HHS Public Access

Author manuscript

J Clin Rheumatol. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

J Clin Rheumatol. 2019 August ; 25(5): 232–236. doi:10.1097/RHU.0000000000000834.

Pain and Catastrophizing in Patients with Rheumatoid Arthritis: A prospective observational cohort study

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Ethics approval and consent to participate: The Partners Institutional Review Board approved this sub-study (2015P001817), as well as the overall CPIRA study (2013P000951). The institutional review boards of each participating site also approved the parent study. Written informed consent was obtained from all participants in CPIRA.

Consent for publication: Not applicable.

Competing interests: CB has served as a consultant to Eli Lilly, Janssen, and UCB regarding patient reported outcomes assessment. MB reports funding from Eli Lilly for a clinical trial as well as trainee funding from Amgen. DC has received consulting fees from Pfizer, Eli Lilly, Nuvo, Cerephex, Tonix, Abbott, Forest Labs, Johnson & Johnson, Merck, Purdue Pharma, Sammumed, Zynerba, Astellas Pharma, Williams & Connolly LLP and Therevance. He has also received research support from Pfizer, Cypress Biosciences, Forest, Merck, Nuvo and Cerephex. YL has received a research grant from Pfizer and has stock in Express Scripts. All other authors report no competing interests.

Authors' contributions: EC designed this sub-study, analyzed the data and wrote the first draft of this manuscript. RE, CB, MB, LM, TN, WM, DC assisted in the design of this sub-study, as well as the overall design of the parent study, CPIRA. AW oversaw subject recruitment and data management, as well as contributed to interpretation of the participant data. YL oversaw the design of this sub-study, as well as the overall design of the parent study, CPIRA, and contributed to data interpretation. All authors read and approved the final manuscript.

Abstract

Background—The aims of this study were to define changes in catastrophizing that occur with initiation of a new disease-modifying antirheumatic drug (DMARD) and to examine the relationship between changes in Clinical Disease Activity Index (CDAI) and changes in catastrophizing.

Methods—Participants in an ongoing multi-site, prospective observational study completed the Pain Catastrophizing Scale (PCS) before and 12-weeks after DMARD initiation. We used multivariable linear regression models to examine the association between changes in CDAI as the exposure and change in pain catastrophizing as the outcome. We also assessed the relationship between changes in each component of CDAI and change in PCS, using multivariable linear regression models.

Results—Among the 165 RA patients with data on CDAI at both time points, CDAI decreased from 22 to 11.5 on a 76-point scale (P <0.0001) after 12-weeks. Pain intensity decreased from a median of 5 to 3 on a 10-point numeric rating scale (P <0.0001), and catastrophizing decreased, from 16.0 to 12.0 on the 52-point Pain Catastrophizing Scale (P =0.0005). Among the 163 with complete data for the regression analysis, changes in CDAI were positively correlated with changes in catastrophizing (standardized β=0.19, p=0.01). Of the components of the CDAI, change in assessor global score was most strongly associated with changes in catastrophizing (standardized beta 0.24, p = 0.003).

Conclusions—Pain catastrophizing decreases, in conjunction with disease activity, after initiation of a new DMARD. These findings provide support for catastrophizing as a dynamic construct that can be altered with treatment directed at decreasing inflammatory disease activity and pain.

Keywords

Rheumatoid arthritis; pain; catastrophizing; disease activity

Background

Pain catastrophizing is the tendency to perseverate on one's pain and imagine its worst possible outcome. In chronic musculoskeletal and rheumatic diseases, pain catastrophizing significantly impacts the pain experience and pain-related outcomes, including disability and length of hospital stays [1–4]. Several studies of rheumatoid arthritis (RA) patients have also reported associations between catastrophizing and pain intensity, both cross-sectionally and longitudinally [5–8].

Significant debate exists regarding whether pain catastrophizing is a state, which is variable depending on the situation, or a trait, which is stable and long-lasting [9]. Several studies have shown that psychologically-based interventions decrease pain catastrophizing, providing evidence that catastrophizing is amenable to intervention. However, few have examined whether treating the underlying pain-causing condition also results in improvements in pain catastrophizing. Recently, a prospective observational study of patients undergoing spine surgery for lumbar spinal stenosis reported that pain

catastrophizing significantly decreased between baseline and three years after surgery [10]. Similarly, a longitudinal observational study of patients with chronic anterior knee pain reported improvements in pain catastrophizing six months after physical therapy or surgery [11], and, in a randomized, controlled trial of physical therapy (PT), cognitive behavioral therapy (CBT) or combination therapy with PT and CBT for chronic low back pain, catastrophizing decreased in all active intervention arms, compared to the wait list control. These observations all suggest that interventions directed at correcting underlying physical conditions also lead to improvements in pain catastrophizing, providing evidence for catastrophizing as a state, responsive to situational changes.

