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BRIEF REPORT

Changes in Descending Pain Modulation During Anti–Tumor Necrosis Factor Therapy: A Prospective Study in Rheumatoid Arthritis and Spondyloarthritis

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Objective. In rheumatoid arthritis (RA) and spondyloarthritis (SpA), managing persistent pain remains challenging. Little is known regarding impaired pain pathways in these patients and the impact of biologic disease-modifying antirheumatic drugs (bDMARDs). The objective of the Rheumatism Pain Inhibitory Descending Pathways study was to assess pain thresholds and descending pain modulation in patients with active RA or SpA following introduction of a tumor necrosis factor inhibitor (TNFi).

Methods. Patients with active disease (50 with RA and 50 with SpA) naive to bDMARDs or targeted synthetic DMARDs and starting a TNFi were included. Patients were observed for six months after TNFi initiation with clinical, psychological, and pain assessment. At all visits, participants underwent quantitative sensory testing with heat and cold pain thresholds and descending inhibition by conditioned pain modulation (CPM). Descending pain control (CPM effect) was assessed as the change in heat pain threshold (°C) following a conditioning stimulus.

Results. Of the 100 patients (59 women, mean ± SD age 45.8 ± 14.6 years), 74 completed the six-month follow-up. Thermal pain thresholds did not significantly change during follow-up. CPM effect improved significantly during follow-up (mean ± SD 0.25 ±2.57°C at baseline and 2.96 ± 2.50°C at six months; $P < 0.001$). At the end of follow-up, the mean CPM effect was significantly higher in patients without significant pain compared with patients with persistent pain (>3 of 10 on the Brief Pain Inventory) (mean ± SD 3.25 ± 2.68°C vs 2.47 ± 2.11°C; $P = 0.04$) and in patients achieving remission or low disease activity compared with patients with active rheumatism (mean ± SD 3.31 ± 2.68°C vs 2.18 ± 1.87°C; $P = 0.01$).

Conclusion. In active inflammatory rheumatisms, impaired descending pain modulation, but not thermal pain thresholds, is improved after TNFi treatment, suggesting a possible effect of TNFi on central pain modulation.

INTRODUCTION

One challenge in the care of chronic inflammatory rheumatism is persistent pain despite low disease activity and/or remission. Reducing joint pain is a primary treatment expectation for patients.[1] However, there is often a failure to adequately address this need for pain relief.[2] Remarkably, pain persists in up to one-third of patients who show a good therapeutic response.[3,4]

Understanding the underlying mechanisms of this persistent pain is of significant clinical importance, as it suggests that its origins are not solely related to peripheral inflammatory processes. Changes in central pain processing may play a role in maintaining and/or amplifying pain independently of peripheral inflammation.[5] Notably, central sensitization (CS), characterized by long-lasting increased responsiveness of the nociceptive systems and clinically associated with widespread hyperalgesia,

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may have a major pathophysiologic role. Proposed mechanisms for CS include enhanced excitatory synaptic transmission in central nociceptive systems and/or alterations of endogenous pain modulation (such as decreased inhibition and/or increased facilitation) resulting in maladaptive plasticity in the spinal cord or brain.[5] Clinical markers of CS are predominantly assessed through quantitative sensory testing (QST) and encompass a decrease in pain threshold and an increased effect of temporal summation of nociceptive stimuli. Alteration of endogenous pain modulation, specifically descending modulation, is typically evaluated using conditioned pain modulation (CPM) paradigms, which measure the modulatory effects (inhibition or facilitation) of a conditioning painful stimulus on a test stimulus applied to a distant body area.[6]

Our recent findings from the prospective Rheumatism Pain Inhibitory Descending Pathways (RAPID) study, which included patients with active rheumatoid arthritis (RA) or spondyloarthritis (SpA), revealed a significant impairment in inhibitory CPM effect, compared to controls, before initiation of biologic disease-modifying antirheumatic drug (bDMARD) treatment.[7] These results, in line with previous studies that demonstrated alterations in CPM in patients with RA and other markers of CS[8,9] highlight the specific role for central mechanisms in the pathophysiology of chronic pain in these patients. However, CPM was not measured after treatment, so to date it is unknown whether CPM alterations are reversible, as this has been shown in other chronic pain conditions after treatments.[10]

In this study, we present the follow-up results of our RAPID study cohort, assessing descending pain modulation through CPM paradigms in patients with RA or SpA up to six months after initiating tumor necrosis factor inhibitor (TNFi) treatment. Our primary objective was to further investigate the changes in CPM over the course of the treatment and the correlations on the overall response to treatment and the persistence of pain post treatment.

