CURRENT CONCEPTS REVIEW

The Current Role of Disease-modifying Osteoarthritis Drugs

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Abstract

Contemporary treatments for osteoarthritis (OA) pursue only to alleviate the pain caused by the illness. Discovering disease-modifying osteoarthritis drugs (DMOADs) that can induce the repair and regeneration of articular tissues would be of substantial usefulness. The purpose of this manuscript is to review the contemporary role of DMOADs in managing OA. A narrative literature review on the subject, exploring the Cochrane Library and PubMed (MEDLINE) was performed. It was encountered that many publications have analyzed the impact of several DMOAD methods, including anti-cytokine therapy (tanezumab, AMG 108, adalimumab, etanercept, anakinra), enzyme inhibitors (M6495, doxycycline, cindunistat, PG-116800), growth factors (bone morphogenetic protein-7, sprifermin), gene therapy (micro ribonucleic acids, antisense oligonucleotides), peptides (calcitonin) and others (SM04690, senolitic, transient receptor potential vanilloid 4, neural EGFL-like 1, TPCA-1, tofacitinib, lorecivivint and quercitrin). Tanezumab has been demonstrated to alleviate hip and knee pain in individuals with OA but can cause major adverse events (osteonecrosis of the knee, rapid illness progression, augmented prevalence of total joint arthroplasty of involved joints, particularly when tanezumab is combined with nonsteroidal anti-inflammatory drugs. SM04690 (a Wnt inhibitor) has been demonstrated to be safe and efficacious in alleviating pain and ameliorating function as measured by the Western Ontario and McMaster Universities Arthritis Index. The intraarticular injection of lorecivivint is deemed safe and well tolerated, with no important reported systemic complications. In conclusion, even though DMOADs seem promising, their clinical effectiveness has not yet been demonstrated for managing OA. Until forthcoming studies can proved the medications' capacity to repair and regenerate tissues affected by OA, physicians should keep using treatments that only intend to alleviate pain.

Level of evidence: III

Keywords: Disease-modifying osteoarthritis drugs, Efficacy, Osteoarthritis, Treatment

Introduction

Osteoarticular diseases cause major disability and morbidity worldwide, with osteoarthritis representing more than 50% of all such cases, with an increasing prevalence throughout the world.[1, 2] Current treatment for osteoarthritis (OA) seeks primarily to relieve or eliminate the pain associated with the disease through drugs. In the advanced stages of OA, however, surgery is usually necessary. Although surgery is often quite effective in relieving pain, it is not usually as effective in restoring function, thus failing to relieve the major socioeconomic burden imposed by this disease on health systems worldwide.[3] Finding more effective treatments is therefore of significant importance. Disease-modifying OA drugs (DMOADs) could offer new therapeutic targets aimed at restoring the quality and function of tissues affected by OA.[4, 5] This article analyzes DMOADs and presents methods for improving their efficacy through various drug delivery systems.

A narrative literature review on the subject, exploring the Cochrane Library and PubMed (MEDLINE) for English-only articles related to the role of DMOADs in OA treatment was performed. Scientific meeting abstracts or other sources of evidence were not considered. The main selection criterion was a focus on the role of DMOADs in OA treatment. The search strategies are shown in [Figure 1]. The searches were dated from the establishment of the search engines (PubMed and Cochrane Library) to September 15, 2021.