The objective of this study was to examine changes in pain catastrophizing in response to disease-modifying antirheumatic drug (DMARD) treatment in RA. Identifying the state vs. trait-like properties of pain catastrophizing in RA has implications for the management of pain in RA.

Specifically, if pain catastrophizing is a fixed trait and does not change with DMARD treatment, additional interventions may be needed to improve pain-related outcomes.

We hypothesized that pain catastrophizing in a treated cohort decreases over time as pain and disease activity decrease. Because studies have suggested an association between catastrophizing and inflammation, independent of pain, we also hypothesized that changes in disease activity are independently associated with changes in catastrophizing in this treated cohort, independent of changes in pain [12,13].

Methods

Study population

Participants were recruited as part of a larger prospective study, Central Pain Mechanisms in Rheumatoid Arthritis (CPIRA) [14]. The purpose of CPIRA was to examine the relationship between central pain processing mechanisms and DMARD response in RA. This study was not registered online because it is not a clinical trial, and registration was not required. Subjects were drawn from rheumatology clinics at 5 academic centers in the United States. Potential participants were identified at different centers by screening schedules of rheumatology providers and infusion centers, screening existing RA patient databases, and running EPIC reports with billing codes for RA. These individuals were next pre-screened by medical record review and contacted by phone or approached directly at the time of a scheduled clinic visit to assess interest and eligibility.

To be included in the study, individuals had to meet the 2010 American College of Rheumatology (ACR) – European League Against Rheumatism (EULAR) classification criteria for RA and be 18 or older [15,16]. Subjects were enrolled within one month before starting or switching to a new DMARD for active disease. Due to the long onset of action (3-6 weeks) of methotrexate, participants starting methotrexate were also included if they had received only one dose of methotrexate prior to the first study visit. Participants starting hydroxychloroquine were not eligible for this study. Participants taking non-steroidal anti-inflammatory drugs (NSAIDs) were included if they were on stable doses. Individuals were

excluded if they: 1) were taking > 10 mg prednisone daily, 2) were taking standing opioids, 3) had Raynaud's phenomenon, peripheral neuropathy or severe peripheral vascular disease (concern for vasospasm during cold water immersion), 4) carried another autoimmune diagnosis, or 5) were taking changing doses of centrally-acting pain medications (e.g., nortriptyline, duloxetine, milnacipran, gabapentin, and pregabalin).

Written informed consent for the CPIRA study was obtained from all participants. Institutional review board approval was obtained at each of the investigators' institutions before initiating recruitment and research protocols. The Partners Institutional Review Board also separately approved this secondary data analysis, examining the relationship between pain and pain catastrophizing.

Assessment of clinical variables

At each of 2 study visits 12 weeks apart, subjects underwent a physical examination and a blood draw, and completed questionnaires assessing pain, fatigue, sleep, mood, catastrophizing and other clinical variables. Pain catastrophizing was measured using the Pain Catastrophizing Scale (PCS) score, a validated 13-item instrument (range 0-52) that assesses negative cognitive and emotional processes with good psychometric properties [17]. The PCS requests that patients recall previous pain and to rate thoughts and feelings on a 5 point scale, with 0 = not at all and 4 = all the time. Pain intensity (ranging from 0-10) was assessed using the question: "How would you rate your pain on average," on the PROMIS Global Health Scale [18]. Trained examiners assessed the 28-swollen and tender joint count. Anxiety was measured using the PROMIS Anxiety computerized adaptive test (CAT), which yields T-scores with a general population mean of 50 and a standard deviation of 10 [19]. Disease activity was measured using the Clinical Disease Activity Index (CDAI; range 0-76), a widely-accepted measure in RA, which sums tender joint count, swollen joint count, patient global assessment (0-100) and assessor global assessment (0-100) [20].

