



# Targeting neuroinflammation in osteoarthritis with intra-articular adelmidrol

© J ORTHOP TRAUMA SURG REL RES

17(8) 2022

Commentary

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Received: 19.08.2022;

Manuscript No. jotsrr-22- 79431;

Editor assigned: 21.08.2022,

PreQC No. jotsrr-22-79431 (PQ);

Reviewed: 2.09.2022,

QC No. jotsrr-22-79431 (Q);

Revised: 3.09.2022,

Manuscript No. jotsrr-22-79431

(R); Published: 8.09.2022,

DOI.

10.37532/1897-2276.2022.17(8).

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## Abstract

In chronic degenerative and autoimmune diseases such as Osteoarthritis (OA) and rheumatoid arthritis, neuroinflammation is an emerging therapeutic target. Mast cells (MCs) play an important role in joint homeostasis, and their activation causes the release of a large number of proteins. mediators that stoke the fires of neuroinflammation Synovial MCs, in particular, release substances that hasten the breakdown of the extracellular matrix, resulting in morphological joint changes and cartilage damage, as well as inducing synovial fibroblast proliferation, angiogenesis, as well as the sprouting of sensory nerve fibres that mediate chronic pain Palmitoylethanolamide (PEA) is a well-known MCs modulator, but its levels are significantly lower in osteoarthritic joints reduced. Adelmidrol is a synthetic azelaic acid derivate from the AL Amides family PEA booster.

**Keywords:** palmitoylethanolamide; adelmidrol; hyaluronic acid; visco-induction, pelvic

## INTRODUCTION

Osteoarthritis (OA), which affects nearly 16% of the population, is a leading cause of musculoskeletal chronic pain characterized by cartilage degeneration and stiffness. A mechanism-based approach to OA should include at least three targets: peripheral inflammatory mechanisms, central pain hypersensitivity mechanisms, and joint destruction prevention. Mast Cells (MCs) have recently received a lot of attention as a potential target for modulating peripheral and central nervous system inflammation. Neuro inflammation targets joints in chronic degenerative and autoimmune diseases such as OA and rheumatoid arthritis, and MC activation has been identified as a prominent feature of synovial tissue in OA patients. The purpose of this review is to present preclinical and clinical evidence for a new intra-articular formulation containing Adelmidrol for neuro inflammation targeting in OA diseases.

## NEURO-IMMUNE MECHANISMS UNDERLYING OA

Neuro-Immune Mechanisms Underlying mechanisms, including inflammation, neuroplasticity, cartilage disruption, and bone damage. When innate immune cells produce allogenetic factors that act on the pain pathway, neuroimmune signalling may occur. Indeed, as OA progresses, locally generated mediators such as inflammatory cytokines and chemokines, Nerve Growth Factor (NGF), and disease-associated molecular patterns can sensitize nociceptors innervating joints. The pathogenesis of OA is largely determined by a disruption in the balance of pro- and anti-inflammatory mediators, which results in chronic low-grade inflammation that contributes to the associated pain condition. The increase in pro inflammatory cytokines leads to the release of enzymes and other inflammatory factors that are involved in the pathogenesis of OA and are responsible for morphological joint changes such as cartilage degeneration, osteophyte formation, and synovitis. Interleukin (IL)-1, a member of the IL-1 superfamily implicated in the pathogenesis of numerous neuro inflammatory diseases, is one of the most important inflammatory mediators involved in this process.

## CONCLUSION

OA is a complex degenerative disease that necessitates a multimodal treatment strategy. Systemic analgesia can help with recurrent episodes of acute inflammation, which, by definition, last only a few days. NSAIDs may be useful in reducing the harmful effects of destructive enzymes, cytokines, and prostaglandins released in the inflamed synovial membrane following leukocyte infiltration. Acetaminophen, opioids, and adjuvants are examples of central analgesics that can be used to target maladaptive neuronal plasticity and central pain mechanisms. Intra-articular therapies may contribute to systemic analgesia by slowing the progression of joint destruction. In my personal experience, however, many unmet needs remain in the currently available intra-articular treatments for OA, including analgesic efficacy, duration, tolerability, anti-inflammatory effect, and cartilage degeneration modulation. Adelmidrol is a novel intra-articular treatment that targets neuroinflammation while also

providing "visco-induction" to OA joints. It is time to "think outside the box": rather than simply providing HA through exogenous administration, we can prevent endogenous HA degradation. Traditional exogenous HA is administered intra-articularly to provide "visco-supplementation" and to improve joint lubrication. However, given the inflammatory environment in which the HA is injected, it is not surprising that its efficacy can be undermined by a large number of locally released substances, such as MC-released tryptases and chymase, hyaluronidases, and hexoaminidases. Furthermore, MCs are important in joint homeostasis, and their degranulation causes neuroinflammation. Pro-inflammatory cytokines released by the MC fuel the fire of inflammation by promoting cartilage damage, angiogenesis, nerve sprouting, and pain sensitization. PEA is a well-known substance that physiologically inhibits MC activation, and its endogenous levels are significantly reduced in OA joints. As a result, extinguishing the fire of joint neuroinflammation should be one of the goals of OA treatment, in addition to preventing the progression of cartilage damage. Adelmidrol, by increasing and normalising PEA levels in the joints, could be the first innovative molecule for "visco-induction," acting via two mechanisms: (a) reducing MC degranulation and thus improving HA efficacy; and (b) normalising MC function and restoring physiological production of heparin, a HA precursor. Unfortunately, there are still many limitations to this emerging evidence. Despite the expected results demonstrated in both animal and clinical studies, more research is needed to determine the exact molecular mechanisms underlying Adelmidrol's effects in the inflamed joint. Second, clinical experience is still limited to the reported multicenter clinical trial by Vulpiani et al. and the subsequent follow-up study, which confirmed the long-term results of this treatment. As a result, more research is needed to confirm these intriguing preliminary findings. Finally, in the context of a multimodal approach to OA, where systemic analgesia plays a role in targeting recurrent acute inflammation and central neuroplasticity leading to chronic pain intra-articular treatment with Adelmidrol can be considered a promising treatment.