PATIENTS AND METHODS

Study population. The RAPID study is a multicenter study that included patients with active RA or SpA before the administration of bDMARDs. The patients were recruited from two French university hospital rheumatology departments (Paris and Boulogne-Billancourt) from February 2019 to June 2021. The inclusion criteria were described previously in the study by Trouvin et al.[7] Patients were included immediately before initiating a TNFi therapy for active articular disease and were observed for six months, with visits at three and six months. The study was reviewed and approved by the Sud-Est IV ethics committee under agreement number 2018-A00248-47. All participants provided written informed consent.

Clinical characteristics were systematically assessed before each visit (ie, at baseline, three months, and six months), before the QST session. The data collected included current treatments, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. Disease activity scores were calculated with the Disease Activity Score in 28 joints using the ESR (DAS28-ESR) for patients with RA or the Ankylosing Spondylitis Disease Activity Score using the CRP level (ASDAS-CRP) for patients with SpA. Pain, functional impact, and psychological impact were assessed using the Brief Pain Inventory (BPI), the Health Assessment Questionnaire score for patients with RA and the Bath Ankylosing Spondylitis Disease Activity Index/Bath Ankylosing Spondylitis Functional Index score for patients with SpA, the Insomnia Severity Index (ISI), the Hospital Anxiety Depression scale (HAD), and the Pain Catastrophizing Scale (PCS).

QST. Patients underwent QST and CPM testing at inclusion and at both follow-up visits after the initiation of the TNFi therapy by a single observer. Thermal (heat and cold) pain thresholds were assessed with the TSA II Neurosensory Analyzer. A contact Peltier thermode (30 × 30 mm) was applied to the skin over the dominant volar forearm. The baseline temperature of the thermode was adjusted to the patient's skin temperature. Thresholds were measured by the method of limits: stimuli of increasing or decreasing intensities were applied, and for each stimulus, the patients pressed a button that reversed the thermal stimulation as soon as the stimulation became painful. The interstimulus intervals used were 15–20 seconds for heat pain thresholds (HPTs) and 20–30 seconds for cold pain thresholds (CPTs). The maximum and minimum temperatures were set to 50°C for heat and 0°C for cold. The thermal rate of change was 2°C/s. Thresholds were calculated as the mean threshold recorded in three successive measures and are expressed as absolute thresholds (°C).

CPM. We used a CPM paradigm involving the application of test stimuli to the dominant upper limb and conditioning stimuli to the lower limb. The test stimulus was the HPT measured as described previously, and the conditioning stimulus was immersion of the nondominant foot in a bath of circulating cold water at 8°C (CORIO CD-900F Refrigerated/Heating Circulator) for one minute. As instructed, patients could withdraw their foot from the cold water bath if they felt the pain was unbearable during the immersion. Most patients withdrew their foot before the end of the one minute with verbal assessment of pain being unbearable. For patients going through the whole minute of immersion, oral pain assessment of the conditioning stimulus was made, and all patients rated pain at 8 of 10 or more. HPT was measured again, as described previously, immediately after conditioning. The CPM effect was calculated as the difference (expressed in °C) between HPT measured after and before the conditioning stimulus. A positive difference (ie, a higher HPT after conditioning than before conditioning) indicated activation of descending pain inhibition.

Statistical analysis. Given that the study was exploratory, there was no power calculation because, to our knowledge, no previous prospective studies on CPM permitted specific calculations, nor do standards regarding sample size.

Results are expressed as means ± SDs for continuous variables or as frequencies and percentages for categorical variables. The primary outcome was the comparison of the CPM effect measured before and six months after TNFi initiation.

Longitudinal paired data were compared using a parametric test (if normal distribution) or nonparametric tests (if not normally distributed). Correlations between CPM and pain intensities using the BPI pain scales (pain right now, worst pain, least pain, and pain in general) were assessed by calculating Spearman's rank correlation coefficient.

