Pain in rheumatoid arthritis: a critical review

P. Sarzi-Puttini1, F. Salaffi2, M. Di Franco3, L. Bazzichi4, G. Cassisi5, R. Casale6, M. Cazzola7, S. Stisi8, M. Battellino1, F. Atzeni1

1Rheumatology Unit, L. Sacco University Hospital, Milan; 2Reumatology Department, Polytechnic University of Marche; 3Reumatology Department, La Sapienza University, Rome; 4Department of Internal Medicine, Division of Rheumatology, S. Chiara Hospital, University of Pisa; 5Rheumatology Branch, Specialist Outpatients’ Department, Belluno; 6Department of Clinical Neurophysiology and Pain Rehabilitation Unit, IRCCS Foundation Salvatore Maugeri, Scientific Institute of Montescano (PV); 7U.O.C. Rehabilitative Medicine, A.O. “Ospedale di Circolo”, Saronno (VA); 8A.O. r.n. “G. Rummo” Benevento, Italy

Corresponding author:
Piercarlo Sarzi-Puttini
Rheumatology Unit
L. Sacco University Hospital, Milan, Italy
E-mail: piercarlo.sarziputtini@gmail.com

SUMMARY

Patients with rheumatoid arthritis (RA) are frequently afflicted by pain, which may be caused by joint inflammation (leading to structural joint damage) or secondary osteoarthritis, and may be increased by central sensitisation. Non-inflammatory pain may also confuse the assessment of disease activity, and so the aim of treatment is not only to combat inflammatory disease, but also relieve painful symptoms. In order to ensure effective treatment stratification, it is necessary to record a patient’s medical history in detail, perform a physical examination, and objectively assess synovitis and joint damage. The management of pain requires various approaches that include pharmacological analgesia and biological and non-biological treatments. Although joint replacement surgery can significantly improve RA-related pain, it may only be available to patients with the most severe advanced disease.

Key words: Rheumatoid arthritis, Pain, Central sensitization, Analgesics.

INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory joint disease that has a major impact on the quality of life, working productivity, and the use of healthcare resources (1,2). RA patients usually declare that pain is their greatest problem and highest priority (3-5) as it causes psychological distress and sleep disturbances, and may even be a more important cause of disability than structural joint damage (6, 7). Pain is frequently considered a marker of inflammation, but there is only a weak correlation between the intensity of pain and measures of peripheral inflammation (8, 9); however, pain is associated with disease activity, and radiographic changes may be linked to future pain (10-13).

Inflammation causes pain, stiffness and progressive joint damage, but it is becoming increasingly possible to suppress it completely and ensure clinical remission (14), and long-term outcomes may be improved if this is rapidly achieved (15, 16). The results of clinical trials indicate that early intensive treatment with disease-modifying modifying anti-inflammatory drugs (DMARDs) and corticosteroids lead to better pain outcomes (17-20), especially when guided by the regular monitoring of disease activity. The effective suppression of inflammatory disease during the first years after a diagnosis of RA tends to decrease the level of pain, although it often does not completely disappear (21-24), and may subsequently increase once again.

The pain associated with RA may occur spontaneously or be evoked by gently moving a joint within its normal working range, and may even be felt in the apparently normal surrounding tissue. Referred pain syndromes have also been reported because the entity of symptoms does not
necessarily correlate with the severity of the underlying disease, and symptoms may continue even in the absence of disease exacerbations (25, 26).

RA-related pain may be worsened by joint damage, which may be secondary to inflammatory disease or due to concomitant osteoarthritis (OA). Moreover, the prevalence of chronic, non-inflammatory pain syndromes such as fibromyalgia (FM) is higher among patients with RA than in the general population (27, 28). Patients with inflammatory arthritis and FM have higher levels of disease activity and a poorer quality of life than their counterparts without FM. Pain therefore not only affects patients directly, but also indirectly contributes to the psychological and social impact of RA, and the need for better analgesia remains an important issue (1, 2).

### PAIN MECHANISMS IN RA

Causes of RA pain may vary between early and late disease, during and between inflammatory flares, and between different individuals. The inflamed synovium generates mediators such as prostaglandins and bradykinin and proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 and nerve growth factor beta (NGF-β) which sensitize peripheral nerves contributing significantly to the generation and maintenance of pain (29-32).

The synovium is unlikely to be the only source of pain in RA, and sensory nerves are also localized to joint capsule, ligaments, the outer regions of menisci, subchondral bone, tendon sheaths, and muscles (29).

