

Osteoarthritis: Advances and Emerging Treatments

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Osteoarthritis (OA) is the most common joint condition globally, affecting 10% of men and 18% of women over the age of 60. Its pathogenesis is multifactorial, which has made identifying modifiable factors to slow the progression or prevent the development of OA challenging. Current treatment focuses largely on lifestyle modification, analgesia and ultimately joint replacement, with no specific therapies currently available. However, research is on-going to provide a disease-modifying drug akin to those available for rheumatoid arthritis. The heterogeneity of OA has allowed a variety of pharmaceutical agents to be considered, each aiming to modify different components of the arthritic joint. Only a limited number of targeted treatments have been found to be efficacious, and those that have been identified have been associated with adverse events, preventing their progression to clinical practice. This article reviews the current management of OA, including tissue-specific approaches and treatments and summarizes the on-going research that aims to identify further therapeutic targets and develop disease-modifying OA drugs.

Keywords

Disease-modifying drug, joints, management, osteoarthritis, therapy

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Globally, osteoarthritis (OA) is the most common joint condition, affecting 10% of men and 18% of women over the age of 60 years.¹ OA represents a group of overlapping disease processes of differing aetiologies, all of which cause a pattern of degenerative disorder of the synovial joints. Classical radiological findings associated with a diagnosis of OA include destruction of the articular cartilage with associated non-uniform joint space loss, osteophyte formation, subchondral bone sclerosis and cyst formation.¹ The order in which each of these changes happens remains disputed, but the overall trajectory is one of increasing pain and joint stiffness for the individual.^{2,3} The initial classification of OA proposed by Kellgren and Lawrence in 1957 was based on radiological findings and was later adopted as the mainstay of OA classification by the World Health Organization in 1961.⁴ This system of classification, and later adaptations, hinders the potential for an early diagnosis of OA because conventional radiology is limited to detecting only relatively advanced diseases. The level of radiological change does not always correspond to the level of disability experienced, further limiting this classification system when used to understand the burden of morbidity.

The development of OA is multifactorial and includes the presence of susceptibility genes, oestrogen status and bone density.⁵ These systemic factors combine with joint-specific biomechanical factors, such as the effect of obesity on lower-limb joints or previous injury to the joint.⁵ The interaction of multiple person-specific factors makes the selection of treatment targets, with the aim of delaying OA progression or preventing disease development, a challenge. Additionally, individuals with OA typically present to healthcare professionals late in the disease, years after the disease process has started within the joint space, which makes intervention and disease modification particularly difficult, as the joint damage may already be severe and well established.⁶

The knee joint is the most affected joint, with the hip and wrist being other common presentation sites.⁷ The prevalence of OA is generally higher in women than in men, especially at the hand and knee, with a polyarticular form affecting multiple sites and commonly emerging during the perimenopausal period.⁷ The susceptibility of each joint site to the development of OA is a complex person-specific process of combined risk factors, each acting as a target for possible intervention. The clinical presentations of OA, namely pain and joint stiffness, are notoriously difficult to quantify; this difficulty hampers the efforts to monitor disease symptoms in individuals or make clear comparisons between individuals' disease experiences. One widely used scale is the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale. This self-administered questionnaire includes points for pain, stiffness and physical function. Although WOMAC is limited by its reliability, it is widely used in the research and evaluation of hip and knee arthritis.⁸

This article aims to review the current management of OA and discusses the mechanisms and treatment options for OA in specific tissues. On-going research to identify therapeutic targets and develop disease-modifying OA drugs is also summarized.

Current management of osteoarthritis

The point of presentation of an individual with OA to a healthcare professional is typically late in the OA disease process, by which time the opportunity for disease modification is limited; therefore, conventional therapy has focused on later disease stages. Globally, multiple societies have produced guidelines detailing the management of OA.⁹ Despite being based on the same extensive body of evidence, the suggested treatment modalities differ considerably,⁹ creating the potential for a range of treatment approaches in clinical practice.

