Treating osteoarthritis pain: recent approaches using pharmacological therapies

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ABSTRACT

Osteoarthritis (OA) is a debilitative, painful condition with significant global burden. Pharmacological options have limited analgesic efficacy and their side-effects often restrict their use. Novel pharmacological options are needed to relieve patient symptoms and their consequent disease impact. A variety of pharmacological options have been investigated in treating OA, including existing therapies previously used for treating other arthritides (such as colchicine and hydroxychloroquine) and new therapies targeting pain (including monoclonal antibodies to nerve growth factor and intra-articular trans-capsaicin). Extended-release triamcinolone may offer more persisting analgesic effects compared to immediate-release preparations. While most studies have been unsuccessful, pharmacological therapies targeting peripheral nociceptive pathways appear promising.

Introduction

Osteoarthritis (OA) is a chronic, painful and debilitating arthritis affecting both individuals and health economies. Around 242 million people worldwide are affected with OA of the hip/knee (1) and around one third of chronic moderate to severe pain is related to OA (2). The prevalence of OA is rising, linked with a growing elderly and obese population (3). The pathogenesis of OA (and its pain) involves a complex interaction of mechanisms including genetic, mechanical, metabolic and inflammatory elements (4).

OA is managed using pharmacological and non-pharmacological approaches. When these fail, surgical interventions such as joint replacement are considered. Analgesics including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs, topical and oral) and opioid medications are the primary pharmacological treatments for symptomatic OA. However, NSAIDs and opioids are unsuitable for many patients given their side effect profile and the benefits from paracetamol and opioids are limited (5). Intra-articular therapies such as corticosteroids are also commonly used in clinical practice, though often with short-term benefits.

As pain plays a significant role in the clinical syndrome of OA, existing and new therapeutics have been trialled and developed to target different elements of pain pathways. Disease-modifying osteoarthritis drugs (DMOADs) are an experimental group of agents targeting key tissues in OA-affected joints to prevent structural progression and therefore improve symptoms; some of these have reached clinical trials.

This narrative review will provide an overview for clinicians of recent advances in knowledge on the use of existing or new pharmacological therapies. These have primarily been investigated for the treatment of knee OA, with some having been trialled in hand OA. Novel treatments discussed are under an advanced stage of investigation (at least in phase II trials) for the treatment of OA. Treatments have been broadly categorised as oral, intra-articular and biologic. Underpinning this review, we conducted a PubMed search and reviewed meeting abstracts on pharmacotherapy trials in OA reported between 2017 and 2019; both positive and negative reporting trials were included. Exercise, therapies marketed as devices (such as hyaluronans), nutraceuticals (such as glucosamine) and other non-pharmacological interventions were not included. Where relevant, older studies were referenced to give background context on the candidate therapy.

Oral therapies

Colchicine

Colchicine is not routinely used in the treatment of OA but is frequently used

for treating crystal arthropathies such as gout and pseudogout. Basic calcium phosphate (BCP) crystals are present in synovial fluid in OA, with hydroxyapatite the most common form found in OA joints (detected in the cartilage of up to 100% of affected joints at the time of joint replacement) (6). Previous research has demonstrated a positive correlation between synovial fluid BCP crystal levels and radiographic OA severity (7). BCP crystals activate the inflammasome through NOD-, LRR- and pyrin domain-containing 3 (NLRP3) which increase IL-1β expression, the levels of which also correlate with OA severity (8, 9). Colchicine was therefore recently trialled in OA as it appears to block IL-1β release by inhibiting NLRP3 (10). Three previous small trials suggested symptomatic benefit with colchicine in OA knee patients (11-13). A more recent double-blind, placebo-controlled, randomised trial compared colchicine 500 micrograms twice daily with placebo over 16 weeks in 109 patients with knee OA. The study failed to achieve its primary end point of a significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at week 16 (14). Although colchicine is therefore unlikely to provide a new OA therapy, understanding the place of treating non-urate crystal disease requires future consideration.

