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Mini Review

Important Considerations in the Pharmacological Management of Osteoarthritis-Related Pain

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Abstract

In the last years, the approach to chronic osteoarthritis pain has moved from a joint-centred viewpoint towards a whole body-based approach, where the central nervous system seems to play a key role in maintaining and amplifying pain pathways. Current therapeutic strategies and future perspectives are discussed in the light of the last clinical evidence. Three targets of treatment must be considered: a) peripheral mechanisms of pain and inflammation; b) central sensitization; and c) joint degeneration. Non-pharmacological strategies are currently the first step of treatment. Among analgesics anti-inflammatory drugs and paracetamol should be preferred, and tramadol added in non-responder. Opioids, despite their efficacy, are currently not recommended for the fear of their abuse potential. Viscosupplementation via intra-articular hyaluronic acid, platelet rich plasma, and mesenchymal stem cells play a role in targeting joint pathology and prevent further damage. Targeted therapy with monoclonal antibodies may represent a viable future option for osteoarthritis and chronic low back pain, but regardless to their efficacy, further clinical studies are evaluating their safety profile before introduction on the market. Similarly, preliminary promising results coming from other biological intra-articular therapies, targeting cartilage anabolism, prevention of cartilage degradation, and subchondral bone changes, need further clinical investigations to be confirmed.

Keywords: *Neuroplasticity; Chronic Pain; Monoclonal Antibodies; Osteoarthritis; Low Back Pain; Opioids*

Introduction

Osteoarthritis (OA) is one of the major reasons for musculoskeletal (MSK) pain, inducing patients to indiscriminate use of pain killers and determining a significant rise in joint replacement surgery. The most evident clinical feature of OA is articular cartilage degradation [1,2]; therefore, the therapeutic approach has been largely focused on the structural pathology and the possible strategies for the prevention of further damage. However, OA is also a painful disease, which can be characterized by abnormal sensations in the area of pain referral (allodynia, hyperalgesia, dysesthesia), widespread diffusion of pain without a plausible neuroanatomical distribution, and often poor responsiveness to traditional analgesics [3]. Moreover, it is common clinical practice to observe that the perceived pain in patients with similar structural damages within the joints may vary substantially.

Increasing evidence highlighted the role of the central sensitization in the maintenance and amplification of chronic pain. The temporal criterion does not account the complex neuroplasticity processes that mediate the transition from acute (adaptive) to chronic

(maladaptive) pain. The perpetuation of peripheral nociceptive inputs to the spinal cord dorsal horn (pain generator) sustains a process of central sensitization, with primary functional and secondly structural modifications of the central nervous system (CNS), which are known as neuroplasticity [4]. Chronic pain is supposed to be the result of the imbalance between amplified ascending pain pathways and inadequate activity of the inhibitory descending pain modulation, as characterized using functional MRI [5]. Most of the chronic pain patients, indeed, suffer from mixed pain syndromes (nociceptive and neuropathic components can be detected at clinical examination), which require a tailored mechanism-based treatment. In the damaged joints, disruption of innervation, neurovascular invasion, and activation of articular pain–sensing fibres may contribute to neuropathic pain [6]. In these patients, often monotherapy may be insufficient and a multimodal approach is needed to obtain adequate pain relief. Therefore, the treatment of OA pain should take into account at least three targets: a) peripheral mechanisms of pain and inflammation, where and when it occurs (flares); b) central sensitization, tailored by using central analgesics, such as antidepressants, anticonvulsants, and opioids, when needed; and c) joint pathology, where drugs that affects the progression of joint destruction may be used locally or by systemic administration.