Articular cartilage and the inner two-thirds of the menisci are normally aneural, permitting normal pain-free weight bearing and joint movement.

Synovitis is associated with altered expression of neurotransmitters, such as γ-aminobutyric acid (GABA), substance P and calcitonin gene-related peptide (CGRP), and their corresponding receptors in the spinal cord (33, 34). Microglia and astrocytes within the spinal cord are activated to produce cytokines such as TNF-α, IL-1, and IL-6, which in turn facilitate pain transmission (35, 36). Enhanced descending activation and reduced descending inhibition may further increase nociceptive transmission (37-39).

Central sensitization may be more widespread than the innervation of the inflamed joint, resulting in reduced pain thresholds in adjacent tissues (1, 2, 40).

Widespread reductions in pain pressure thresholds have been associated with low mood and sleep disturbance (41, 42), features shared with FM. Indeed, approximately 8% of patients with RA may satisfy classification criteria for FM in cross-sectional surveys (43, 44). Application of FM classification criteria in RA may identify a subgroup of patients with the most abnormal pain processing, but may conceal a larger number of patients in whom similar pain mechanisms make an important contribution to their symptoms.

Pain in RA may be further exacerbated by joint damage, either secondary to inflammatory disease, or because of comorbid OA. This may be the case particularly in long-established disease.

RA structural changes (erosions and joint space narrowing) are associated with greater pain, although they may explain only 2% of pain intensity after adjustment for other factors such as current disease activity (45).

Psychological factors contribute to the pain experience, and in addition, pain itself imposes a psychological burden. Psychological factors influence pain reporting in RA (46, 47), and high depression indices have been associated with greater RA pain (48). The pain experience may be modified by beliefs about its causes and consequences, and expectations about prognosis and response to treatment.

The pain experience is complex and multifaceted, comprising both sensory and emotional components.

Despite the undoubted contribution of inflammation to RA pain, persistent pain despite adequate control of inflammation indicates contributions from multiple pain mechanisms (1, 2).
CLINICAL EXPRESSION OF PAIN IN RA

Pain is a major risk factor for a poor outcome. Patients with early RA who report high levels of bodily pain at the time of presentation are more likely to report greater disability after one year (49). Patients describe the severity, quality and periodicity of their joint pain in different ways. It is often described as “gnawing” or aching, which suggest nociceptive mechanisms directly mediated by inflammation or joint damage, but other descriptors such as “burning” or “shooting” are more characteristic of neuropathic pain and suggest possible nerve damage. Finally, the frequent descriptions of the more widespread pain associated with sleep disturbances, fatigue and mood (50) suggest abnormal central pain processing.

The 28-joint Disease Activity Score (DAS28) is frequently used to assess joint inflammation in randomised controlled trials (RCTs) and to guide treatment decisions in clinical practice (51). Intensive ‘treat-to-target’ regimens require treatment escalation in patients with active disease defined by their DAS28, and some national guidelines (such as those of the United Kingdom) restrict the use of biological to patients with a high score. However, the relationship between DAS28 and inflammatory disease activity is confounded by other factors (52). Although visual analogue scales (VAS) and tender joint counts certainly increase with inflammation, and are both closely related with reported bodily pain (53), they may also be increased by concomitant painful conditions such as OA, which usually affects the hands and knees (joints included in the DAS28), or by changes in pain processing such as central sensitisation, which coincides with joint inflammation and may make it difficult to interpret the DAS28 (54). For example, patients who fulfill the diagnostic criteria for both RA and FM report higher levels of pain (55) and have a higher DAS28 (56) than those with RA alone, which may indicate that central sensitisation or a painful comorbidity affects the scoring.

Two recent studies have found that pain significantly affects patients’ assessments of RA disease activity. The first involved 7,028 patients from the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database receiving “usual care” at 83 centres in 30 countries (57), and showed that pain was the single most important determinant of patient global assessment. The second involved 646 RA patients starting methotrexate (MTX) treatment at an academic outpatient clinic, and found that pain explained 75.6% of the variability patient global assessment scores (58).

Although pain contributes less to physician global assessments, it was the fourth most important determinant of the physician global assessment in the QUEST-RA study, after swollen joint counts, the erythrocyte sedimentation rate, and tender joint counts (57), and second only to swollen joint counts in the physician global assessment of the MTX study (58). The fact that it was also one of the most significantly discordant variables between the patient and physician global assessments in both studies further underlines the importance of pain to patients and suggests that it is insufficiently considered by physicians.