The primary outcome (change in CPM) was considered regarding two disease end points with the following stratification: (1) disease activity at the end of follow-up, with patients achieving remission or low disease activity (DAS28 ≤ 3.2 or ASDAS < 2.1) compared to patients with residual activity, and (2) residual pain at the end of follow-up, with patients measuring pain intensity (using the BPI scale "pain in general") as ≤3 of 10 compared to patients with residual pain. Comparison of thermal QST and CPM between patients stratified by these two end points was performed using Student's *t*-test or the Mann–Whitney U test depending on the distribution of the data.

A multivariate analysis using two models to predict the achievement of each of the two end points: remission or low activity and pain ≤3 of 10. The variables integrated into the models were tested in three stages: (1) demographic variables package (age, sex, disease duration); (2) clinical data (disease duration, disease activity, worst pain, pain in general), questionnaires (positive Fibromyalgia Rapid Screening Tool questionnaire, positive Central Sensitization index questionnaire, HAD anxiety, HAD depression, ISI, PCS), and CPM upon inclusion package; and (3) the third package, with CPM at three months and patients' reported outcomes of efficacy and satisfaction. Regarding this absence of power calculation, the RAPID study might be underpowered for such hypothesis testing. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc). The data supporting this article will be shared on reasonable request to the corresponding author.

RESULTS

Patients' characteristics and clinical effects of treatment. One hundred patients with active disease were included (50 with RA and 50 with SpA), 59 were women, and the mean ± SD age was 45.8 ± 14.6 years. Baseline clinical characteristics and disease activity have been previously described.[7] Because of the COVID-19 pandemic, only 87 patients from the initial cohort initiated bDMARD treatment with a TNFi (50 patients received etanercept, 33 received adalimumab, 2 received infliximab, and 2 received certolizumab).

Of the cohort, 74 patients completed the six-month follow-up (36 with RA and 38 with SpA) (Sup Material 1). At six months, remission was achieved by 20 patients with RA (55.6% of the patients with RA) and 12 patients with SpA (31.6% of the patients with SpA); low disease activity was achieved by 6 patients with RA (16.7% of the patients with RA) and 13 patients with SpA (34.2% of the patients with SpA); 8 patients with RA (22.2% of the patients with RA) had moderate activity; 12 patients with SpA (31.6% of the patients with SpA) had high disease activity; 2 patients with RA (5.5% of the patients with RA) had high disease activity; and 1 patient with SpA (2.6% of the patients with SpA) had very high disease activity. At the end of follow-up, the average pain intensity significantly decreased across the patient population (Table 1): 47 patients (63.5%) reported no significant residual pain (average daily pain intensity ≤3 of 10), whereas 27 (36.5%) reported persistent pain (average daily pain intensity >3). The changes in other outcomes are summarized in Table 1, showing significant reductions in functional impact, HAD depression, PCS, and ISI scores at the six-month assessment.

Changes in CPM effect and in pain thresholds. The overall CPM effect exhibited a significant increase at three months (mean ± SD 2.64 ± 2.12°C; $P < 0.001$) compared to baseline values (mean ± SD 0.25 ± 2.57°C), and this effect was sustained at six months (mean ± SD 2.96 ± 2.50°C; $P < 0.001$) (Figure 1). At three months follow-up, the mean CPM effect in patients who achieved remission or low disease activity (n = 42) was not significantly different than the mean CPM effect in patients who still had an active disease (n= 35). The mean CPM effect in patients with no significant residual pain (BPI pain scale ≤3 of 10) (n = 45) was not significantly different from the mean CPM effect of patients with residual pain (BPI pain scale >3 of 10) (n = 32). At the end of the six-month follow-up, the mean CPM effect in patients who achieved remission or low disease activity (n = 51) was significantly different from the mean CPM effect in patients who still had an active disease (n = 23) (mean ± SD 3.31 ± 2.68°C vs 2.18 ± 1.87°C, respectively; $P = 0.018$), and the mean CPM effect in patients with no significant residual pain (BPI pain scale ≤3 of 10) (n = 47) was significantly different from the mean CPM effect of patients with residual pain (BPI pain scale >3 of 10) (n = 27) (mean ± SD 3.25 ± 2.68°C vs 2.47 ± 2.11°C, respectively; $P = 0.046$) (Sup Material 2).

