J Rheum Dis 2023;30(1):1-2
https://doi.org/10.4078/jrd.22.0047
pISSN: 2093-940X, eISSN: 2233-4718

Editorial

A Challenging Target: Persistent Pain During the Remission State in Rheumatoid Arthritis Patients

Doo-Ho Lim, M.D., Ph.D.

Division of Rheumatology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Pain is an important symptom in patients with rheumatoid arthritis (RA) and can cause various physical and psychological impairments [1]. Despite recent advances in disease-modifying anti-rheumatic drugs (DMARDs) and the treat-to-target approaches for improved management of inflammation, rheumatologists often encounter patients in the clinic with complaints of moderate to severe pain [2]. In this point, a study by Kim et al. [3] reported in the previous issue of the *Journal of Rheumatic Diseases* provides important implications of using a multidimensional approach to pain management in RA patients.

Pain in RA patients is caused due to several underlying mechanisms. In addition to the inflammatory pain caused by local and systemic cytokine effects, arthritis pain results from simple mechanical stimulations such as weight-bearing and joint movement (nociceptive pain). Changes in the articular environment due to structural joint damage and chronic inflammation can increase neuronal innervation or sensitize peripheral nociceptors at the joint site (peripheral pain sensitization) [4]. Recent studies using functional magnetic resonance imaging have shown increased and modulated cortical responses to pain stimuli in the central nervous system, suggesting a role of central processing in RA-associated pain (central pain sensitization) [5,6]. Moreover, RA patients have a higher prevalence of mood disorders including depression and anxiety compared to healthy individuals, and the psychological distress has been associated with increased levels of pain [7].

The pain characteristics described in RA patients may include symptoms such as aches, shooting or sharp pain, among others, which may be temporary, constant, or weight bearing-related [8]. An appropriate description of pain obtained from the clinical history and physical examination may aid in elucidation of each pain mechanism underlying RA, or indicate the mechanisms triggered by separate comorbid conditions, including osteoarthritis, fibromyalgia, carpal tunnel syndrome, and depression. Imaging plays a supportive role in measuring disease activity of RA and detecting comorbidities [9]. Plain radiography can detect osteopenia, joint space narrowing, erosion, and osteophytes; however, it is not sensitive so to be better at diagnosing late-stage disease. In recent years, musculoskeletal ultrasonography has emerged as an imaging modality for measuring disease states in RA and osteoarthritis with greater sensitivity and specificity compared to plain radiography. A negative result obtained by musculoskeletal ultrasonography may also be suggestive of other etiologies of pain including fibromyalgia.

Persistent or residual pain accompanying an inflammatory remission state is one of the most significant unmet needs in RA patients. In a previous study, Lee et al. [10] mentioned that approximately 47 percent of RA patients with low levels of inflammation reported moderate to high levels of pain, and that fatigue, pain catastrophe, and sleep disturbance were presented as relevant factors, indicating chronic widespread pain syndrome. Considering the disease duration, about 60% of established RA patients complained of dissatisfaction with pain treatment; however, persistent pain is still known to affect approximately one-

Received October 11, 2022; **Revised** October 30, 2022; **Accepted** November 8, 2022, **Published online** November 15, 2022

Corresponding author: Doo-Ho Lim, https://orcid.org/0000-0002-8012-7364
Division of Rheumatology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, 25 Daehakbyeongwon-ro, Dong-gu, Ulsan 44033, Korea. **E-mail:** dlaengh@hanmail.net

third of early RA patients despite a good clinical response [11]. Vergne-Salle et al. [2] showed that despite the high proportion of RA patients on biological DMARDs treatment (83%), 38.4% of patients continue to report moderate to severe pain, which is primarily associated with anxiety and depression scores as well as RA activity scores.

