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REVIEW

Cartilage Targeting Therapies in Osteoarthritis: A Narrative Review

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Abstract

Osteoarthritis, recognized as the most prevalent musculoskeletal disorder, represents a significant public health challenge as its impact continues to escalate with an aging population and rising obesity rates. Due to its progressive character leading to chronic joint pain and impaired physical function, osteoarthritis gains increasingly more attention in finding effective therapeutic strategies. Given the well-known adverse reactions of orally administered drugs (e.g. non-steroidal anti-inflammatory drugs, as well as analgesics and corticosteroids), the need for treatments that achieve a higher local concentration is evident. The literature surrounding novel osteoarthritis therapies reveals a dynamic landscape of research aimed at addressing the limitations of traditional treatment modalities, which primarily concentrate on symptom management rather than cartilage repair or regeneration. In this review, we summarized some of the recent advances in cartilage targeting therapies, focusing on injection-based treatments for the osteoarthritic joints.

Keywords: osteoarthritis, cartilage repair, intra-articular injections, hyaluronic acid.

Introduction

Osteoarthritis (OA) is a chronic, progressive and multifactorial disease characterized by the deterioration of the structure and function of articular cartilage. The immune system plays an important role in the mechanisms of extracellular matrix degradation and cartilage loss, as well as the reduction of cell number within the matrix, particularly in the advanced stages of the disease. Current OA management focuses on relieving pain, delaying disease progression, restoring joint function, and improving the quality of life of patients, using non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular injection with steroids and hyaluronic acid. In most cases, surgical interventions are only a last option, especially in the latest stages of OA when the definitive solution to provide pain relief is joint replacement [1].

Recent research has emphasized the importance of developing new symptom-modifying drugs alongside disease-modifying osteoarthritis drugs (DMOADs). Currently, there are no DMOADs available, highlighting a significant gap in treatment options for osteoarthritis. Symptom modifiers currently in trial include: the monoclonal antibody against NGF (neuronal growth factor), Tanezumab, and the inhibitor of Nav1.7 sodium channel in neuronal cells, OLP-1002.

The landscape of DMOAD research is very diverse, currently these treatments are still under development and work towards altering the underlying OA pathophysiology and reducing the associated structural damage, thereby preventing long-term disability.

Materials and Methods

In this review, we begin by highlighting the relevant features of OA pathogenesis and also state of the art therapeutic approaches that are being developed. We will then focus on the present options for the conservative management of knee OA, highlighting the significance and possible benefits of different intra-articular therapies. We will also evaluate the reasoning and existing evidence supporting the application of intra-articular autologous blood products, an emerging area that may offer effective and safe therapeutic solutions for osteoarthritis.

Electronic databases such as Embase, Medline, Cochrane and Google Scholar were used to search for articles employing the keywords: disease modifying osteoarthritis drugs, symptom modifying drugs, intraarticular injections, hyaluronic acid, platelet rich plasma (PRP), mesenchymal stem cells, osteoarthritis. The articles and meta-analyses included were published in the last ten years. Only articles that were

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full-text and written in English were considered for inclusion, while several articles were eliminated following this initial review process.

Results

Of the initial 417 articles found using the aforementioned keywords, a number of 17 articles were selected for this review which included 13 systematic and narrative reviews, 2 meta-analyses, 1 observational study and 1 double-blinded placebo-controlled trial. Overall, almost all the papers agreed that the intraarticular injected treatments have resulted in clinical improvement over baseline pain, stiffness and function up to 3 to 6 months. Only one single-center double-blinded, placebo-controlled study did not find any short- or long-term superior effects compared to placebo in patients with low pain level at baseline and early to middle stage OA.

Mechanisms of Cartilage Damage in Osteoarthritis

The pathophysiology of OA involves complex interactions within the osteochondral unit, where changes in cartilage and subchondral bone contribute to disease progression. Although, traditionally, OA is regarded as a passive degenerative disease caused by long-term wear and tear, new insights suggest that OA is actually an active dynamic process arising from imbalance of joint damage and repair [2].