The changes in CPM were significantly correlated with changes in pain intensity ratings (Table 2). This indicates that a higher increase in CPM was associated with a greater decrease in pain intensity. This is in line with the previous finding of a mean CPM effect significantly higher at six months in patients without significant residual pain compared to those patients with persistent pain. In contrast, the changes in CPM effect did not show any significant correlation with changes in disease activity scores (Table 2), with the changes in blood inflammatory biomarkers at three months (ESR: r = 0.16, $P = 0.21$; CRP: r = –0.13,

Table 1. Clinical characteristics of patients throughout follow-up*

	Inclusion (N = 100 patients; 50 with RA and 50 with SpA)	3 mo (n = 81 patients; 40 with RA and 41 with SpA)	6 mo (n = 74 patients; 36 with RA and 38 with SpA)	Comparison (baseline to 6 mo), *P*
Activity score				
Patients with RA: DAS28-ESR	4.97 ± 0.94	3.1 ± 1.3	2.5 ± 1.35	<0.0001
Patients with SpA: ASDAS-CRP	3.27 ± 0.86	1.9 ± 0.8	1.8 ± 0.89	<0.0001
Functional impact				
Patients with RA: HAQ (of 3)	1.1 ± 0.8	0.7 ± 0.8	0.6 ± 0.8	<0.0001
Patients with SpA: BASFI (of 10)	4.2 ± 2.6	2.5 ± 2.5	1.9 ± 1.9	<0.0001
Mean pain intensity in general (of 10)	5.7 ± 1.4	3.2 ± 2.3	2.9 ± 2.5	<0.0001
HAD anxiety (of 21)	8.5 ± 5.4	7.3 ± 4.7	7.6 ± 5	NS
HAD depression (of 21)	7.2 ± 4.5	5.7 ± 4.5	5.6 ± 4.2	0.0009
Insomnia Severity Index (of 28)	12.9 ± 7.1	10 ± 7.1	9.8 ± 7	<0.0001
Pain Catastrophizing Scale (of 52)	23.3 ± 13.9	17.5 ± 14.8	16.1 ± 14.5	<0.0001

* Data are expressed as the mean ± SD unless otherwise stated. ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level; BASFI, Bath Ankylosing Spondylitis Functional Index; DAS28-ESR, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HAD, Hospital Anxiety Depression Scale; NS, not significant; RA, rheumatoid arthritis; SpA, spondyloarthritis.

P = 0.28) and six months (ESR: r = 0.1, *P* = 0.42; CRP: r = –0.02, *P* = 0.89), or with any of the other functional and psychological scores. Finally, variation of the CPM effect over the six-month follow-up was not explained by any of the baseline parameters (Sup Material 3). For the multivariate analysis to predict the achievement of each of the two end points (remission or low activity and pain ≤3 of 10) for all two models, none of the baseline data, in particular CPM effect, were predictive of achieving remission or low activity or absence of residual pain at the end of follow-up (Sup Material 4).

Thermal pain thresholds did not significantly change during the course of the treatment (Sup Material 5). There was no ceiling effect for the HPT. Maximal possible stimulation temperature was 50°C, and no patient ever reached this temperature as their HPT. In contrast, a few patients reached 0°C as their CPT. The mean ± SD HPT was 42.35 ± 3.68°C at baseline, 41.89 ± 3.65°C at