Hydroxychloroquine

Hydroxychloroquine is routinely used for treating rheumatoid arthritis (RA) synovitis and has a good safety profile (15, 16). It has also previously been used in clinical practice to treat inflammatory hand OA with anecdotal evidence of its benefit. Hydroxychloroquine was considered to be beneficial in treating OA due to its inhibitory action on toll-like receptor (TLR) signalling (17); TLRs are upregulated in OA cartilage and thought to stimulate cartilage breakdown via pro-inflammatory pathways (18, 19). In addition, patients with hand OA have been found to have synovitis (20, 21). Preliminary studies suggested improvements in symptoms after hydroxychloroquine treatment (22, 23). This was followed by a larger randomised, double-blind, placebo-controlled clinical trial of 248 patients over a 12 month period (24). Patients with moderate to severe hand pain were randomised to hydroxychloroquine or placebo, in addition to their usual analgesia. A significant reduction in hand pain with additional hydroxychloroquine compared to placebo was not detected at 6 months, therefore not achieving primary end point. Hydroxychloroquine also did not demonstrate a reduction in radiographic progression at 12 months. In a study subset, stratification for (commonly found) ultrasound-detected synovitis did not change the study results. A further randomised controlled trial compared hydroxychloroquine 400 mg to placebo in 196 patients with hand OA (who were not receiving concomitant NSAID or corticosteroid treatment) and did not detect a significant reduction in pain after 24 weeks of treatment (25).

Intra-articular therapies

Intra-articular capsaicin

The nociceptive nerve fibres (Aδ and C) express a receptor for capsaicin called transient receptor potential cation channel subfamily V member 1 (TRPV1). Its activation leads to a prolonged refractory state known as desensitisation (26). Capsaicin has therefore been an attractive candidate for treating OA pain. Initial capsaicin preparations were topical, with evidence of therapeutic efficacy treating OA pain (27-30). CNTX-4975 is a highly purified, synthetic trans-capsaicin which acts on TRPV1-containing pain nociceptors and is the first intra-articular capsaicin preparation (31). It does not activate other sensory fibres touch and pressure (31). A 24-week, randomised, double-blind, placebo-controlled, dose-ranging study demonstrated significant improvement in WOMAC A1 pain score (for the level of pain a patient has when walking on a flat surface) at 12 and 24 weeks following a single dose CNTX-4975 1mg knee injection in patients with moderately painful knee OA (32). Data on adverse events is limited currently but the most common treatment-emergent adverse event is reported to be procedural pain (32). This largely subsides by 2 hours post injection and there were no withdrawals from the study due to adverse events. A Phase III trial and a study examining efficacy of repeated doses of CNTX-4975 are currently in progress (33, 34).

Injectable corticosteroids

Intra-articular corticosteroids have been shown to significantly reduce pain in OA; however, the benefit tends to be short-lived and no associated benefit is seen at 6 months (35). Most trials have focused on knee OA. A Cochrane review of 27 trials demonstrated an association with small to moderate improvement in function at up to 6 weeks post injection, but no improvement beyond this period (36). There was also moderate to large heterogeneity between trials.

Intraarticular triamcinolone acetonide extended release

In order to overcome the short-lived benefits of corticosteroid, a novel preparation of triamcinolone acetonide extended release (TA-ER) called FX006 was produced using microsphere technology, with the aim of giving prolonged benefits in knee OA. A 12-week, phase IIa randomised, double blind, controlled, dose-finding trial comparing TA-ER at doses 10mg, 40mg and 60mg to immediate-release triamcinolone 40mg in 228 patients with knee OA, demonstrated a significant improvement in mean daily pain intensity scores with single injection TA-ER 40mg *versus* immediate-release triamcinolone 40mg at weeks 5–10 (37). Furthermore, all WOMAC subscale scores were superior with TA-ER 40mg compared to immediate-release triamcinolone at 8 weeks. TA-ER 10mg and 60mg were not reported to be significantly superior to immediate-release triamcinolone 40mg. Similar frequencies of adverse events (AEs) were reported for TA-ER compared to immediate-release triamcinolone.