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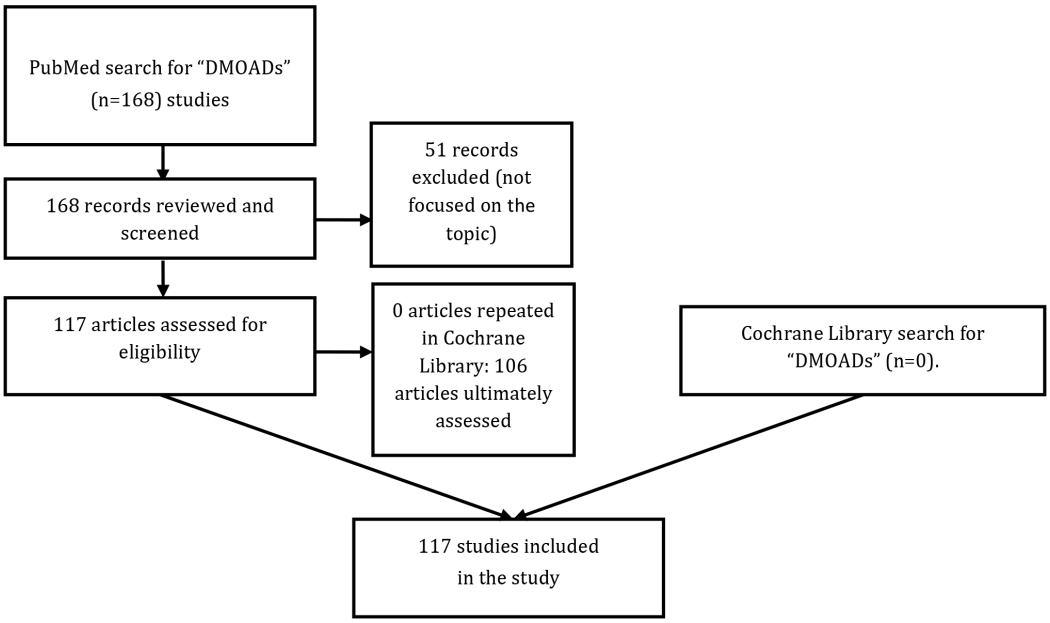

Figure 1. Flow chart for the search strategy for disease-modifying osteoarthritis (OA) drugs (DMOADs).

[Table 1] summarizes the main DMOADs studied in the literature so far. To date, the most widely employed treatments are those using monoclonal antibodies and cytokine inhibitors (anticytokine therapy).

Table 1. Main disease-modifying osteoarthritis (OA) drugs (DMOADs) studied in the literature

Bone active drugs
Strontium ranelate
Zoledronic acid
Risedronate
Anticytokine therapy
Antibodies
Tanezumab, a monoclonal antibody against nerve growth factor
AMG 108, an antibody against interleukin-1 (IL-1) receptor type 1
Adalimumab, an antibody against tumor necrosis factor alpha
Bispecific antibodies
Lutikizumab (bispecific antibody for IL-1a and IL-1β)
Canakinumab
Receptor antagonists
Anakinra, a IL-1 receptor antagonist
Enzyme inhibitors
Nanobodies
M6495 (Anti-ADAMTS5)
Small molecules inhibitors
Doxycycline
Cindunistat (SD-6010)
Growth factors
Transforming growth factor beta family
Bone morphogenetic protein 7
Fibroblast growth factor (FGF) family
FGF-18 (sprifermin)

Table 1. Continued

Nucleic acids (gene therapy)
microARNs
Antisense oligonucleotides
Peptides
Calcitonin
Other DMOADs
SM04690 (a Wnt inhibitor)
UBX101 (Senolitic)
Transient receptor potential vanilloid 4
Neural EGFL-like 1
TPCA-1 (a κB kinase inhibitor) and tofacitinib (a Janus kinase inhibitor)
Lorecivivint
Quercitrin

Bone active drugs

Strontium ranelate

A study suggested a positive impact of strontium ranelate in patients with OA, through changes in functional ability and decrease of progression of morphological parameters and joint degradation.[6] However, in other report no difference was found between strontium ranelate and placebo.[7]

In an animal model of OA reported by Paulino Silva et al the utilization of this medication diminished the amount of type II collagen biomarkers (CTX-II) in the urine, which explains the reduced degeneration, known to diminish the bone resorption, while augmenting bone creation, ameliorating the structure of the osteoarticular system.[8] Nonetheless, with no evident reason, in face of so many

advantages, it is not known the reasons for market withdrawal of this drug. There are no major effects or severe complications associated with strontium ranelate (50 mg/kg in a single daily dose, orally, for ten days).[8]