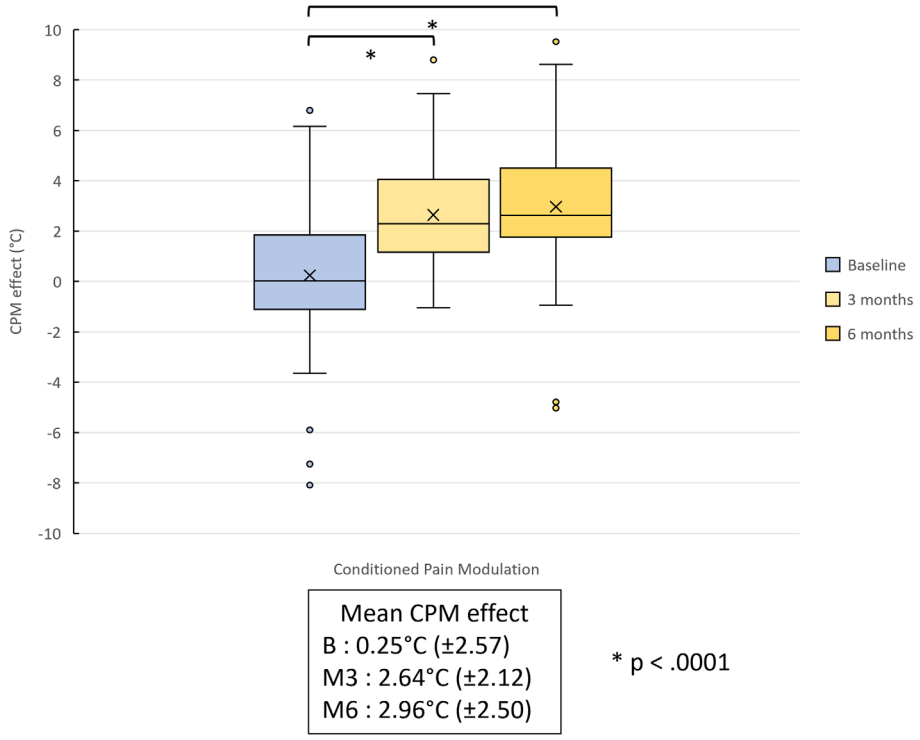

Figure 1. CPM effect evolution during follow-up. Box and whisker plots of CPM effect at baseline, three months' follow-up, and six months' follow-up. Box plots represent the upper quartile, lower quartile, the median (horizontal line), and the mean (X). Whiskers enclose 1.5 × the interquartile range. CPM, conditioned pain modulation.

Table 2. Spearman rank correlation coefficient between variation of CPM effect throughout follow-up and clinical and biologic variation during follow-up*

Variation of the considered data between baseline and 6 mo	Spearman rank correlation coefficient (r)	*P* value
Δ DAS28 (n = 36 patients)	−0.178	0.3
Δ ASDAS (n = 38 patients)	−0.33	0.4
Δ ESR (n = 74 patients)	0.105	0.42
Δ CRP (n = 74 patients)	−0.016	0.89
Δ HAQ (n = 36 patients)	0.00719	0.97
Δ BASFI (n = 38 patients)	−0.11211	0.5
Δ pain right now (n = 74 patients)	−0.39	**0.0005**
Δ worst pain (n = 74 patients)	−0.38	**0.0007**
Δ least pain (n = 74 patients)	−0.24	**0.04**
Δ pain in general (n = 74 patients)	−0.47	**<0.0001**
Δ HAD anxiety (n = 74 patients)	0.0341	0.77
Δ HAD depression (n = 74 patients)	−0.0886	0.45
Δ Insomnia Severity Index (n = 74 patients)	−0.1281	0.28
Δ Pain Catastrophizing Scale (n = 74 patients)	−0.0106	0.93

* Bold values indicate significant Spearman correlation. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; CPM, conditioned pain modulation; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAD, Hospital Anxiety Depression Scale; HAQ, Health Assessment Questionnaire; Δ, variation.

three months, and 42.17 ± 3.67°C at six months. The mean ± SD CPT was 13.11 ± 10.04°C at baseline, 13.47 ± 9.31°C at three months, and 12.86 ± 9.45°C at six months. At the end of follow-up, there was no significant difference between patients with and without persistent pain (HPT mean ± SD: 42.26 ± 3.74°C vs 42.12 ± 3.67°C, *P* = 0.99; CPT mean ± SD: 13.04 ± 9.54°C vs 12.77 ± 9.49°C, *P* = 0.76) or between patients in remission or with low disease activity and those with active disease (HPT mean ± SD: 41.97 ± 3.67°C vs 42.63 ± 3.71°C, *P* = 0.43; CPT mean ± SD: 13.33 ± 9.36°C vs 11.83 ± 9.76°C, *P* = 0.54). There was no significant difference in the variation of thermal thresholds between baseline and six months in patients with or without persistent pain or between patients in remission or with low disease activity and those with active disease (Sup Material 6).

DISCUSSION

The RAPID study was the first prospective study with repeated QST and CPM before and after bDMARD initiation. This study, in a homogenous group of patients with active disease at inclusion and naive to bDMARD demonstrates an improvement of descending modulation after TNFi initiation.