Articular cartilage is a specialized, avascular tissue characterized by a dense network comprising a high concentration of negatively charged aggrecans (35% of dry weight), collagen type II (50–60% of dry weight), and less than 5% of dry weight chondrocytes. These components collectively play a vital role in the structural integrity and functionality of the tissue. Aggrecans are equipped with multiple highly sulphated glycosaminoglycan (GAG) side chains, which impart a significant negative fixed charge density (FCD) to the cartilage, facilitating hydration, generating swelling pressures, and enhancing compressive stiffness [2]. While these negatively charged aggrecans are essential for the proper functioning of the tissue, they pose significant challenges for the penetration and delivery of therapeutic agents into the cartilage. It is crucial for drugs and their carriers to access the deeper zones of the tissue, as the majority of cells and matrix target sites are located in these areas [2].

It is supposed that the first pathological event in OA is the deterioration of the extracellular matrix (ECM). The abnormal increase in metalloproteinases and aggrecans within the ECM cause degradation of macromolecular substances such as collagen fibres. Further damage is inflicted by the inflammatory cytokines (IL-1β, IL-6, and TNF), reactive oxygen species (ROS), and peroxynitrite released by various cells at the lesion. Matrix metalloproteinases (MMPs) rely on Ca2+, Zn+ as cofactors to exert their function of matrix resolution [3]. The increased content of chemokines leads to phenotypical changes of chondrocytes which, in general, show a tendency to repair the damage. In the subsequent phase of osteoarthritis, chondrocytes are stimulated by the presence of arthritis. This stimulation leads to an increased production of catabolic enzymes and other factors, which accelerates the degradation of cartilage and further promoting apoptosis in the chondrocytes [3].

Moreover, existing research demonstrates that chondrocyte ferroptosis significantly contributes to OA progression. Ferroptosis, characterized by excessive lipid peroxidation and iron accumulation, is a nonapoptotic cell death process. ROS overproduction enhances oxidative stress and lipid peroxidation, ultimately leading to chondrocyte ferroptosis and cartilage deterioration in OA development. Thus, the development of inhibitors simultaneously targeting inflammation and ferroptosis holds considerable potential for enhancing the effectiveness of current OA treatments [4].

It is now recognized that synovium inflammation can also be present in OA through inflammatory factors (IL-1, IL-6, TNF) and MMPs synthesis and release. In early-stage arthritis the macrophages in the synovium are stimulated by inflammatory factors (LPS, IFN-γ, and TNF-α), and polarize towards the M1 pro-inflammatory phenotype. The M1 cells would release even more inflammatory factors (IL-6, IL-12, IL-23, TNF-α) and also ROS, NO, MMP-1,3,13 which can also harm the articular cartilage directly [3]

Understanding the pathogenesis of osteoarthritis offers valuable insights for the development of disease-modifying drugs and also the possibility to identify patients who are at higher risk of progression, which in turn could be used to guide clinical decision-making and facilitate the development of more effective and specific therapeutic interventions [5].

New Developments in Symptom Modifying Drugs for Osteoarthritis

Promising results come from developing intra-articular and intra-cartilage targeting drug delivery systems (DDS) to enable long-term therapeutic response. Synovial joint targeting hybrid systems utilizing combinations of hydrogels, liposomes, and particle-based carriers are considered for pain-inflammation relief [2].

Intraarticular injection of crystalline corticosteroid (triamcinolone) can be improved by combining it with poly lactic-co-glycolic acid (PLGA) hydrogel, obtaining 35–55μm microspheres that show superior therapeutic efficacy, improved viscoelastic properties of synovial fluid and limited adverse effects [6].

In addition, incorporating dexamethasone sodium phosphate into lipid-bilayer encapsulated liposome nanoparticles showed superior chondroprotective effects compared to intra-articular extended-release triamcinolone acetonide (IR/SR-TCA) in preclinical and clinical research [7]. Because of their small size and mobility (0-300nm), compared to microspheres, nanoparticle-liposome coated SR-DSP could have higher cell uptake and a wider range of cellular and intracellular targets [8].

In OA, vascular growth factors such VEGF and PDGF induce angiogenesis in subchondral bone resorption. Neurogenesis further causes increased release of NGFs, leading to peripheral sensitization that progress to central pain sensitization with widespread body ache in OA [8]. Tanezumab, a monoclonal antibody against NGF, can inhibit mechanical peripheral sensitization and central sensitization. A meta-analysis showed tanezumab's superior efficacy over placebo and NSAIDs in OA (dose-dependent subcutaneous). However, rapid progressive OA is prevalent with higher doses, raising safety concerns about all anti-TNF clinical research [8,9].