In the 2019 guidelines from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)¹⁰ and the Osteoarthritis Research Society International (OARSI),¹¹ the mainstay of initial management is broadly based on behavioural adaptation, such as exercise and weight reduction, combined with the analgesic agents of paracetamol or topical non-steroidal anti-inflammatory drugs (NSAIDs). ESCEO recommends the use of prescription-grade glucosamine sulphate and/or chondroitin sulphate, whereas the OARSI guideline does not recommend these medications, demonstrating the discrepancies between management guidelines despite being produced in the same year and from a comparable body of evidence.¹² Both guidelines are similar in suggesting that if treatment remains ineffective or symptomatology increases over time, then oral NSAIDs may be added, although their use is limited in some individuals due to comorbidities, such as poor renal function or previous gastrointestinal bleeding. An alternative or additional therapy includes direct injection of a pharmacological agent (corticosteroids or hyaluronate) into the joint itself. Once the joint disease is impacting quality of life, the joint might be replaced despite maximal therapeutic agents. While waiting for this, a short course of weak opioid medication may be used, and in patients who are not candidates for surgery, longer-term opioids may be required.^{8,9}

This stepwise approach to management demonstrates symptom control, with some effort to delay OA progression; for instance, weight reduction to reduce joint stress but with no inclusion of disease-preventing measures or modification of disease process prior to symptom onset.

The role of steroids

For patients unable to tolerate NSAIDs or those with a clearer inflammatory component to their OA, the possibility of oral steroid treatment has been explored. A 2019 study investigating a 6-week treatment with daily prednisolone for hand OA found that it had significant benefit in improving OA symptoms compared with placebo.¹³ In this double-blind study, eligible patients had to have experienced a flare of pain during a 48-hour NSAID washout period and show signs of inflammation, such as erythema, in at least one hand joint, both indicating poorly controlled inflammatory OA. Additionally, patients were required to have ultrasound-proven signs of OA and at least four finger joints with OA nodes. Although steroids do not represent a disease-modifying medication, they present a possible option for the treatment of an OA flare, separate from the current stepwise approach, although the study was limited to hand OA only.

Pharmacological prevention of osteoarthritis

The 'Holy Grail' of OA management has been the development of a drug to treat the bone changes that lead to OA. Such disease-modifying OA drugs (DMOADs) are the new therapeutic target in OA.

A 2019 paper looking at these novel agents, which were often pre-existing drugs licensed for other joint conditions that were repurposed to target the development of OA, concluded that one of the main limitations was

the much slower loss of cartilage associated with OA compared, for example, with rheumatoid arthritis, combined with symptoms that do not directly correlate with the level of joint destruction.¹⁴

The consideration of the specific joint site of OA is important in identifying DMOAD targets because the different factors that contribute to the development and progression of OA have varying levels of importance at each site. Chondrocyte phenotype is modified in all osteoarthritic joints, with hypertrophy and enhanced production of pro-inflammatory molecules. Despite this, a comparison of knee and wrist synovial fluid showed that the knee synovial fluid produces more pro-inflammatory cytokines and chemokines than the wrist, suggesting that the same cellular change may lead to different results depending on the joint site.¹⁵

Tissue-specific management of osteoarthritis

Bone

Bisphosphonates are considered DMOADs because they reduce subchondral bone turnover and loss and reduce cartilage degeneration and loss. Bone turnover rate increases as the severity of OA increases,¹⁶ although, during later stages, bone turnover declines.¹⁷ This bone remodelling affects the overlying cartilage, although it remains unclear whether, in OA development, the bone remodelling triggers changes in the cartilage or vice versa. Animal studies have suggested that the subchondral bone changes precede cartilage degeneration, making this a key early OA target.¹⁸

Clinical studies of bisphosphonates as a treatment for OA have been disappointing; no significant improvement in pain or function was reported in a 2020 review of six large trials comparing bisphosphonates with placebo.¹⁹ A systematic review published in 2021 and covering 20 years of preclinical animal studies concluded that the efficacy of bisphosphonates was both dose dependent (higher doses being more efficacious at reducing OA burden) but also time dependent.²⁰ By initiating treatment with bisphosphonates early in the disease course or pre-emptively, chondrocyte remodelling could be suppressed.²¹ The implications of these findings for clinical practice may be limited by the fact that the presentation of OA typically occurs once the disease has advanced beyond the usefulness of bisphosphonate treatment.