Zoledronic acid

A study reported by Cai et al did not back the utilization of zoledronic acid in the management of knee OA. In patients with bone marrow lesions, annual zoledronic acid infusions, compared with placebo, did not substantially diminish cartilage volume loss over two years.[9]

Risedronate

Vaysbrot et al reported that risedronate neither render symptomatic alleviation nor delay radiographic progression in knee OA. However, this drug might still be beneficial in individuals who have elevated rates of subchondral bone turnover.[10]

In an animal model reported by Salman et al, risedronate (actonel 35 mg, Sanofi Aventis Pharmaceutical Company, Cairo, Egypt) was given orally to rats in a dose of 0.2 mg/kg/day.[11]

In rabbit models, risedronic acid showed a protective effect on mechanical properties of the ligaments and periarticular bone and diminished the mineral loss at the bony attachment of the anterior cruciate ligament.[12] Furthermore, it diminished joint cartilage lesion in guinea pig models.[13] In the early phases of OA of a rat model, utilizing non-steroidal anti-inflammatory drug (NSAID) and risedronate, they reduced the effect of osteophyte bony adaptations and maintained trabecular bone mass.[14]

Anticytokine therapy

Antibodies

Tanezumab, a monoclonal antibody against nerve growth factor

Tanezumab relieves hip and knee pain in individuals with OA15 but can cause significant adverse evcnts (osteonecrosis of the knee, rapid illness progression, augmented prevalence of total joint arthroplasty), particularly when combined with NSAIDs.[15-17] The subcutaneous use of tanezumab also relieves hip and knee pain but with similar complications.[18]

Tanezumab is a nerve growth factor inhibitor. Oral administration of 5 mg for 56 weeks was recommended by Song et al.19 However Berenbaum et al recommended 5 mg for 24 weeks. [20]

AMG 108, an antibody against interleukin-1 receptor type 1

In patients with osteoarthritis, the subcutaneous or intravenous use of AMG 108 produced no beneficial effects when compared with placebo after a 3-month follow-up.[21]

According to Cohen et al, AMG 108 is a entirely human, immunoglobulin subclass G2 (IgG2) monoclonal antibody that binds the human interleukin-1 (IL-1) receptor type 1, restraining the activity of IL-1a and IL-1b. In preclinical investigations, IL-1 constraint was demonstrated to be helpful in models of OA. The safety profile of AMG 108 [subcutaneously (75 mg or 300 mg) or intravenously (100 mg or 300 mg) once every 4 weeks for 12 weeks] was equivalent to placebo in individuals with OA of the knee. Individuals treated with AMG 108 had statistically insignificant but numerically greater ameliorations in pain; minimal, if any, clinical benefit was encountered (trial registration: This study is registered with ClinicalTrials.gov with the identifier NCT00110942).[21]

Adalimumab, an antibody against tumor necrosis factor alpha (TNF-a)

One study on knee OA found that the intraarticular utilization of adalimumab reduced pain.[22] Besides, an article on erosive OA of the hand also demonstrated that the utilization of adalimumab relieved pain.[23] Wang evaluated the effectiveness and safety of adalimumab (ADA) versus hyaluronic acid (HA) by intraarticular injection for moderate to severe knee OA. Fifty-six individuals with moderate to severe knee OA were randomly assigned to either the ADA cohort or HA cohort. On day 0, individuals in the ADA cohort were given 10 mg of ADA by intraarticular injection, while those in the HA cohort were given 25 mg of HA. All individuals were given celecoxib at 200 mg/day for 4 weeks.[22]

Bispecific antibodies

Lutikizumab, a bispecific antibody for IL-1a and IL-1β

In one study, the subcutaneous use of lutikizumab every 2 weeks for 50 weeks in individuals with knee OA did not reduce pain, the degree of synovitis, or joint cartilage thickness.[24] Similar results were found in another article on individuals with erosive OA of the hand.[25]