OLP-1002, a drug that selectively inhibits the mRNA expression of the Nav1.7 sodium channel in neuronal cells, has been shown to reduce pain in knee OA patients. A phase-2a study compared the efficacy of a single SC injection of 1 and 2 mcg OLP-1002 and placebo, showing consistent improvement in average WOMAC pain scores over time. 2 mcg is demonstrated to elicit strong analgesic efficacy with an injection frequency of once every two months [8].

Local Injection-Based Therapies Available Today for the Osteoarthritic Knee

In knee OA, repairing and restoring the damaged cartilage may be possible in Kellgren–Lawrence grade 1–2, but in the more advanced stages is problematic to reverse the progression of this condition [1].

The literature indicates that ultrasound-guided intra-articular (IA) injections significantly enhance the accuracy of administering injectates into knee joints compared to landmark-guided (blind) injections, with reported accuracy rates of 96% versus 73% and 96% versus 84% in two separate studies involving 89 and 99 participants, respectively [10]. The improved accuracy associated with ultrasound guidance not only leads to better clinical outcomes reported by patients but also enhances cost-effectiveness and overall patient satisfaction [8, 10].

Hyaluronic acid (HA) is a non-inflammatory, non-toxic, and non-immune disaccharide also used in drug delivery systems. HA comes in three molecular weights: low (500-730 kDa), intermediate (800-2000 kDa), and high (2000-6000 kDa), including crosslinked formulations [11]. Higher molecular weight HA provides greater anti-inflammatory and proteoglycan synthesis effects, joint lubrication, and viscoelasticity maintenance [11]. One study demonstrated the favourable matrix metalloproteinase (MMP) inhibitory effect of lower molecular weight (LMW) products. HA's efficacy for pain and joint function depends on time, with the maximum effect on pain occurring 8-24 weeks after injection. HA is particularly beneficial for knee OA patients with less severe radiographic changes [11].

A review article stating the position of the Italian Orthopaedic and Traumatology Society (SIOT) on the non-surgical management of knee OA, recommended intra-articular hyaluronic acid (IA-HA) as first line intraarticular treatment, as it shows a more favourable long-term safety profile than intra-articular corticosteroids. HA was recommended for early/mild knee OA, while high-molecular-weight intra-articular hyaluronic acid is preferable in patient with severe OA who either are poor surgical candidates or must postpone total knee replacement [12].

However, one randomized trial of intra-articular injection therapy for knee osteoarthritis compared the clinical outcomes after intra-articular injections of glucocorticoid, hyaluronic acid, platelet-rich plasma (PRP), or placebo in 95 patients with mild or moderate OA of the knee. The study did not find any significant difference in pain relief comparing the aforementioned therapies during the first 6 months after injection [13]. Secondary outcomes including stiffness and clinical parameters of knee mobility were small and comparable among treatment groups. However, starting conditions played a relevant role. In particular, patients with low pain starting values (<20 pain NRS units) showed no to little improvement over time (i.e., flooring effect) [13].

The IA autologous blood therapies include platelet-rich plasma (PRP) and autologous conditioned serum (ACS) [14].

PRP, a plasma fraction containing an increased concentration of platelets and a low concentration of erythrocytes, is obtained by centrifuging an anticoagulated sample of the patient’s venous blood. After injecting the plasma coagulates, the platelets are activated and undergo degranulation, releasing a range of growth factors, including transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor, vascular endothelial growth factors, epidermal growth factors and basic fibroblast growth factor. These growth factors are thought to activate a variety of signalling pathways, which promote healing of bone and soft tissue. Injection with PRP has the potential to improve pain and function for up to 1 year after treatment in patients with mild-to-moderate knee OA [12].

Contraindications to PRP injections include haematologic blood disorders with platelet dysfunction; anaemia (less than 10g/dl) sepsis or fever; cutaneous infections in the area to be injected; malignancy (particularly with hematologic or bony involvement [12].