A further phase IIb study compared TA-ER to placebo in 306 knee OA patients. The study did not achieve its primary outcome of a significant improvement in average daily pain (ADP) intensity *versus* placebo at time point of 12 weeks; however, there were significant improvements in ADP inten-

sity scores with TA-ER 32mg *versus* placebo at weeks 1–11 and at week 13 (38). A subsequent phase III, multicentre, double-blinded, randomised, controlled trial compared TA-ER (32mg) to immediate-release triamcinolone (40mg) and placebo in 484 knee OA patients (39). It achieved its primary end point of a significant improvement in ADP intensity compared to placebo at 12 weeks although TA-ER did not significantly reduce ADP intensity compared to immediate-release triamcinolone at 12 weeks. However, TA-ER 32mg significantly improved WOMAC pain, stiffness and physical function scores, and the Knee injury and Osteoarthritis Outcome Score (Quality of Life subdomain - KOOS-QOL) compared to both placebo and immediate-release triamcinolone at 12 weeks. The differences with the active comparator seen when using different patient-reported outcome measures may be related to a greater sensitivity for the disease-specific, multi-item WOMAC tool over the ADP single item question. Given the significant improvement over placebo, TA-ER has been licensed by the FDA for managing OA-related knee pain. A further advantage of TA-ER's mechanism of action with slow intra-articular release is reduced systemic exposure compared to immediate release triamcinolone (40). TA-ER 32mg causes less glycaemic disruption compared to standard triamcinolone 40mg in type 2 diabetic patients (41).

Intramuscular corticosteroid

Intra-articular corticosteroid injections are known to give short-term benefit in hip OA (42). This procedure, however, requires a degree of technical ability to perform. Intramuscular injections require less training and would be of potential benefit in primary care management of OA. A recent randomised, double-blind, trial compared a single intramuscular triamcinolone acetate 40mg with placebo in 106 patients with hip OA (43). Pain levels at rest and on walking using an 11-point numeric rating scale (NRS: 0–10, 0=no pain) and WOMAC pain levels were recorded at 2, 4, 6 and 12 weeks post injection. A significant reduction in NRS hip pain at rest was detected in the triamcinolone group compared to the placebo control group at 2 weeks, which persisted for the whole 12 weeks of the trial period. No significant difference in pain on walking and WOMAC pain was demonstrated at 2 weeks. However, triamcinolone was significantly superior to placebo at reducing pain on walking at 4, 6 and 12 weeks. Triamcinolone was also significantly superior in reducing WOMAC pain, function, stiffness and total scores compared to placebo at weeks 4, 6 and 12. The level of improvement in NRS pain at 2 weeks was reported as probably clinically relevant, but not for beyond that time point. Furthermore, the study only achieved only one out of the three primary outcome measurements at 2 weeks.

Biologic therapies

Interleukin-1 α and β inhibition

Interleukin 1 alpha (IL-1α) and interleukin 1 beta (IL-1β) have increased expression within the cartilage and synovial membrane in OA (44, 45). Samples of OA fluids and tissue with elevated IL-1 levels have also demonstrated increased levels of OA pathophysiology markers including catabolic enzymes, prostaglandins, nitric oxide and other markers (46). Interleukin 1 inhibition has been shown to slow OA progression in animal models (47-50).

Interleukin-1 has previously been targeted in OA using anakinra, a recombinant form of interleukin-1 receptor antagonist (IL-1Ra). A multicentre, double-blind, placebo-controlled study randomised 170 patients to receive a single intra-articular injection of placebo, anakinra 50 mg, or anakinra 150 mg in their symptomatic knee. Although anakinra was well tolerated, a significant difference in mean WOMAC pain score improvements from baseline to week 4 was not detected between the treatment groups (51).