Canakinumab

Schieker et al have observed that canakinumab use reduces the need for a hip- or knee prostheses.26 They analyzed a randomized trial (ClinicalTrials.gov: NCT01327846). The intervention consisted of a random assignment to placebo or canakinumab (50, 150, or 300 mg) subcutaneously once every 3 months. The median follow-up was 3.7 years. In the pooled canakinumab groups, compared with the placebo group, incidence rates for total hip arthroplasty (THA)/Total knee arthroplasty (TKA) were 0.31 and 0.54 events per 100 person-years, respectively. The hazard ratio (HR) for the secondary end point of OA related complications was 0.73. Similar data were encountered in analyses restricted to participants with a history of OA.[26]

Canakinumab is a human IgGκ monoclonal antibody that annuls the activity of IL 1β blocking interaction with IL-1β receptors (50, 150, or 300 mg) subcutaneously once every 3 months).[27]

Receptor antagonists

Anakinra, an IL-1 receptor antagonist

There were no substantial differences when comparing the use of anakinra with that of placebo in individuals with OA at 3 months of follow-up.[28] Anakinra drug is an

interleukin-1 receptor antagonist (IL-1Ra). Chevalier et al reported that anakinra was well tolerated as a single 50-mg or 150-mg intraarticular injection in individuals with OA of the knee. However, anakinra was not associated with ameliorations in OA symptoms compared to placebo.[28]

Combined antibody-mediated inhibition

Experimental mice models of OA have shown that combined antibody-mediated inhibition (IL-17 / TNF-α or IL-1α / IL-1β) protects cartilage better than single inhibition.[29] These studies have shown the beneficial therapeutic effects of multi-target blockade.

Enzyme inhibitors

Enzyme inhibitors (inhibitors of matrix metallo-proteinases that mimic the role of tissue inhibitors of metalloproteinases) have been demonstrated to have a chondroprotective impact in preclinical OA reports.[30-32] However, clinical research on osteoarthritis has not only been unable to demonstrate the efficacy of enzyme inhibitors but has also detected significant adverse effects.[33-36] Matrix metalloproteinase 13 (MMP-13) is currently considered the most important matrix metalloproteinase with respect to cartilage in osteoarthritis.[33,37-40]

Nanobodies

M6495, an anti-ADAMTS-5 inhibiting nanobody

The ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family of enzymes (a disintegrin and metalloproteinase with thrombospondin motifs) plays a fundamental in the degradation of articular cartilage. Studies are investigating the efficacy of subcutaneous M6495, a nanobody with demonstrated chondroprotective effect.[41]

Siebuhr et al investigated M6495 on cartilage turnover ex vivo.[41] M6495 showed cartilage protective impact by dose-dependently restraining ADAMTS-5 mediated cartilage degradation and restraining overall cartilage deterioration in ex vivo cartilage cultures.[41]

Small molecule inhibitors

Doxycycline

Oral doxycycline (a general MMP inhibitor) has not been shown to be efficacious in managing OA and has produced significant adverse effects.[42]

Doxycycline has broad-spectrum activity as a matrix MMP inhibitor. In a murine ACL rupture model Zhang et al used different doses (10 mg/kg/d; doxycycline, 50 mg/kg/d; and doxycycline, 100 mg/kg/d), administered in drinking water.[43]

Cindunistat (SD-6010)

Inducible nitric oxide synthase has been linked to the progressive degeneration that occurs in OA.[43] In an experimental study on dogs, its inhibition caused catabolic effectors levels to fall.[39] However, a study comparing oral cindunistat (a selective inducible nitric oxide synthase inhibitor) with placebo demonstrated no difference in pain alleviation in individuals with knee OA.[35] Therefore, the role of cindunistat in clinical practice is controversial.

According to Hellio le Gravenand et al this drug restrains inducible nitric oxide synthase (iNOS).[35] In a double-blind, placebo-controlled, multicentre study of oral cindunistat (50 or 200 mg/day), the drug did not decrease the rate of joint space narrowing (JSN) versus placebo. After 48-weeks, Kellgren and Lawrence Grade 2 individuals demonstrated less JSN; however, the amelioration was not maintained at 96-weeks. iNOS constraint did not reduce OA progression in Kellgren and Lawrence Grade 3 individuals.[35]

Growth factors

Growth factors have also been studied for managing knee OA.