PHARMACOLOGICAL MANAGEMENT OF RA-RELATED PAIN

The 3e (evidence, expertise, exchange) initiative, a 17-country collaborative project that promotes evidence-based practice in rheumatology, has recently published recommendations for the pharmacological management of pain in patients with inflammatory arthritis (59), many of which were based on a series of Cochrane database systematic reviews published in 2011-2012.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to manage pain in RA patients, but are not appropriate for long-term disease control (60, 61); furthermore, although the early use of DMARDs is very important (62, 83), the significance of pain
to the patients means that they often take analgesics from the start of the disease. According to the European League Against Rheumatism (EULAR), symptomatic patients presenting with early arthritis should be treated with NSAIDs after their gastrointestinal, renal, and cardiovascular status has been carefully evaluated (64), whereas the British Society for Rheumatology (BSR) guideline for the long-term management of RA recommends the short-term use of a stepped approach combining NSAIDs with a proton pump inhibitor (64), and the National Institute for Health and Care Excellence (NICE) guideline suggests analgesics (e.g. paracetamol, codeine or fixed-dose combinations) as a means of reducing the need for long-term NSAID or cyclo-oxygenase (COX)-2 inhibitor treatment (64).

However, the use of analgesics in RA is often only indirectly supported as the evidence comes from RCTs involving patients with other conditions, and publication biases may conceal some findings of inefficacy in arthritis. Furthermore, although paracetamol is readily available, there is little RCT-based evidence supporting its use (65-69), and the trials have often used it in combination with another analgesic of a different class. Paracetamol is often a component of combined products, and one potential concern is that they may mask the patient’s cumulative paracetamol intake, which should not exceed four grams in healthy adults. On the other hand, typical paracetamol-containing products include opioid combinations (codeine, tramadol, oxycodone, etc.), which may actually be opioid sparing because they provide effective analgesia at lower opioid doses than single opioids (89), and it has been demonstrated that the fixed-dose combination of tramadol and paracetamol leads to synergistic benefits (70, 71).

Nevertheless, it does seem to offer some short-term analgesic benefit and, in combination with a COX inhibitor, may be more effective than either alone, although there is no evidence that this maintained in the long term.

A systematic review (72) of 11 randomised or quasi-RCTs comparing opioids with placebo or an active analgesic has concluded that the evidence in favour of the use of weak opioids (codeine, dextropropoxyphene, pentazosine, tilidine and tramadol) is itself weak. Furthermore, the risk ratio for study withdrawal due to the frequent side effects of constipation, dizziness, nausea and vomiting between the opioid- and placebo-treated participants was 2.7, and the use of opioids may also lead to opioid-induced hyperalgesia, which is associated with heightened pain sensitivity and increased clinical pain intensity. Consequently, it is generally recommended that long-term opioid prescriptions should be minimised and, when opioids are necessary, their use should be regularly and carefully monitored (73-78).

A Cochrane systematic review found that the evidence in favour of using neuromodulators to treat RA-related pain was also weak (79), although it only considered four small randomised, placebo-controlled trials: two of nefopam (a centrally acting analgesic used in Europe but not the United States), one of topical capsaicin, and one of oro-mucosal cannabis. The authors concluded that topical capsaicin could be considered as adjuvant therapy for RA-related pain (80). Other potential adjuvant treatments options for pain in inflammatory arthritis recommended by the 3e initiative are gabapentin and pregabalin, although it should be remembered that these recommendations are mainly based on their efficacy in studies of pain in FM, a non-inflammatory, chronic widespread pain condition (81, 82).

Biological therapies (83-85), are reserved for patients with the most advanced or severe disease, whereas disease control in the majority of patients depends on glucocorticosteroids and traditional DMARDs such as MTX (86, 87). Glucocorticosteroids and DMARDs reduce RA-related pain, but the analgesic effects of the former may only last for three months (88, 89). The early suppression of inflammatory disease activity is not only important to reduce pain in the short term because delaying the introduction of DMARDs is associated with
worse pain 12 months after presentation. Finally, DMARD combinations may be more effective than monotherapy. It must also be remembered that inflammation is only one component contributing to the pain experienced by many arthritic patients, and incomplete symptomatic relief is frequent even when there is other evidence of inflammatory control such as reductions in swollen joint counts, the levels of acute-phase reactants, and ultrasound findings of synovitis. These clinical observations and the often slow action of disease-modifying treatments mean that alternative strategies are necessary. Although adequate analgesia may have a positive effect on disease activity scores by reducing joint tenderness and improving patient-reported general health, it is necessary not to mistake this for the suppression of the underlying disease.