Statistical analysis

Descriptive measures, including mean or median values, standard deviations or interquartile ranges (IQRs) and frequencies, were determined. To determine if CDAI and catastrophizing scores changed over 12-weeks of DMARD treatment, Wilcoxon signed-rank and paired t-test were used, respectively. Pairwise Spearman's correlation coefficients were calculated for univariate associations between baseline characteristics. We used multivariable linear regression models to examine the association between changes in CDAI as the exposure and change in pain catastrophizing as the outcome. We also performed regression models using each component of CDAI as the exposure variable with change in PCS as the outcome. Age, gender, disease duration, and baseline pain and anxiety were included as potential confounders based upon prior literature [21,22]. Depression was not included because depression and anxiety were strongly correlated and likely to be collinear with each other. Standardized beta coefficients were used to enable comparisons across models with different independent variables [23]. The threshold for significance was set as a two-tailed p-value <0.05. All statistical analyses were performed using Stata version 14.0. Two out of 165 participants were dropped from the regression analyses due to missing data.

Results

Patient characteristics

From January 2014 to April 2017, 165 RA patients with complete data for the CDAI were enrolled in the CPIRA cohort and had completed both baseline and 12-week visits. The median age was 56.2 years. Median disease duration was 4.6 years, and 83.6% were female (Table 1). The median CDAI was 22.0 (IQR 12.5-34.0), which indicates that half of the participants had high baseline disease activity. The median baseline CRP was 3.3 mg/L (IQR 1.0-10.2). At baseline, 41.2% were newly starting a DMARD. Out of the entire group, 43.0% were taking a non-biologic DMARD, and 24.2% were taking a biologic DMARD. Immediately after baseline, 43.6% of patients switched to or added a non-biologic DMARD, and 56.3% switched to or added a biologic DMARD.

Baseline associations

There were significant correlations between baseline PCS score and baseline pain ($r=0.31$, $p<0.001$), baseline PROMIS depression ($r=0.49$, $p<0.001$) and anxiety ($r=0.47$, $p<0.001$). Baseline pain was significantly correlated with baseline CDAI ($r=0.40$, $p<0.001$), baseline anxiety ($r=0.32$, $p<0.001$), and baseline depression ($r=0.27$, $p<0.001$). Baseline CDAI was significantly correlated with baseline anxiety ($r=0.18$, $p=0.020$), and baseline anxiety was strongly correlated with baseline depression ($r=0.76$, $p<0.001$).

Changes in catastrophizing, pain intensity and disease activity over 12 weeks

PCS score decreased significantly from 16.0 (median, with IQR 8.0-28.0) to 12.0 (median, with IQR 4.0-23.0) ($p<0.001$) between baseline and follow-up, as did CDAI from 22 (median, with IQR 12.5-34.0) to 11.5 (median, with IQR 4.1-23.0) ($p<0.001$). Pain intensity decreased from 5 (median, with IQR 3-7) to 3 (median, with IQR 2-5) ($p<0.001$) during this period.

Regression analysis

The assumptions of regression models include: 1) a linear relationship between the independent and dependent variables, 2) homoscedasticity, 3) the absence of multicollinearity and 4) the normality of residuals. We tested linearity by comparing scatter plots of residuals against each independent and dependent variable, none of which showed non-linear trends. We tested homoscedasticity with the Breusch-Pagan test, and the p-value was 0.11, indicating that the data are homoscedastic. We tested multicollinearity using variance inflation factors, all of which were < 1.2. The distribution of residuals appeared normal by inspection. Using a simple linear regression model with change in CDAI as the only exposure variable, we found a significant relationship between change in CDAI and change in pain catastrophizing, with standardized $\beta = 0.21$ ($p = 0.008$) (Table 2). After the sequential addition of age, gender, disease duration, and baseline pain and anxiety as covariates, the standardized beta remained similar at 0.19 ($p = 0.020$). The association between these covariates and change in pain catastrophizing did not reach statistical significance.

In addition, we examined changes in the separate components of the CDAI to examine which components were driving this association (Table 3). Changes in assessor global score were significantly associated with changes in pain catastrophizing, with a standardized β of 0.24. Changes in tender joint count and patient global score were of marginal significance, with standardized beta's of 0.15 and 0.16. We also examined whether change in CRP were associated with changes in PCS, and it was not.

Discussion

In summary, we found that, in addition to pain and disease activity, pain catastrophizing decreases over time in RA patients treated for active inflammatory disease. Further, we found that changes in CDAI were associated with changes in catastrophizing, controlling for age, gender, disease duration, and baseline pain and anxiety. When we separately examined the components of the CDAI, changes in assessor global was associated with changes in catastrophizing, and changes in tender joint count and patient global assessment approached statistical significance.