Transforming growth factor beta (TGF-beta) family

Bone morphogenetic protein 7 (BMP-7)

The intraarticular use of BMP-7 in individuals with knee OA has been shown to be safe and well tolerated.[37,44] However, its effectiveness has not yet been shown.

Fibroblast growth factor family

Fibroblast growth factor 18 (FGF-18 or sprifermin)

Muller et al reported that sprifermin reduced type I collagen expression and had no hypertrophic effect. Therefore they concluded that sprifermin was a promising DMOAD.[45] In another study on sprifermin with a 1-year follow-up, intraarticular injections (single or multiple dose for 3 weeks) of sprifermin in individuals with knee OA resulted in less cartilage volume loss and augmented joint width in the lateral compartment than in the placebo group. However, pain alleviation was greater in the placebo cohort.[46]

According to Li et al sprifermin is a recombinant human fibroblast growth factor 18 (rhFGF18) that have anabolic impact on joint cartilage, which makes it a promising DMOAD.[47] The recommended administration route is intra-articular (100 µg or 30 µg every 6 months or 12 months, for 18 months).[48]

Nucleic acids (gene therapy)

Several gene therapy options are known that attempt to slow down the degeneration of the affected areas and simultaneously improve their repair and regeneration.[49] All of them try to regulate genes using plasmid deoxyribonucleic acid (DNA), messenger ribonucleic acid (RNA) and short oligonucleotides.

Micro RNAs

There are published articles on the interest of various microRNAs (miRNAs) in preserving cartilage homeostasis, that is, their importance in the disease processes that precede or sustain OA and cartilage degradation.[50-55] MiRNA-140 has been demonstrated to play a fundamental role in the development of cartilage.[56,57] In fact, several experimental studies have shown that intraarticular injections of miRNA-140 have an anti-inflammatory effect and slow the progression of OA.[58,59]

Antisense oligonucleotides

Preclinical studies have shown the possibility of antisense oligonucleotide-mediated silencing of miRNA-181a-5p.[51] MicroRNA levels have also been encountered to be increased in osteoarthritic cartilage.[53]

Wijesinjhe et al have recently analyzed the possibility for the development of oligonucleotide treatments for OA by studying the evidence that oligonucleotides can modulate the key cellular pathways that drive the pathology of the inflammatory diseased joint pathology, as well as evidence in preclinical in vivo models that oligonucleotides can change illness progression.[60]

Peptides

Calcitonin

Although preclinical studies have claimed that calcitonin has a protective impact on cartilage and bone,[61,62] a phase III trial conducted on patients with OA was unable to demonstrate the drug's clinical efficacy.[63] The authors indicated that this was possibly due to low exposure to the drug.

Stokl et al analyzed and compared the molecular effects of substance P (SP) and alpha-calcitonin gene-related peptide (αCGRP) on the metabolism of articular chondrocytes from OA patients and non-OA cartilage donors. They suggested that a switch between the G-subunits of the corresponding receptors after binding their ligands SP or αCGRP was paramount in mediating the impact of sensory neuropeptides on chondrocytes.[64]

Other DMOADs

SM04690, a Wnt inhibitor

Considering that the Wnt signaling pathway is implicated in regulating joint development and function and in joint disease and degeneration, 65 the use of SM04690 has been evaluated for treating OA.[66] Several clinical trials on OA have confirmed the safety and efficacy of SM04690, as well as diminished pain and ameliorated function as measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[67]

UBX101 (Senolitic)

Another therapeutic method to managing OA is the utilization of drugs that target the mechanisms of senescence.[68] In an experimental study of OA in mice, UBX101 (senolitic) was demonstrated to be efficacious in eliminating senescent cells and slowing down illness progression.[69] Considering that UBX101 increases the activity of p53 (a gene that codes for the protein that regulates the cell cycle and hence functions as a tumor suppressor) and, therefore, induces apoptosis in senescent cells, clinical trials are being performed to assess the safety and tolerability of UBX101 in individuals with OA.[70]

Transient receptor potential vanilloid 4

According to Atobe et al, the local injection of a transient receptor potential vanilloid 4 (TRPV4) agonist is a potential treatment for OA.[71] TRPV4 belongs to the TRPV subfamily of TRP ion channels. TRPV4 channels play a crucial role in chondrocytes, and therefore TRPV4 is an attractive goal of DMOADs.

