Rheumatoid Arthritis and Pain Management: Literature Review

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic inflammatory disease of the synovial joints that influences approximately 0.5-1% of the population global. Degrees of RA vary in different patients and are assessed according to intensity, pain, and disability in daily life. Purpose: The purpose of this literature review is to review RA pain, and mediators primarily cytokines, inflammation mediators, and various RA mechanisms. Method: This is a descriptive review. Relevant literature was identified by searching PubMed using key search terms, including arthritis, cytokines, cytokine signaling, inflammation, Janus kinases, pain, mechanisms, rheumatoid arthritis. Results: Several cytokines that target the treatment of RA, such as TNF-α, IL-1, and IL-6, have been well characterized in the pathogenesis of RA and associated pain through autoimmunity promotion, chronic inflammatory synovitis, and destruction of adjacent joint tissue. The range of epigenetic and other mechanisms by which such variants could disrupt cytokine homeostasis to increase disease risk is only beginning to be understood, along with the recognition that in relevant disease contexts they are best dissected at the cellular level. Another descriptive review talks about the role of the central nervous system. Many studies have explored the mechanisms of CNS pain in fibromyalgia and research on CNS pain mechanisms in osteoarthritis is growing. Conclusions: We conclude that there are different pathways to explain pain in rheumatoid arthritis.

Keywords: *pain, rheumatoid arthritis, literature review, patients*

1. Introduction

Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic inflammatory disease of the synovial joints that influences approximately 0.5-1% of the population global. One of the main manifestations of RA is pain. The worldwide association for the take a look at of pain defines ache as "an uncomfortable sensory and emotional experience associated with, or defined as such, real or capability tissue damage". RA is characterized by way of ache that manifests itself in a patient with various stages of first-class, distribution, and intensity, and through the years for the same patient. Inflammatory mediators along with cytokines can bind to primary afferent nociceptors and decrease the activation thresholds of transducers for evoked stimuli, resulting in improved pain, a primary mechanism of peripheral sensitization.

several cytokines, which are at once or circuitously regulated via the Jak / STAT pathway, play crucial roles in mediating numerous mechanisms that underlie ache in RA.

2. Method

This is a descriptive review. Relevant literature was identified by searching PubMed using key search terms, including arthritis, cytokines, cytokine signaling, inflammation, Janus kinases, pain, mechanisms, rheumatoid arthritis. Pain is classified into nociceptive pain, NeP, and mixed pain.

3. Results

The following results on the role of cytokines were obtained in a descriptive review (1). According to Simon et al. (2020), several cytokines that target the treatment of RA, such as TNF-α, IL-1, and IL-6, have been well characterized in the pathogenesis of RA and associated pain through autoimmunity promotion, chronic inflammatory synovitis, and destruction of adjacent joint tissue. IL-1β, a proinflammatory cytokine, is largely upregulated in RA, including in the synovial milieu. TNF-α is a ligand for TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), both of which were detected in the DRG in animal experiments. Additional evidence from animal studies suggests that the binding of TNF to one of these receptors contributes to hyperalgesia in chronic inflammation.

Zhang et al., (2018) (2) describes the role of cytokines in the early stages of RA. The range of epigenetic and other mechanisms by which such variants could disrupt cytokine homeostasis to increase disease risk is only beginning to be understood, along with the recognition that in relevant disease contexts they are best dissected at the cellular level. This becomes relevant when one considers measurable changes in a range of circulating cytokines observed with some consistency prior to the onset of symptoms in those who later develop rheumatoid arthritis as compared to healthy subjects.

Interestingly, patients with this subgroup of the disease typically describe shorter symptom duration when presenting with arthritis, but with evidence of more pronounced IL-6-mediated lymphocyte activation in the periphery compared to their seropositive counterparts, indicating an "explosive", pro-inflammatory component of the natural course of seronegative disease.

Zheng et al., (2019) (3) concludes that nerve damage from RA may increase the production of LTB4, which activates their receptors, leading to increased release of proinflammatory cytokines and ROS to reduce neuron function and pain threshold. In addition, activation of LTB4-BLT1 may also increase intracellular calcium intake and excitability of neurons and activate the NF-κB pathway, which further stimulates the production of MMP-9 and CXC3R-1. The same promotion of LTB4 and neutrophil collection accelerates the release of TNF-α and IL-β, increasing your sensitivity to both the peripheral and central nervous system. LTB4 is also involved in TrpV1 channel activation and P2X3 receptor activation. All of the above methods contribute to the development of RA pain.