Impaired descending pain modulation and altered descending inhibitory controls have already been found in inflammatory rheumatic diseases.[7,8] This alteration of descending modulation seems to be correlated with pain intensity in patients with active disease,[7] and an inverse association of CPM with tender joint count was also highlighted by Lee et al.[9] These modifications of descending pain inhibition might be the counterpart of excessive TNFα. Descending inhibitory controls have not previously been assessed continuously before and after TNFi initiation, and the RAPID study shows modification of descending inhibitory controls after treatment introduction. Descending controls were not improved to the same level in patients with residual pain or with residual disease activity at the end of follow-up. Regarding the latter group, maintenance of altered CPM effect might be explained by persistent active disease and the presence of proinflammatory cytokines.[5,7,9] We would like to stress that, as of today, there are very few insights regarding clinical significance of CPM variation. It is thought that a negative or null CPM effect becoming positive would indicate (re)appearance of descending inhibiting control; however, it is unknown if this is clinically significant for +1°C of CPM effect or +3°C.

Modification of descending modulation contributes to CS; however, the influence of TNFi on the pain pathways is not totally understood. The role of TNFi in human pain pathways in rheumatic settings has barely been studied. In patients with RA, two studies using functional magnetic resonance imaging reported a rapid decrease in activity in brain structures of the pain matrix after one infliximab infusion[11] or certolizumab pegol injection.[12] This decrease in cerebral activity was observed as soon as 24 hours[11] to 3 days[12] after TNFi injection and preceded clinical response, which was only observed 28 days after treatment initiation.[12] Another study on patients with RA using imaging revealed a central action of TNFi; Cavanagh et al[13] used single-photon emission computed tomography to measure the effect of adalimumab over the density and activity of the serotonin transporter (SERT) in the brain. Both SERT activity and density are increased by proinflammatory cytokines, and adalimumab infusion significantly decreased SERT density.

In the central nervous system, descending inhibitory controls are mainly modulated through the periaqueductal gray (PAG) and rostral ventromedial medulla.[5,10] In these central structures, the descending inhibitory signal is mainly mediated by noradrenaline, serotonin, and opioids and potentially by other neurotransmitters, such as γ-aminobutyric acid (GABA).[14] Rodent studies have shown a possible effect of TNFα on PAG neurons; Xu et al[14] reported elevated TNFα levels in the PAG in rodents with neuropathic pain, and this correlated with an impaired GABAergic descending inhibitory system. In the study by Hess et al[11] on TNFα transgenic mice that developed inflammatory arthritis, they used functional magnetic resonance imaging to detect higher amplitudes and more widespread activation of the pain matrix. When infliximab was administered to the animals, the first changes in the pain matrix brain activation appeared as early as 24 hours after TNFi injection. The increased activity was totally reversed by TNFi, and the expanded activation was partially reversed. Moreover, a higher degree of connectivity in a cluster comprising the thalamus, PAG, and amygdala was observed in TNF transgenic mice compared with wild-type animals. TNF inhibition

resulted in a rapid but partial dissolution of this cluster.[11] TNFi are large molecules that cannot cross the blood–brain barrier, these results regarding their action on the pain have yet to be understood.

Regarding thermal QST, the thermal pain threshold did not significantly change during follow-up in our study. In inflammatory rheumatisms, thermal pain thresholds might not be the most suitable QST modality. In other studies using this QST modality, most reported no difference in HPT or CPT in patients with RA or SpA[15] compared to controls. Overall, these results question the use of thermal QST in patients with chronic inflammatory rheumatism. The choice of QST modality is still a matter of debate, and there is no consensus today regarding the appropriate measures to assess CS in chronic inflammatory rheumatisms. A few patients had floor ceiling effect with the CPT, but this had no consequences regarding CPM assessment because all patients either withdrew their foot before the whole minute of conditioning or rated their pain as 8 of 10 or more.

The RAPID study has some limitations. There was no control group throughout the follow-up. All participants initiated a TNFi, preventing conclusion to a specific TNF inhibition effect. Finally, given the limited knowledge of the CPM effect in rheumatic disease, power calculation was not possible; therefore, negative results might be due to a possibly underpowered analysis. The prediction models finding only the CPM at three months as being predictive of remission or low disease activity achievement might be due to underpower, larger studies could test the hypothesis of CPM at baseline being predictive of treatment response.

The RAPID study demonstrated that altered inhibitory pain controls in active RA and SpA are improved after TNFi treatment. These results indicate the presence of different descending controls in patients with residual pain, and future studies should focus on exploring pain pathways in patients in remission or with low disease activity, as targeted treatments of the descending pain pathways may be of interest for these patients.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Trouvin confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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