Neural EGFL-like 1

In Nell-1-haploinsufficient mice it has been observed that osteoarthritis progresses and worsens at a faster rate than normal. Therefore, neural EGFL-like 1 (NELL-1) is considered a promising DMOAD with prochondrogenic and anti-inflammatory effects.[72]

TPCA-1 (a κB kinase inhibitor) and tofacitinib (a Janus kinase inhibitor)

Using a pre-clinical model, Kjelgaard-Petersen et al reported that TPCA-1 and tofacitinib maintain and help conserve cartilage extracellular matrix (ECM) under inflammatory conditions and could be explored further as a DMOAD for inflammation-driven OA.[73]

Lorecivivint

Intraarticular injections of lorecivivint have been shown to be safe and well tolerated.[74] This drug serves to modulate the Wnt signaling pathway. A 24-week phase 2b trial demonstrated the effectiveness of lorecivivint on patient-related outcomes in knee OA patients. The ideal dose for forthcoming studies was determined as 0.07 mg.[75]

Quercitrin

Immunohistochemical data have shown that quercitrin exerts an anti-osteoarthritic effect by deferring ECM degradation.[76] Therefore, quercitrin could be a prospective DMOAD to prevent and manage the early stages of OA.

Drug delivery systems

There are three important strategies for prolonging the effectiveness of drugs: microparticles, nanoparticles, and hydrogels [Figure 2].

Microparticles

Because of their small size, if microparticles are injected into a joint they are retained in the joint. In addition, microparticles can encapsulate DMOADs.[77,78]

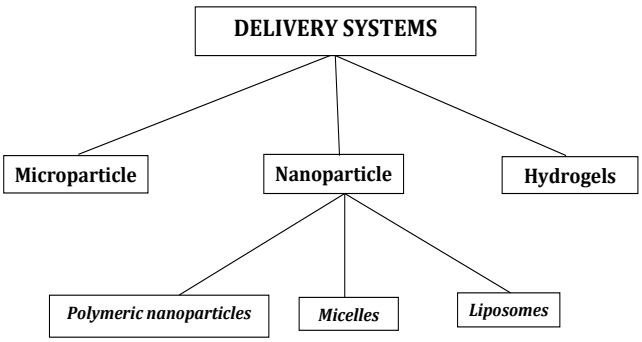

Figure 2. Main delivery systems studied in the literature for delivering disease-modifying osteoarthritis (OA) drugs (DMOADs).

Table 2. Main delivery systems studied in the literature for delivering disease-modifying osteoarthritis drugs

Microparticles
Nanoparticles
Polymeric nanoparticles
Micelles
Liposomes
Hydrogels

Nanoparticles

Nanoparticles (polymeric, micelles, liposomes) can penetrate the cartilage matrix because of their small size and thereby increase the retention time of a given drug.[79-87]

A study using a mouse model of OA showed that the intraarticular administration of rapamycin-loaded micelles in a gelatin hydrogel delayed disease progression.85 In a rat osteoarthritis model, PEGylated kartogenin-based micelles delivered in a HA hydrogel were observed to avert illness progression.[86]

HA-coated liposomes were also found to have a greater impact than collagen-coated liposomes.[87, 88]

Hydrogels

HA-doxycycline hydrogel showed decreased cartilage fibrillation and reduced osteophyte formation.[89] Regarding the intraarticular injection of hydrogels, the main limitation is extrusion or fragmentation due to mechanical loading and high pressure.[90] It is therefore advisable to use a rapid-solidification hydrogel, because it is less likely to be extruded.[90] One of the advantages of hydrogels over other delivery systems in treating OA is that, in addition to providing a prolonged release of bioactive compounds, hydrogels can act as scaffolds for repairing endogenous tissues.[91-93]