Strontium ranelate (SrRan) has been trialled as a bone-targeting DMOAD as part of the Strontium ranelate efficacy in knee osteoarthritis (SEKOIA) trial (The efficacy and safety of two doses of strontium ranelate versus placebo, administered orally for three years in the treatment of knee osteoarthritis; ISRCTN identifier: ISRCTN41323372).²² SrRan, when tested on human subchondral bone, was found to inhibit bone resorption by inhibiting proteolytic enzymes produced mainly by osteoblasts, offering a potential treatment to prevent the development of OA.²³ SEKOIA compared SrRan doses of 1 g/day, 2 g/day and placebo over 3 years in patients with primary knee OA.²² Outcome measures included joint space narrowing (a radiological measure of OA progression) and improvements on clinical reporting scores of patient symptoms, including WOMAC. Both dosages showed radiological benefits with significantly less joint space narrowing; however, only the higher dose of 2 g/day showed significant benefit with regards to self-reported pain using the WOMAC score.²² The benefits of this orally available medication will continue to be studied and may present a DMOAD for wider future use. One area of concern for the use of SrRan is its association with increased risk of thromboembolic events.²⁴ Initially, SrRan was withdrawn by the manufacturer, but it is now available as a generic form licensed for severe osteoporosis in patients without cardiovascular risk factors.²⁵ Although on-going investigation of SrRan

as a DMOAD would be needed before licensing, the potential safety implications for its use will also require further analysis.

Cartilage

One area of particular interest in the development of DMOADs is the Wnt signalling pathway, a signal transduction pathway thought to be involved in cartilage degradation and the pathogenesis of OA by its direct effect on bone, cartilage and synovial tissue.²⁶ Mechanical stress and inflammation both contribute to the upregulation of the Wnt pathway. This contributes to the progression of OA in two distinct ways: progenitor cells in the synovium and subchondral bone differentiate into osteoblasts instead of chondrocytes, and pro-inflammatory cytokines and catabolic enzymes that drive cartilage degradation and OA symptoms are increased.²⁷

SM04690, an intra-articular injectable small molecule, is an inhibitor of the Wnt signalling pathway. In preclinical trials, SM04690 induced human primary mesenchymal stem cells (MSCs) into chondrogenesis.²⁸ The production of proteases by chondrocytes was also inhibited, showing the potential to block a key mediator in cartilage degradation.²⁸ SM04690 also inhibited the interleukin-1 β -induced production of tumour necrosis factor α and interleukin-6, suggesting that it may reduce the inflammatory component of OA.²⁸ On-going clinical trials of SM04690 have confirmed *in vivo* benefits, including reduced joint space narrowing and improved WOMAC pain and physical function scores.^{29,30} A phase I trial identified that even at the highest trialled dose of 0.23 mg of SM04690, plasma levels remained below detectable levels, thus reducing the risk of systemic side effects (Phase 1, dose escalation study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of SM04690 in moderate to severe knee osteoarthritis [OA]; ClinicalTrials.gov identifier: NCT02095548).²⁹ In phase II trials to establish the minimum effective dose, 0.07 mg was found to significantly improve both pain and function on the WOMAC scale, compared with placebo.³⁰ This was especially evident in patients with unilateral knee pain compared with those with widespread comorbid pain.³⁰

Synovium

Synovitis, or inflammation in the synovium, has become a treatment target following increasing recognition that low-grade long-term inflammation is a key mediator in the development of OA.³¹ Histological findings suggest that 50% of patients with early OA, and almost all of those with later stages, have synovitis, making it a potential therapeutic target for all-stage OA.³²

Conventional and biological disease-modifying antirheumatic drugs (DMARDs) have been repurposed as potential DMOADs in a series of randomized controlled trials.³³ These drugs are typically used in inflammatory arthritis, where they suppress the primary inflammation driving the disease process. A 2018 meta-analysis of 11 randomized placebo-controlled trials (six evaluating conventional DMARDs and five investigating the use of biologics in OA) found that DMARDs did not offer clinically significant pain relief compared with placebo.³³ Several reasons for the poor response to treatment were postulated in this review, including inflammation not being a key driver for the pain caused by OA, the role of inflammation differing between OA and inflammatory arthritis, incorrect drug dosage or that DMARDs target different inflammatory pathways to those responsible for the synovitis observed in OA.³³