Lutikizumab (formerly ABT-981) is a newly developed human dual variable domain immunoglobulin that directly inhibits the actions of IL-1α and IL-1β (52). A randomised, double-blind, placebo-controlled, parallel-group phase II trial (ILLUSTRATE-K) compared fortnightly subcutaneous injections of lutikizumab at 25mg, 100mg, or 200mg in patients with knee OA for 50 weeks (53). A significant improvement in WOMAC pain score at 16 weeks with lutikizumab 100mg compared to placebo was detected (achieving the primary end point). However, this was not shown with lutikizumab 25mg or 200mg. Cartilage thickness, MRI synovitis, and other structural endpoints were similar between lutikizumab and placebo, although lutikizumab was generally well tolerated. As the results did not demonstrate a dose response and the study failed to meet structural endpoints, the clinical efficacy of lutikizumab remains uncertain.

Lutikizumab has also been investigated in treating erosive hand OA. A phase IIa, placebo-controlled, randomised study measured clinical and radiological outcomes in 131 patients with hand OA as per American College Rheumatology criteria (≥3 inflamed interphalangeal joints which are tender, swollen, or both, hand pain ≥6 (scale 0-10), and ≥1 erosive interphalangeal joint on x-ray). 67 patients received lutikizumab 200mg and 64 patients received placebo every 2 weeks for 26 weeks. There was no significant difference in Australian/Canadian Hand OA Index (AUSCAN) pain improvement scores between treatment groups at 16 weeks. Moreover, there was no significant difference in x-ray or MRI changes between treatment groups (54).

Despite the negative trials above, *in vitro* work using canakinumab, a monoclonal antibody targeting IL-1β, demonstrated increased proteoglycan and reduced nitric oxide synthesis, with potential for reduced cartilage breakdown (55). Canakinumab was employed in the recent CANTOS trial – a very large randomised, placebo-controlled trial investigating the cardiovascular benefits of subcutaneous canakinumab. Patients with previous myocardial infarction and a high-sensitivity C-reactive protein level ≥2 mg/L on blood testing received canakinumab doses 50 mg, 150 mg or 300 mg every 3 months for a median of 3.7 years (56). The results demonstrated canakinumab 150 mg was associated with a significantly

lower rate of recurrent cardiovascular events. A posthoc analysis of this trial reported a reduced incidence of OA symptoms and joint replacements in the patients who received canakinumab (57).

Tumour necrosis factor inhibitors

Tumour necrosis factor alpha (TNF-α) is another interleukin implicated in OA pathophysiology (58). However, anti-TNF-α agents have generally been unsuccessful in improving OA symptoms. One agent extensively studied is adalimumab, which has not demonstrated efficacy compared to placebo in reducing hand OA symptoms (59, 60). The recent HUMOR trial compared subcutaneous adalimumab 40mg alternate weeks with placebo over 12 weeks in a crossover trial involving 43 patients with erosive hand OA and evidence of magnetic resonance imaging (MRI)-defined synovitis (61). There was an 8 week washout period before treatment groups crossed over. No significant difference was detected in visual analogue scale (VAS) scores for pain between the treatment groups. In addition, no significant differences were detected for any secondary outcomes including change in MRI-detected synovitis and bone marrow lesions.

Another anti-TNF α agent, etanercept, has also recently been trialled in a 1 year, double-blind, randomised, placebo-controlled, multicentre trial of 90 patients with symptomatic erosive inflammatory hand OA. The study did not achieve its primary end point of a significant improvement in VAS pain at 24 weeks with etanercept 50mg weekly (62). In addition, etanercept was not shown to significantly reduce ultrasonographic or MRI-detected synovitis after 1 year. A significant reduction in MRI-detected bone marrow lesions in the interphalangeal joints of one hand after 1 year was detected with etanercept, although this was in a very small subgroup (n=10 in each treatment group).