Discussion

The current treatments for OA are often aimed at alleviating pain and ameliorating the function of the affected joint and typically employ a combination of pharmacological and non-pharmacological analgesic treatments. Non-pharmacologic treatment includes exercise and physical and rehabilitation medicine, while pharmacologic treatment is primarily performed with analgesics, NSAIDs and opioids.[94-96] For mild pain, the first choice is usually oral paracetamol (acetaminophen),which is not always effective, prompting physicians to prescribe NSAIDs (e.g., ibuprofen) at the lowest effective dosage and for the shortest duration possible due to the risk of gastrointestinal complications and their antiplatelet activity.[96-99] Cyclooxygenase-2 selective NSAIDs are also employed due to the anti-inflammatory and analgesic effectiveness of classical nonselective NSAIDs but have fewer adverse effects in the gastrointestinal tract.[100] However, their potential cardiovascular effects are of major concern.[101,102]

Opioids are an alternative to NSAIDs for treating osteoarthritis, although the use of opioids carries a substantial risk of adverse effects and addiction.[97,98, 103, 104] The local injection of corticosteroids has also been employed in clinical practice for treating moderate to severe osteoarthritic pain.[105] However, corticosteroids can cause adverse reactions (tissue injury from repeated injections, infection, and stimulation of inflammation from crystallized corticosteroids).[99]

Intraarticular HA injections are also frequently employed to relieve osteoarthritic pain, with the theoretical objective of restoring the viscoelasticity of the synovial fluid.[99,106] A published study indicated that the analgesic effect of HA depends on its molecular weight and that a higher molecular weight appears to provide more efficacious and long-lasting effects.[107]

The intraarticular injection of platelet-rich plasma (PRP) is another alternative for managing OA, with articles suggesting that it has anti-inflammatory and pain-relieving effects and that it is more effective than HA.[108,109]

When non-surgical treatment fails to control joint pain in advanced OA, surgery (joint distraction, high tibial osteotomy, total joint arthroplasty is required.[83,110,111] The problem is that total joint arthroplasties have a limited life and eventually require revision surgery (which has a much higher risk of failure), which is a significantly problematic situation for younger patients.[83]

All of the above demonstrates that current treatments for OA are primarily aimed at relieving pain rather than at diminishing, stopping, or even reversing the progression of OA.[112, 113] A disease-modifying agent should inhibit the catabolic pathways or stimulate repair and regeneration.[114,115] To date, however, no disease-modifying agent has been approved for OA, due to their adverse effects when administered systemically, their short half-life in tissues when injected locally and their lack of effectiveness.[106,116]

Despite numerous preclinical tests on the efficacy of various disease-modifying agents (growth factors and cytokine inhibitors), there are currently no disease-modifying agents available for repairing and regenerating tissues.[33,66] In fact, the clinical trials published so far have produced disappointing outcomes, given that the medications have only been effective in the short term or have shown no efficacy.[33] These disappointing findings might be due to the fact that, in the physiopathology of OA, various tissues and pathways are involved, from inflammation to degeneration.[33,66] Another important fact is that the short half-life of the disease-modifying agents within the joint means that their therapeutic activity is highly limited, which reduces their effectiveness.[33,77] Precisely because of this limited activity, drug delivery systems could contribute to improving the efficacy and therapeutic effect of disease-modifying agents by concentrating and prolonging the presence of the drugs in the tissues.[77]

Oo et al have recently summarized the effectiveness and safety profile of a range of targeted medications in phase 2 and 3 clinical trials directed to cartilage-drive .[117]

In conclusion, although various types of DMOAD

approaches (anticytokine therapy, enzyme inhibitors, growth factors, gene therapy, peptides, and others) have been researched, they have not yet been shown to be fully effective and safe for treating OA. Furthermore, significant adverse effects have been reported when DMOADs have been administered systemically. Until future studies can prove that DMOADs are effective in patients with OA in repairing and regenerating diseased tissues, treatments that solely seek to relieve joint pain should continue to be employed.

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