Companion CNS Disord* 2013;15:PCC.13m01536.
39 Thorn BE, Clements KL, Ward LC, *et al*. Personality factors in the explanation of sex differences in pain Catastrophizing and response to experimental pain. *Clin J Pain* 2004;20:275–82.
40 Taylor PC, Lee YC, Fleischmann R, *et al*. Achieving pain control in rheumatoid arthritis with baricitinib or adalimumab plus methotrexate: results from the RA-BEAM trial. *J Clin Med* 2019;8:831.
41 De Stefano L, Bozzalla Cassione E, Bottazzi F, *et al*. Janus kinase inhibitors effectively improve pain across different disease activity States in rheumatoid arthritis. *Intern Emerg Med* 2023;18:1733–40.
42 Wilk M, Łosińska K, Pripp AH, *et al*. Pain catastrophizing in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: biopsychosocial perspective and impact on health-related quality of life. *Rheumatol Int* 2022;42:669–82.
43 Shim E-J, Hahm B-J, Go DJ, *et al*. Modeling quality of life in patients with rheumatic diseases: the role of pain Catastrophizing, fear-avoidance beliefs, physical disability, and depression. *Disabil Rehabil* 2018;40:1509–16.
44 Edwards RR, Cahalan C, Mensing G, *et al*. Pain, catastrophizing, and depression in the rheumatic diseases. *Nat Rev Rheumatol* 2011;7:216–24.
45 Lerman SF, Haythornthwaite JA. The role of catastrophising in rheumatic diseases. *Clin Exp Rheumatol* 2017;35 Suppl 107:32–6.
46 Englbrecht M, Alten R, Aringer M, *et al*. New insights into the prevalence of depressive symptoms and depression in rheumatoid arthritis – implications from the prospective multicenter VADERA II study. *PLOS one* 2019;14:e0217412.
47 Behrens F, Burmester G-R, Feuchtenberger M, *et al*. Characterisation of depressive symptoms in rheumatoid arthritis patients treated with tocilizumab during routine daily care. Pathog Rheumatoid Arthritis 2022;40:551–9.