In the literature, significant debate exists regarding the nature of catastrophizing as a state (temporary and situational) or trait (constant and enduring). A study of 223 RA patients on stable treatment regimens reported that pain catastrophizing was a stable trait that did not change over time [6]. In contrast, a 30-day daily diary study of patients with RA reported that catastrophizing had both state and trait components [24], and a recent study of 209 RA patients reported that pain catastrophizing decreased significantly over 12 months after starting a biologic DMARD [25]. These studies all used items from the Coping Strategies Questionnaire to measure catastrophizing, but their study populations differed. The initial study, by Keefe et al., focused on a population of RA patients on stable treatment regimens, whereas the latter study, by Hammer et al., recruited a population of RA patients starting a biologic DMARD.

Our data validate the results by Hammer et al. and extend the data to include individuals starting a non-biologic DMARD [25]. Our study also strengthens the generalizability of these findings, since the data were obtained from a multi-site observational study, including five academic centers in the U.S. An additional strength was the use of the composite PCS score, including items evaluating three dimensions of catastrophizing (rumination, magnification and helplessness). In the previous two studies reporting state-like qualities of pain catastrophizing, only the dimension of helplessness was assessed [24,25].

The association between treatment-related reduction in catastrophizing and change in assessor global score was a surprising result, particularly given that changes in patient global assessment were not as strongly correlated with changes in catastrophizing. In our study, assessors were research staff members who underwent standardized training. These assessors may have perceived and integrated negative non-verbal cues (reflecting feelings of frustration or helplessness) into their assessments of disease activity, whereas practicing physicians, with more patient-care experience, may not. Interestingly, however, a similar association between baseline assessor global score and catastrophizing was observed in a study of children with juvenile inflammatory arthritis, in which physicians were the

assessors [26], suggesting that factors other than training impact assessments of disease activity. In particular, these physicians had established relationships with the children and their families, which may have influenced their assessments.

The observed marginal association between changes in tender joint count and changes in pain catastrophizing indicates a possible relationship between pain sensitivity and catastrophizing. In our multivariable regression model, including baseline self-reported pain intensity, tender joint count likely represents a combination of constructs – joint-specific hyperalgesia due to peripheral sensitization from peripheral inflammation, as well as overall hyperalgesia due to central sensitization [27,28]. As sensitivity to pain at joint sites decreases, catastrophizing also decreases. A similar relationship between joint tenderness and pain catastrophizing has been reported in other studies of RA and OA [29,30].

The absence of an association between changes in swollen joint count or CRP and changes in pain catastrophizing raises questions regarding the relationship between inflammation and catastrophizing in RA. Studies in healthy populations have shown an association between pain catastrophizing and higher levels of interleukin-6 reactivity [12]. However, to our knowledge, only one other study examined the relationship between catastrophizing and measures of inflammation in RA patients[25]. This study found weak associations between the erythrocyte sedimentation rate and pain catastrophizing and no associations between either swollen joint count or ultrasound measures of synovitis and pain catastrophizing. Similar to this study, we also did not observe any associations between changes in clinical and laboratory markers of inflammation and changes in catastrophizing. Taken together, these observations support the hypothesis that the marginal associations between changes in tenderness and changes in pain catastrophizing may be due to non-inflammatory mechanisms, such as central sensitization.

Our study had a number of strengths. We examined catastrophizing in a cohort of subjects where disease activity was likely to change, because they were starting or switching DMARDs for symptomatic disease. Most other existing studies in RA did not examine catastrophizing over time in a group in which treatments were changing, resulting in more acute and evident changes in disease activity. In addition, we were able to control for psychological factors related to catastrophizing with the questionnaire data we obtained from participants.

There were also several limitations to our study. First, participants in this study were prescribed many different DMARDs that work via different mechanisms, and this study was not powered to assess differences in these subgroups. Second, we assumed that decreases in disease activity over the study period were due to treatment. However, because this is a prospective cohort study and not a randomized controlled trial, we were unable to exclude the Hawthorne effect, which describes the phenomenon of symptom improvement in response to being observed [31]. In addition, we did not exclude individuals who were seeking psychotherapy during the study period. Because catastrophizing is not assessed during routine clinical visits, it is unlikely that patients would be receiving care psychotherapy directed specifically at reducing catastrophizing. It is possible that some patients may be receiving mental health services to treat depression and/or anxiety, though

the numbers are likely low. We also did not control for disability, current employment or sleep interference which may account for differences. Further, because many rheumatologic diseases, including RA, have a waxing and waning course, these fluctuations might have contributed to the decrease in disease activity and catastrophizing observed during the course of the study. Finally, though we examined 2 time points, a longer study with more data points would have allowed us to have more confidence in the observed changes.