The duration of the positive effects of PRP injections remains uncertain. Current research suggests that for a minimum of 12 months, PRP can enhance pain relief and functional improvement in patients suffering from symptomatic knee osteoarthritis (OA). However, some studies have reported favourable outcomes lasting up to 24 months following the initiation of treatment. A literature review published in 2021 by Testa et al., concluded that, when compared to other injectable therapies such as hyaluronic acid (HA), intra-articular steroid injections (IASI), and saline, PRP treatment has demonstrated a clinically superior ability to alleviate OA-related pain and improve functional outcomes, while presenting similar or reduced risks of adverse events [11].

The literature lacks a unified stance on the formulation of PRP, and the majority of existing society guidelines do not offer clear recommendations regarding its application. Nevertheless, the growing body of clinical studies indicating improved clinical outcomes in comparison to traditional injectable treatments has led the Italian Orthopaedic and Traumatology Society (SIOT) to endorse the use of growth factor and/or PRP injections for symptomatic knee osteoarthritis. The SIOT conditionally advocates for PRP utilization when other treatment options have been exhausted or have not yielded satisfactory results [12].

Autologous conditioned serum (ACS) is a newer treatment method and only limited clinical data are available so far, therefore this method will not be covered in this article as comparing the clinical efficacy between PRP and ACS is difficult [14].

Mesenchymal stem cells (MSCs) are harvested from adipose tissue or bone marrow and are known to produce growth factors such as TGF, VEGF, and FGF. These factors facilitate the differentiation of various cell types, including the potential to form chondral tissue, thereby aiding in tissue repair [6,11]. Adipose-derived stromal cells (ADSCs) exhibit numerous characteristics similar to those of bone marrow stem cells, including paracrine activity and significant angiogenic properties. Furthermore, ADSCs are recognized for their pronounced chondrogenic differentiation capabilities. According to a limited number of published studies, the application of ADSCs in the treatment of osteoarthritis has been deemed safe and effective for stabilizing the disease and alleviating pain, particularly when administered through multiple infiltrations or at elevated dosages. The optimal dosage appears to exceed 5 × 10^7/mL, with the timeframe for observing improvements in symptoms and cartilage volume ranging from 24 to 72 weeks [11]. Conversely, some studies have highlighted the specific laboratory facilities required for the isolation and expansion of ADSCs, while others have addressed the need for cryopreservation, although clear cost assessments remain unspecified [6, 11].

Although some studies showed superior clinical improvements at 1-year follow-up in MSC groups compared to HA groups, there is a need for a larger sample size and a long-term prospective randomized study to demonstrate their efficacy [15].

Disease-Modifying Osteoarthritis Drugs

The disease-modifying osteoarthritis drugs (DMOADs) hold significant promise, targeting key factors in the pathogeny of OA, aiming to inhibit the deterioration in the biological, structural of joint and improving physical function, not only reducing pain. Currently, DMOADs target inflammatory factors, matrix-degrading proteases, Wnt signalling pathway or promote cartilage repair factors [16]. While DMOADs fall outside the focus of this review, some of these therapies are worth mentioning, including enzyme inhibitors such as Anti-ADAMTS5, as well as growth factors from the transforming growth factor beta family or the Fibroblast growth factor (FGF) family (e.g. sprifermin) and Loricivint, an inhibitor of the Wnt signalling pathway [16]. To combat abnormal remodelling of subchondral bone, antiresorptive agents are being studied, but Zoledronic acid failed to substantially diminish cartilage volume loss over two years and Risedronate, did not have any symptomatic alleviation or delay radiographic progression in knee OA. Further trials are still needed to establish the clinical effectiveness of DMOADs. Additionally, concerns regarding safety and cost continue to be the main topic of discussion [16].

Conclusions

The intraarticular injections using corticosteroids, hyaluronic acid, PRP or MSC have a limited role in treatment of knee osteoarthritis. These interventions are recommended in mild to moderate knee osteoarthritis in patients who do not have sufficient pain relief with topical or oral medication and physical therapy. While these injections can provide significant pain relief and functional enhancement, the benefits are typically short-lived, lasting up to six months, regardless of the number of injections administered or the specific formulations used [17].

The development of disease-modifying osteoarthritis drugs continues to be an important and challenging area. The advancement of nano-drug delivery systems represents an important optimization of intraarticular therapies, facilitating essential biological functions such as drug penetration, prolonged retention, and sustained release, but remain largely inaccessible due to their high costs, side effects and insufficient clinical trials to demonstrate their efficacy.

Conflicts of Interest: The authors declare no conflicts of interest.

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