EDITORIAL

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Efficacy of hydroxychloroquine for knee osteoarthritis

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Knee osteoarthritis (OA) is the most common cause of pain and movement impairment in older adults [1]. The pathogenesis of OA involves a complex combination of genetic, mechanical, metabolic, and inflammatory processes [2,3]. OA treatments target swelling, reduce disability, and enhance quality of life [4]. Pharmacological treatments include analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular corticosteroids. Other treatments include symptomatic slow-acting drugs for osteoarthritis (SYSADOA) and disease-modifying osteoarthritis drugs (DMOADs), which have the potential to retard disease progression [5]. Because pain is a clinical hallmark of OA, treatments have been developed to target various pain pathways. The DMOADs are a novel group of medicines used to inhibit OA progression and alleviate symptoms in the affected joints [5]. A wide variety of disease-modifying drugs are available for inflammatory joint disorders, but there is currently no licensed medicine with disease-modifying capabilities for OA. Although NSAIDs are frequently administered for pain relief and enhancement of functional capacity, their use is associated with an increased risk of gastrointestinal and cardiovascular problems [6].

Conventional disease-modifying anti-rheumatic drugs have been tested in patients with OA [4]. The anti-malarial agent hydroxychloroquine (HCQ) exhibits immunomodulatory and anti-inflammatory properties [7], and has been used to treat rheumatoid arthritis and systemic lupus erythematosus. Toll-like receptors (TLRs) are expressed in OA cartilage and promote the degradation thereof through pro-inflammatory pathways [8]. Because of its inhibitory action on TLR signaling, HCQ has potential as an OA treatment. In addition, HCQ has antioxidant capabilities and may protect against free radical tissue damage [9]. In the current issue of the *Korean Journal of Internal Medicine*, Singh et al. [10] demonstrated that HCQ does not reduce pain or improve physical function in patients with hand or knee OA. Their meta-analysis included six randomized controlled trials (RCTs) on HCQ. They found that HCQ did not improve physical function in patients with hand or knee OA. However, a subgroup analysis of two trials revealed a statistically significant reduction in knee OA-related functionality (standardized mean difference [SMD], –0.48; 95% confidence interval [CI], –0.82 to –0.14). Furthermore, the meta-analysis revealed a moderate effect size for pain reduction in knee OA, although it was not statistically significant (SMD, –0.72; 95% CI, –1.57 to 0.14). One of the two

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trials showed significant differences between the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and the subscale scores (of pain, stiffness, and function) at 4, 8, 12, 16, 20, and 24 weeks in an RCT with 44 patients [11]. That study concluded that HCQ provided considerable relief from knee OA symptoms. Another knee OA RCT, of 166 patients, found a statistically significant decrease in WOMAC knee pain and physical function subscale scores in the HCQ group (400 mg once daily) compared to the placebo group after 36 weeks [12]. This second trial indicated that HCQ reduced pain and enhanced physical function in patients with knee OA. Despite the small sample size, and the fact that one study was only published as an abstract for an academic conference, both RCTs consistently demonstrated that HCQ is beneficial for reducing knee pain and enhancing physical function in patients with knee OA.

The varying responses to treatment of different joints with OA may complicate interpretation of the therapeutic impact. The inability of HCQ to outperform placebo in the meta-analysis should not dissuade researchers and medication developers. The insights obtained regarding the mechanisms and clinical effectiveness of HCQ suggest that its disease-modifying potential should be given more consideration. Therefore, future clinical studies based on current understanding of OA pathophysiology are warranted to fully assess the efficacy of HCQ as a DMOAD for knee OA.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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