Tricyclic antidepressants (TCAs such as amitriptyline, dothiepin and imipramine) inhibit serotonin and norepinephrine reuptake and neuronal sodium channels (90), but it is believed that the differences in the antinociceptive effects of the various TCAs are substantially due their non-serotonergic properties. The results of clinical trials of TCAs have led to equivocal results in RA patients (91). A Cochrane systematic review of eight RCTs comparing antidepressant therapy with placebo or an active intervention found insufficient evidence to recommend its use to treat RA-related pain (91), whereas the 3e recommendations include TCAs as a potential adjuvant treatment for patients with inflammatory arthritis (59), although it was specifically noted that the still-incomplete data mean that they should only be considered for a subset of patients. Nevertheless, TCAs offer RA patients significantly more pain relief than placebo (91-93), and their use has become so widespread that it has been proposed that, like anticonvulsants, they should be considered “pain-modifying drugs”.

The current stratification of analgesic treatment is based on potency or sequential trials, beginning with the least expensive, low-risk treatments. However, individual failures of analgesic or anti-inflammatory therapy may indicate that other pain mechanisms are involved, and that patients may benefit more if stratified care is based on the careful evaluation of the contributions of inflammation, joint damage and central sensitisation.

The multi-dimensional nature of RA and most other chronic pain indications suggests that a combined approach to analgesia may be more appropriate, and findings of the 23 studies published so far have been summarised in a recent Cochrane systematic review (94). No meta-analysis was made because of the heterogeneity of these studies, but 18 reported no significant difference in a standardised pain outcome between the monotherapy and combination therapy groups: however, it is unclear whether these results can be generalised.

Non-pharmacological pain management can be important because chronic pain acceptance, coping skills and self-efficacy contribute to the quality of life of RA patients, and psychological interventions such as cognitive behavioural therapy may also help (95-98). A better understanding of pain mechanisms can limit catastrophic thoughts concerning the meaning of pain, and combined psychological and pharmacological strategies can facilitate pain control. In some cases cognitive therapy may be an effective treatment for RA and need not necessarily include behavioral strategies (99, 100).

Patients with RA who have moderate disease activity and limited joint erosions may benefit from short-term exercise including aerobic capacity and dynamic strength training. Short-term, land-based aerobic exercise is likely to improve aerobic capacity immediately following the intervention but may not affect muscle strength or functional ability. Short-term and long-term, land-based aerobic and strength training may improve aerobic capacity and muscle strength. Exercise also does not appear to produce any negative effects with respect
to increased pain or disease activity (101). Resistance exercise in RA is safe, and the improvement in most outcomes was statistically significant and possibly clinically relevant for RA pain and disability (102). In the case of patients with severe, unremitting pain localised to a single joint, joint replacement surgery can offer substantial relief (103-105). The underlying reasons for this are not fully understood, but may include the physical protection of subchondral nerves or the avoidance of the development of synovitis from an origin in the articular cartilage.

CONCLUSIONS

Rheumatoid arthritis is a frequent and chronic painful condition affecting the synovial joints. Current treatments concentrate on suppressing inflammation, but rarely provide complete pain relief. Pain is not only an important outcome for RA patients, but also aggravates disability and psychological distress. RA-related pain may be mediated by mechanisms such as inflammation, structural damage or altered central pain processing, and a better understanding of the different contributions of these mechanisms should lead to more effective treatment targeting as well as the development of new and more efficacious treatments with fewer side effects. The two most important advances in the treatment of arthritic pain over the last 40 years have been the introduction of total joint replacement surgery into routine clinical practice, and the more recent development of biological therapies that suppress the underlying inflammatory disease (1, 2). Both have improved the quality of life of large numbers of patients, but both are now associated with substantial healthcare expenditure. Furthermore, 15% of the patients undergoing total knee replacement surgery may continue to experience persistent and disabling pain, and up to 25% of those receiving anti-TNF therapy for presumed active RA receive no meaningful benefit. RA treatments targeting inflammatory mechanisms not only relieve pain by suppressing synovitis, but may also reduce central sensitisation by modulating neuro-immune interactions in the central nervous system: they should therefore be offered together with pharmacological and non-pharmacological treatments for RA-related pain in order to optimise both short- and long-term outcomes (106).

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