Sarzi-Putini at al, (2014) conducted that the three main components of CNS pain management procedures are: (1) descending dynamic pathways, (2) descending dynamic pathways, and (3) moderate sensitivity. Decreased stimulants and obstructive pathways travel from the brain through the trunk of the brain to the spinal cord. Two important control centers periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). Although many studies have explored the mechanisms of CNS pain in fibromyalgia and research on CNS pain mechanisms in osteoarthritis is growing, research examining moderate pain in RA is still in its infancy. Recent research suggests that non-inflammatory factors may play a role in the maintenance of pain, such as inflammation.

Three hundred consecutive patients with RA diagnosis who agreed to participate in the study were enrolled in a study on neuropathic pain in RA (Ito et al., 2018). DETECT Questionnaire (PD-Q) is a NeP detection tool reported from Germany. Ahmed et al. reported that 33% of RA patients may have NeP components. Based on the outcome analysis, 3.0% of patients were classified as likely to have NeP, while 11.3% of patients were classified as having possible NeP. Although we do not include patients with conditions that may affect NeP, a certain number of patients with RA may still have NeP components. t it is possible that, in addition to nociceptive pain, the pain of RA patients includes mixed, partial NeP pain. To date, pain in RA patients has been considered nociceptive pain due to the presence of inflammation, but patients with joint deformity without inflammation may experience mixed pain or NeP. Additionally, multivariate analysis also showed that BMI & 22 was associated with NeP (5).

In a recent study (Heisler et al., 2020), a total of 263 RA patients with active disease underwent quantitative sensory testing (QST), including assessments of extra-articular pressure pain thresholds (PPT), temporal sum (TS), and

pain conditioning modulation (CPM). Pain perception was assessed using a numerical pain intensity scale and the computerized adaptive pain interference test of the Patient Reported Outcome Measurement Information System. From January 2014 to June 2017, two hundred and ninety-five subjects were recruited from 5 academic medical centers in the United States. It is believed that low PPTs at extra-articular sites represent a centralization of pain. To assess the clinical impact of the relationship between PPT and pain intensity, we considered the least clinically significant difference (MCID) in pain intensity. In this study they report an adjusted difference in pain intensity of 1.02 between the more and less centrally dysregulated PPT groups, which is above the MCID, indicating that this change is of clinical importance. Finally, no association was found between the measures of inflammation and our primary result of pain intensity (6).

Another study emphasizes the role of non-nociceptive pain in rheumatoid arthritis. A cross-sectional study was carried out with 112 RA patients (Rocha et al., 2018). The female sex was predictive of PN in both tests, and disease duration was inversely associated with the LANSS-NP. After adjusting for these two variables, VAS and TJC pain were positive predictors of PN in both tests. The same was not true for SJC, ESR, or CRP scores. DAS28-CRP was significantly associated with PDQ NP and lost its statistical significance after adjusting for TJC and VAS of pain. The HAQ score increased the likelihood of NP for both tests, regardless of DAS 28-CRP. Positivity for ACPA and previous / current hydroxychloroquine treatment had a lower likelihood of NP. Greater structural damage, longer disease duration, and ACPA positivity do not seem to increase the likelihood of PN (7).

One hundred and eighty certified RA patients were classified as nociceptive (61%) or non-nociceptive (39%) pain-based phenotype based on their responses to a DETECT questionnaire in another non-invasive longitudinal study (Klooster et al., 2019). Previous research by Christensen et al., Who also used PD-Q in RA. in 2016 they showed similar levels of nociceptive and non-nociceptive pain phenotypes: 65% of RA patients had nociceptive pain and the remaining 35% had non-nociceptive pain. In the present study, RA patients with a phenotype of non-nociceptive pain were found to have approximately 12 additional risks of simultaneous diagnosis at a fibromyalgia clinic. Patients in the present group of non-nociceptive pain phenotype had more severe rheumatic disease and more severe side effects; H. Medium disease activity scores and low levels of remission. In addition, some studies in patients with a moderate to severe pain experience report more severe pain and lower rates in health-related quality of life areas. Interestingly, patients with non-nociceptive pain tend to have slightly lower BMI and may have anti-CCP negative (8).

Conclusions

We conclude that there are different pathways to explain pain in rheumatoid arthritis (9). In different studies and reviews, these pathways are conducted. For example, the role of cytokines is described thoroughly in several studies. Also, the non-nociceptive mechanism is further explained. The importance of this review lies not only in knowing the mechanisms but also in understanding the ways to relieve the pain and disability. However further studies are needed to explain further the mechanism of pain and disability in RA.

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