Anti-nerve growth factor monoclonal antibodies

Nerve growth factor (NGF) is a neurotrophin which stimulates the growth of nociceptive nerve fibres and expression of nociceptive cell surface receptors. It has also been found to have increased expression in OA (63). A variety of structures within the knee joint are highly innervated with nociceptive nerve fibres and potential sources of knee pain in OA: including the joint capsule, ligaments, periosteum, menisci, subchondral bone and synovium (64). The peripheral nociceptive pathway is therefore an attractive target for novel analgesic agents.

Tanezumab, fasinumab and fulranumab are monoclonal antibodies which have been developed to target NGF preventing it from binding its receptor with the overall aim of reducing pain (65). Development of fulranumab has recently terminated. A meta-analysis of 9 studies with 10 randomised controlled trials enrolling 7665 patients comparing tanezumab to placebo/active comparator in knee or hip OA demonstrated superiority in efficacy (WOMAC pain subscale, WOMAC function subscale, patient global assessment) with tanezumab (66). Recent studies have investigated subcutaneous (SC) preparations but before this IV tanezumab was used. In the phase III trials, fixed doses of tanezumab were used (2.5mg, 5mg and 10mg). A recent phase III trial compared fixed doses 8 weeks apart of SC tanezumab and step up dosing (2.5mg administered at baseline, 5mg administered at week 8) *versus* placebo in 696 OA hip/knee patients who had not responded to, or unable to tolerate, standard pain treatments. The results demonstrated tanezumab 2.5mg fixed and 2.5mg/5mg step up dosing was superior to placebo in improving WOMAC Pain, WOMAC function and patient global assessment scores at week 16. Exploratory analyses suggest nominally greater improvement with tanezumab 5mg compared to fixed 2.5mg dosing after 16 weeks (67). A greater number of joint replacements were observed in patients receiving tanezumab although the majority of these were elective and not associated with an AE. Two joint replacements were thought to be due to rapidly progressive OA (see below).

Tanezumab monotherapy has demonstrated analgesic superiority over NSAIDs (celecoxib 100 mg and naproxen 500 mg) and oxycodone 10-40 mg, at both 5mg and 10mg (68, 69). Combined tanezumab and NSAID therapy also demonstrated significantly greater analgesic efficacy compared to NSAID monotherapy, although not compared to tanezumab monotherapy (69).

Recently, the efficacy of fasinumab was investigated in a phase IIb/III double-blind, placebo-controlled, randomised clinical trial (70). 421 patients with moderate-to-severe knee or hip OA and inadequate response or intolerance to analgesics were randomised to receive fasinumab 1mg, 3mg, 6mg, 9mg or placebo every 4 weeks over 16 weeks with follow up until week 36. 346 patients completed the study. All the doses of fasinumab demonstrated statistically significant and clinically important improvement in WOMAC pain and physical function subscale and patient global assessment scores compared to placebo at week 16. These improvements were not dose-dependent.

Discontinuation rates in anti-NGF trials are low but tanezumab (the most widely studied drug) has been associated with a number of adverse effects (66). These include paraesthesia, headaches, arthralgia, peripheral oedema, peripheral neuropathy, hypo- and hyper- aesthesia. Arthralgia was the most commonly reported side effect (8% of tanezumab-treated patients). Lower doses of tanezumab are associated with fewer adverse events (66).

Rapidly progressive OA (RPOA) is the most serious adverse event reported with tanezumab, fasinumab and fulranumab, with the risk being dose-responsive (70, 71). It is a painful condition diagnosed radiographically by rapid joint space narrowing and severe progressive atrophic bone and has been reported in 1% of patients who received tanezumab (72). Recent trials have used a maximal 5mg dose of tanezumab in patients with hip or knee OA as the RPOA risk appears lower and is outweighed by its potential therapeutic benefit (73). Combination tanezumab and NSAID therapy appears to increase the risk of RPOA compared to tanezumab alone (73).

Conclusion

Current treatment options in OA remain limited. Conventional rheumatoid arthritis DMARDs have not so far demonstrated benefit in managing OA symptoms; further data on methotrexate is expected soon (74). However, recent trials involving peripheral nociceptive targets have demonstrated promising analgesic results in knee OA.

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