Current treatments

The prevention and treatment of central sensitization in OA pain should target specific mechanisms involved in each single patient. Central sensitization can be damped by blocking peripheral inputs that sustains long term potentiation, and by interacting directly with the central nervous system (CNS) neurotransmitters. Therefore, an appropriate selection of therapeutics should suggest the use of NSAIDs in acute pain associated with inflammatory phenomena, and central analgesics in chronic pain, including drugs that modulate noradrenaline reuptake, when neuroplasticity phenomena are detected [7]. Conversely to these principles, current available guidelines suggest or preclude the use of specific analgesics, according to few selected published clinical trials, on the basis of the expert opinion of reviewers involved in the meta-analysis; and often the fear of their potential side effects weights more than the actual analgesic efficacy, as in the case of opioids and their abuse potential [8]. Limits of applicability of evidence in chronic pain management are well-known: a) evidence is often based on placebo-controlled trials; b) most of these studies are sponsored by the manufacturer and conducted in research centres; c) number of involved patients if often too small; d) duration of treatment too short compared with real world clinical practice to make conclusion on long-term efficacy; e) most patients are middle-aged, while in clinical practice the majority are elderly; f) the number needed to treat (NNT) or to harm (NNH) do not offer a measure of the gradual response to treatment; and g) combination therapy is an under-researched solution.

According to current available guidelines, OA pain is mainly addressed with non-pharmacological interventions, such as patient education, physical therapy, exercise, weight loss, and occupational therapy [9]. Pharmacological treatment includes first line drugs, such as acetaminophen and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), which are indicated only for short-term treatment of recurrent flares of inflammatory activation [10]. Tramadol is the only opioid included in all guidelines on hand, knee, and hip OA, when the pain intensity becomes moderate to severe. Due to the risk of drug abuse, nowadays most of the guidelines on OA strongly discourage the use of opioids [11]. A recent RCT comparing opioid vs non-opioid therapy did not support initiation of opioid treatment for moderate to severe hip or knee OA [12]. However, it should be considered that not all opioids are equal in the modulation of pain chronification. Morphine has been shown to have a limited efficacy in mixed pain condition, when central neuroplasticity modifies pain perception. However, among opioids, the atypical molecule, named tapentadol, has been widely investigated in patients with OA [13], chronic low back pain (CLBP) [14] and neck pain [15]. The dual mechanism of action (mu-opioid receptor agonist and inhibitor of noradrenaline reuptake) makes tapentadol ideal for mixed pain syndromes. The serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine has been included as third step of therapy, together with short term weak opioids [16], while gabapentinoids (calcium channel alpha-2-delta ligands) are not recommended in most guidelines, for the lack of efficacy and their potential risk of abuse [17].

Viscosupplementation, through intra-articular hyaluronic acid (IA-HA) injections, is widely used in patients with OA. There is enough evidence to support multiple injection regimens to provide sustained pain relief, but further studies are required to investigate the effects

of other variables, such as the molecular weight of the different products and the addition of other components, such as sorbitol, for its free radical scavenging capacity [18].

Intra-articular injections include also biological agents, such as the platelet rich plasma (PRP), which may be a useful treatment for delivering a supra-physiological amount of growth factors and cytokines in the injured area. There is high quality level of evidence that PRP is effective and safe for OA of the knee and lateral epicondylitis, while additional trials are required in other possible indications, such as OA of the hip, tendinopathy, and plantar fasciitis. Moreover, the heterogeneity of PRP preparations make difficult to give specific clinical recommendations on their use [19]. In 2019, NICE recommendations stated that PRP injections can be considered safe, but the evidence on efficacy is still limited in quality [20].

Another potential cell source for cartilage repair are the mesenchymal stem cells (MSCs), obtained from bone marrow, adipose tissue, and amnion. MCSs have the potentiality of chondro-differentiation, rapid proliferation, and immunosuppression. The effects of intra-articular MCSs injections are encouraging, but larger human studies, using standardized protocols, are needed to confirm their role and assess the safety of these strategies [21].

Symptomatic slow-acting drugs for OA (SYSADOAs) have been widely used in Europe for the treatment for OA; however, glucosamine sulfate (GS) and chondroitin sulfate (CS) have been shown to have limited benefit in controlling pain and there is a fair evidence of their disease-modifying effect with long term treatment. Avocado soybean unsaponifiables (ASU) also require further investigation, because all ASU studies allowed the use of NSAIDs, which may result as a confounding factor [22].