Using the Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry data, Kim et al. [3] reported that 21.5% of RA patients complained of persistent moderate to severe pain despite clinical remission while being managed with biological or targeted synthetic DMARDs. Further, foot erosions, neurological disorders, and corticosteroid use were independent risk factors for moderate-to-severe pain in these patients on multivariate regression analysis. This study explored the prevalence and risk factors for persistent pain in Korean RA patients in remission, suggesting the importance of a physicians' evaluation of the causes of pain using a multi-angle approach for appropriate therapeutic planning based on the underlying pain mechanisms. No association was found between persistent pain and mental illness, such as depression or anxiety as predicted, since knowledge about these factors were not accurately collected in the KOBIO registry, as mentioned by the authors. Interestingly, despite the small number of cases, the use of Janus kinase inhibitors was inversely associated with moderate to severe pain. This is consistent with the results of a previous study [12] wherein, baricitinib monotherapy displayed superior pain-reducing ability compared to adalimumab monotherapy and tocilizumab monotherapy. However, the exact mechanisms underlying the potential differences between the efficacies of various DMARDs in pain modulation are still unknown.

In conclusion, persistent pain in RA patients, despite remission, remains clinically challenging. In these patients, a multidimensional evaluation, including clinical symptoms and signs, laboratory tests, imaging, and comorbidities, should be performed to identify the dominant and most appropriate pain mechanism. This could prevent inappropriate treatment escalation with DMARDs and provide a personalized pain management. Thus, further research is required for development of simplified tools in order to assess various aspects of the pain in RA and to provide guidance to the physicians.

FUNDING

None.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

D.H.L. has been an editorial board member since June 2020, but has no role in the decision to publish this article.

REFERENCES

1. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:581-92.
2. Vergne-Salle P, Pouplin S, Trouvin AP, Bera-Louville A, Soubrier M, Richez C, et al. The burden of pain in rheumatoid arthritis: impact of disease activity and psychological factors. Eur J Pain 2020;24:1979-89.
3. Kim HA, Park SY, Shin K. Implications of persistent pain in patients with rheumatoid arthritis despite remission status: data from the KOBIO registry. J Rheum Dis 2022;29:215-22.
4. Shinoda M, Honda T, Ozaki N, Hattori H, Mizutani H, Ueda M, et al. Nerve terminals extend into the temporomandibular joint of adjuvant arthritic rats. Eur J Pain 2003;7:493-505.
5. Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, et al. Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A 2011;108:3731-6.
6. Basu N, Kaplan CM, Ichesco E, Larkin T, Harris RE, Murray A, et al. Neurobiologic features of fibromyalgia are also present among rheumatoid arthritis patients. Arthritis Rheumatol 2018;70:1000-7.
7. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216-24. Erratum in: Nat Rev Rheumatol 2011;7:314.
8. Burckhardt CS. The use of the McGill Pain Questionnaire in assessing arthritis pain. Pain 1984;19:305-14.
9. Sakellariou G, Scirè CA, Adinolfi A, Batticciotto A, Bortoluzzi A, Delle Sedie A, et al. Differential diagnosis of inflammatory arthropathies by musculoskeletal ultrasonography: a systematic literature review. Front Med (Lausanne) 2020;7:141.
10. Lee YC, Frits ML, Iannaccone CK, Weinblatt ME, Shadick NA, Williams DA, et al. Subgrouping of patients with rheumatoid arthritis based on pain, fatigue, inflammation, and psychosocial factors. Arthritis Rheumatol 2014;66:2006-14.
11. Altawil R, Saevarsdottir S, Wedrén S, Alfredsson L, Klareskog L, Lampa J. Remaining pain in early rheumatoid arthritis patients treated with methotrexate. Arthritis Care Res (Hoboken) 2016;68:1061-8.
12. Fautrel B, Zhu B, Taylor PC, van de Laar M, Emery P, De Leonardis F, et al. Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab and tofacitinib monotherapies in rheumatoid arthritis patients who are naïve to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison. RMD Open 2020;6:e001131.