Nerve

In OA, the pain pathway itself presents a DMOAD target. Specialized sensory neurons (nociceptors) are triggered by a variety of receptors to send a signal to the dorsal horn and ultimately transmit to the medial

prefrontal cortex. Nociceptors and immune cells respond to tissue injury by increasing neuro-inflammatory signalling, increasing pain and facilitating tissue repair. When a joint remains damaged, as in OA, the persistent pro-inflammatory environment leads to peripheral and central sensitization. Sensitization leads to gene changes resulting in altered neuronal protein expression and immune cell infiltration, further potentiating on-going inflammation and causing chronic pain.^{34,35}

One signalling molecule of particular interest is the nerve growth factor (NGF), a ligand for tropomyosin receptor kinase A. The binding of ligand to receptor has several outcomes, including the stimulation of nociceptors responsible for the transmission of pain pathway signals.³⁴ Monoclonal antibodies to NGF were developed initially for non-musculoskeletal pain but have become a focus of clinical trials for use as DMOADs. Of several monoclonal antibodies initially trialled, two remain in clinical trials: tanezumab and fasinumab.

Studies have typically found that these monoclonal antibodies reduce pain and increase joint function compared with placebo; however, there are higher risks of adverse events than with placebo, mainly peripheral neuropathy.³⁶ Neither the adverse event of peripheral neuropathy nor rapidly progressive OA was predicted from phase I clinical trials, and work is on-going to understand the mechanisms underlying these events and to continue investigating NGF-neutralizing antibodies as a DMOAD, given their significant impact on pain and function for many trial participants.³⁷

A recent systematic review and meta-analysis was undertaken to consider the efficacy of anti-NGF monoclonal antibodies in knee and hip OA pain.³⁸ Included in the analysis were 13 studies involving 8,145 participants. The authors concluded that anti-NGF antibody treatment was associated with a significant improvement in the WOMAC score compared with placebo. Although these agents were not associated with a significantly increased incidence of serious adverse events, they were associated with significant increases in therapy discontinuation due to adverse events or side effects such as peripheral neuropathy.

Future potential developments

Despite several on-going areas of research that aim to provide a safe, effective DMOAD, there are still no options available at this time, which has prompted interest in regenerative medicine as a potential treatment modality in OA. Adult MSCs have been investigated based on their known anti-inflammatory and immunomodulatory properties, which would provide a potentially beneficial local environment for chondrocyte regeneration.³⁹ Despite several trials of MSCs, the findings have suggested very limited benefits from this therapy and are too modest to justify the current high costs associated with regenerative medicine.³⁹ One problem with MSCs, despite their multi-functionality, is how rapidly they disappear from the tissue after injection. To increase the longevity of treatment, a series of surgical methods to 'implant' the MSC into the joint space has been considered; however, all attempts have had limitations, not least the need for surgery on already damaged and painful joints.^{40,41} MSC-derived exosomes, which could be injected into the joint space without surgical intervention, offer a potential alternative strategy for increasing the benefits of MSCs by prolonging their lifespan in the joint space. These exosomes contain a variety of microRNAs with the ability to directly alter gene expression. By altering gene expression, the microRNA is able to regulate cartilage regeneration and downregulate inflammation.⁴² The exosomes themselves are much smaller than MSCs, which is advantageous in terms of delivery; however, it is not yet fully understood what the off-target effects of microRNA will

be, and this will require considerable study before the hope of a licensed DMOAD can be realized.⁴³

Finally, matrix metalloproteinase-13 is expressed by chondrocytes and synovial cells in human OA and is thought to play a critical role in cartilage destruction. A recent publication has reported the development of a new allosteric metalloproteinase-13 inhibitor, AQU-019, which has been developed as a new DMOAD.⁴⁴ Initial studies have shown promise in a rat model of OA.⁴⁴

Conclusion

In conclusion, OA is the most common joint condition, but therapeutic options to date have been limited. Its management has largely been focused on symptomatic control only; while a number of disease-modifying agents have been considered, none has made it to clinical use, largely because of adverse side effects. Several therapeutic agents are currently under development for the management of OA however; progression in this field will be welcomed by clinicians managing patients with OA and, of course, by patients themselves. □

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