Emerging treatments

The future of OA pain treatment is moving in a different direction. The experience coming from the rheumatology, where biologic therapies have dramatically changed the natural history of immunological diseases, such as rheumatoid arthritis, led to investigation on possible novel targets in managing chronic pain. Monoclonal antibodies (mAbs) have been used in the clinical trials for chronic OA pain, but they are still in the phase III pre-marketing studies. One of the mAbs targets better investigated for OA is the nerve growth factor (NGF), which is a neurotrophin that plays a key role in both nociceptive and neuropathic pain. NGF pain signalling has been detected in the early stage of the inflammatory response and in the process of sensitization of primary afferent fibres, leading to hyperalgesia.

Tanezumab (Pfizer and Eli Lilly), Fulranumab (Janssen and Amgen), and Fasinumab (Regeneron and Teva) are anti-NGF antibodies, which have been investigated in various MSK pain conditions, such as OA and CLBP. Despite their proven efficacy as pain reliever, from 2010 to 2015, the Food and Drug Administration (FDA) imposed a hold on all clinical trials on anti-NGF, because of severe joint-related adverse events (rapidly progressive osteoarthritis) and safety concerns related to the anatomical changes seen in the sympathetic nervous system of animal models [23]. Clinical studies were resumed in 2015 with reduced dosages and in co-administration with NSAIDs, to minimize the dose and related side effects. Tanezumab and Fasinumab are currently under investigation. They have been demonstrated statistically superior compared to NSAIDs and opioids in terms of pain relief in OA and CLBP, with acceptable tolerability [24]. In patients with moderate to severe OA and inadequate response to traditional analgesics, including opioids, Tanezumab was shown to be superior to placebo in term of pain scores and improvement of physical functioning [25].

Another target for the immunological treatment of OA is the IL-1, found at elevated levels in the synovial fluid of OA patients and held responsible for the joint degenerative process. However, AMG 108, which is a fully human immunoglobulin G2 against IL-1 receptor type 1, failed to show a significant improvement in pain and functionality scores in OA patients, and its use was associated with a decreased neutrophil count [26].

Future targets of treatment have been identified in molecules involved in cartilage anabolism, prevention of cartilage degradation, and subchondral bone changes: the transforming growth factor-beta (TGF-β) and alpha (TGF-α), the fibroblast growth factor (FGF) and the Wnt/b-catenin signaling pathway. All these potential therapeutic pathways require further elucidation [27].

Finally, another emerging option in the treatment of OA is the use of nanomaterials for intra-articular injections, in order to improve joint drug delivery, where localization and prolonged joint retention are considered critical issues for the efficacy of the drug. Nanomaterials are studied for enhancing whole joint retention and for targeting specific intra-articular elements, such as the cartilage (chondrocytes and extracellular matrix) to increase chondroprotection and the synovium (endothelium and synoviocytes) to reduce inflammation. The interaction between nanomaterials and the joint tissue, together with the role of synovial fluid on drug pharmacodynamics need to be clarified [28].

Expert Opinion and Conclusion

The complex pathophysiology of OA pain has moved the attention of physicians from a joint-centred viewpoint towards a whole body-based approach to diseases. CNS play a key role in the maintenance of chronic pain conditions and multimodal approach are necessary to modulate neuroplasticity in OA pain. The exact joint-brain relationship and circuits are still far from being elucidated.

Biological therapies, both systemic and intra-articular, seem to be a promising approach. The introduction of monoclonal antibodies (mAbs) for OA pain is an appealing perspective for a condition where currently available drugs are still poorly effective and limited by the high incidence of adverse events. Due to their high affinity and specificity for their target, mAbs could present the advantage of the relative absence of adverse events on other systems. Moreover, the less frequent dosing of mAbs compared with traditional analgesics, related to their long elimination half-life, may increase the adherence of patients to treatment. However, they still present some important limitations, such as the gastric degradation, which precludes the oral route and requires the parenteral routes of administration; the large molecular size that reduces their access to the CNS; and the high costs of these treatments which will limit their diffusion worldwide. Surely, mAbs represent an opportunity beyond the joint, however, nowadays results from clinical trials have been less that remarkable and further investigations are warranted to validate their role in the management of chronic OA pain.

Disclosure

No conflict of interest for this paper.

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