Conclusions

This study demonstrated that pain catastrophizing decreases over time in a cohort of RA patients initiating DMARD treatment who respond. Decreases in CDAI were associated with decreases in catastrophizing. These findings suggest that effective management of disease activity, particularly as it relates to joint tenderness, may be useful in reducing pain catastrophizing, with resultant impact on psychological processes and patient perception [32].

Acknowledgments

We would like to thank the study coordinators at all of our sites, including Cassandra Corrigan, Joshual Colls and Dee Luo (Brigham and Women's Hospital), Malini Moni and Grazyna Purwin (Johns Hopkins), Alieysa Patel and Melanie Woods (University of Michigan), Joyce Goggins (Boston University) and Laurie Hope and Kelly Reckley (University of Pittsburgh). We would also like to acknowledge all of our referring physician and patient participants.

Funding: The CPIRA cohort was funded by NIH grant AR064850. EC's work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health. CB's work was funded in part by NIH/NIAMS P30-AR053503 Cores A and D, and by awards SC14-1401-10818 and IP2-PI000737 from the Patient Centered Outcomes Research Institute (PCORI). All statements in this report, including its conclusions, are solely those of the authors and do not represent those of PCORI, its Methodology Committee, or its Board of Governors, or of the NIH or NIAMS. TN reports funding from P60 AR47785, R01 AR062506, K24 AR070892, as well 5R01AR064850-03. KP's work was funded in part by NIH/NIAMS K23AR060241 and UL1TR000433.

List of abbreviations

RA	Rheumatoid arthritis
DMARD	disease-modifying anti-rheumatic drug
CDAI	Clinical Disease Activity Index
PCS	Pain Catastrophizing Scale
CPIRA	Central Pain in Rheumatoid Arthritis
EULAR	European League Against Rheumatism
NSAID	non-steroidal anti-inflammatory drug
PROMIS	Patient-Reported Outcomes Measurement Information System

CAT	computerized adaptive test
IQR	inter-quartile range

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Key messages

- Among individuals with rheumatoid arthritis (RA), catastrophizing is associated with poor pain outcomes
- In some studies, catastrophizing appears to be a “trait” phenomenon (fixed) while in others it appears to have “state” characteristics (susceptible to change)
- Catastrophizing decreases with DMARD treatment in a cohort of patients with active RA
- Aggressive DMARD treatment of RA may impact patient perception and other psychological processes which influence pain

Table 1

Baseline demographic characteristics (N = 165)

Clinical characteristic	Values*
Age, years	56.2 (44.1–66.4)
Gender (% F)	83.6
Swollen joint count	3 (2–8)
Tender joint count	9 (3–18)
CDAI	22.0 (12.5–34.0)
CRP (mg/L)	3.3 (1.0–10.2)
Disease duration, years	4.6 (1.4–16.4)
PROMIS Global Health Pain Numeric Rating Score	5.2 (2.3)
Pain Catastrophizing Scale Score	16 (8–28)
PROMIS Depression Score	49.9 (45.7–56.5)
PROMIS Anxiety Score	54.0 (8.6)
Patient Global Assessment Score	40.2 (23.1)
Assessor Global Score	30 (20–50)
DMARD use (in the past 6 weeks, %)	58.8
Non-biological DMARD use (in the past 6 weeks, %)	43.0
Biological DMARD use (in the past 6 weeks, %)	24.2

*Numbers in parentheses correspond to median (25^{th}-75^{th} percentile) or mean (standard deviation). *TNF* = tumor necrosis factor. *DMARD* = disease-modifying antirheumatic drug. In the 6 weeks prior to study, some patients were on both biological and non-biological DMARDs.

Table 2

Changes in CDAI are associated with changes of catastrophizing, independent of pain*

	Standardized β	p-value
Model 1: ΔCDAI	0.21	0.008
Model 2: Model 1 + age, RA duration, gender	0.20	0.010
Model 3: Model 2 + baseline anxiety	0.19	0.018
Model 4: Model 3 + baseline pain	0.19	0.018

*Standardized β's and p-values are for the association between change in CDAI and change in pain catastrophizing. All models are additive, with additional covariates listed on each line.

Table 3

Changes in components of CDAI are associated with changes in catastrophizing *

Independent Variable	Standardized β	p-value
Δ Assessor global	0.24	0.003
Δ Tender joint count	0.15	0.059
Δ Swollen joint count	0.07	0.351
Δ Patient global	0.16	0.053

* Each row refers to a different exposure variable, with change in catastrophizing as the outcome. Each model is adjusted for baseline PCS, age, gender, RA duration, baseline pain, and baseline anxiety.