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New developments in osteoarthritis pharmacological therapies

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Abstract

OA is an increasingly common, painful condition with complex aetiology and limited therapies. Approaches to expanding our therapeutic armamentarium have included repurposing existing therapies used for other rheumatological conditions, modifying existing OA preparations to enhance their benefits, and identifying new therapeutics. HCQ and low-dose MTX have been unsuccessful in improving hand OA pain or reducing structural progression. Anti-IL-6 and anti-GM-CSF also did not improve symptoms in hand OA trials, but IL-1 remains an intriguing target for large-joint OA, based on reduced joint replacements in a *post hoc* analysis from a large cardiovascular disease trial. The peripheral nociceptive pathway appears an attractive target, with mAbs to nerve growth factor and IA capsaicin demonstrating efficacy; tropomyosin receptor kinase A inhibitors are at an earlier stage of development. Limited evidence suggests pharmacological therapies can modify cartilage and bone structural progression, though evidence of synchronous symptom benefits are lacking.

Key words: OA, cartilage, NSAID, DMARD, inflammation, synovitis, nociceptive pain

Rheumatology key messages

- The peripheral nociceptive pathway is a promising therapeutic candidate in symptomatic knee and hip OA.
- The role of IL-1β as a target in hip and knee OA needs further consideration.
- There are some data supporting the therapeutic potential of structure-modifying OA drugs, though their symptomatic benefits are unclear.

Introduction

OA is a chronic, debilitating condition characterized by joint pain, stiffness and loss of function. The knee is most commonly affected, with ~263 million people afflicted worldwide [1]. OA pathology is complex, with multiple processes being involved [2]. There are also challenges to measuring and treating OA-related pain, as the structure–pain relationship in OA remains incompletely understood, and multiple tissues contribute to OA-related pain with varying degrees [3]. In addition, the various patient-reported outcome measures used in clinical trials have limitations in determining the pain experience. Despite the high prevalence of OA, treatment options remain limited. Paracetamol, NSAIDs and (less recommended) opiates remain the standard pharmacological therapy, though they have small to modest analgesic benefits and substantial side effects [4].

This review explores recent randomized control trials (RCTs) of potential OA therapies involving existing OA pharmacological therapies, novel preparations of existing therapies, and therapies in development. A systematic search of Medline and EMBASE (2019 to April 2021), limited to English articles and at least phase 2 trials in humans, was conducted. Additionally recent relevant meeting abstracts were also reviewed. Trials before 2019 are included occasionally to add context to recent data. Nutraceuticals, serum-derived products and devices such as hyaluronic acid were not included (for recent reviews in these areas see references [5–8]). Table 1 summarizes the primary efficacy outcomes for the included RCTs [9–36].

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Novel use of existing therapies

Oral prednisolone was trialled in the Hand Osteoarthritis Prednisolone Efficacy study [9]. The 92 nodular hand OA participants with finger pain and clinical and US-detected inflammation in ≥1 IP joint were randomized to receive prednisolone 10 mg or placebo daily for 6 weeks, followed by a 2-week tapering. Visual analogue scale (VAS) finger pain improvement at week 6 was significantly greater in the prednisolone group. However, after tapering, mean group differences became non-significant.

US-guided IA CS was also trialled for hip OA [10]. In that study, the 199 participants were randomized to receive US-guided IA hip injection (USGI) of 40 mg triamcinolone acetonide and 4 ml 1% lidocaine hydrochloride combined with best current treatment (BCT) *vs* BCT alone and USGI of 5 ml 1% lidocaine only combined with BCT. There was greater mean numeric rating scale (NRS) improvement in hip pain intensity over 6 months with BCT plus triamcinolone/lidocaine compared with BCT alone. There was no significant difference over 6 months between BCT plus triamcinolone/lidocaine and BCT plus lidocaine only for hip pain intensity improvement, and the true effect of IA CSs for hip OA remains uncertain.

A number of DMARDs used for treating synovitis in inflammatory arthritis have been explored. Three large RCTs previously showed no significant structural or symptomatic improvement for HCQ over placebo for hand OA [37–39].

MTX was investigated as an analgesic at a low dose (10 mg) in an erosive hand OA trial [12]. Preliminary data showed no improvement in VAS pain at 3 months (primary end point). Preliminary data from a study of MTX in knee OA (dose increasing from 10 mg to 25 mg weekly) showed significant improvement in the primary outcome (VAS knee pain) but not in the secondary outcome (WOMAC pain) at 6 months [13]. MTX significantly improved WOMAC stiffness and physical function compared with placebo at 6 months, but failed to reduce MRI-assessed synovitis at 6 months.

The effects of IL-6 on cartilage are incompletely understood, though animal models suggest they drive progressive OA cartilage loss [40]. It may also play a role in pain sensitivity [41]. However, a 12-week RCT of 91 participants with symptomatic hand OA did not demonstrate a significant improvement in VAS pain at 6 weeks with anti-IL-6 tocilizumab *vs* placebo. Secondary end points, including painful and swollen joints, duration of morning stiffness, patients' and physicians' global assessment and function scores, were also not met [14].

Colchicine has traditionally been used for treating crystal arthropathies and crystal-induced inflammation has been reported in OA [42]. RCTs of colchicine in knee OA [43] and more recently hand OA [15], failed to show efficacy in reducing pain.

Subchondral MRI-detected bone marrow lesions (BMLs) are important in knee OA pain and structural progression [44]. Bisphosphonates have been investigated for their benefits in suppressing subchondral bone remodelling. In a recent study, 223 participants with knee OA and at least one BML were randomized to receive an infusion of zoledronic acid 5 mg or placebo at baseline and 12 months. Zoledronic acid was not superior to placebo in reducing knee pain or BML size [16].

Novel delivery mechanisms

Topical and oral NSAIDs are established OA analgesic therapies. AMZ001 is a novel, longer-acting, topical 3.06% diclofenac gel requiring fewer daily applications than the standard topical NSAID regime (four times a day). This was assessed in a phase 2 trial that randomized 444 knee OA participants to receive AMZ001 once daily, AMZ001 twice daily, placebo twice daily or diclofenac 1% gel four times daily [17]. AMZ001 once daily improved WOMAC pain *vs* placebo at week 4 (primary outcome), but the twice daily regimen and diclofenac 1% failed. The lack of a dose response limits the evidence that either of the AMZ001 regimens are more effective than placebo. Diclofenac in a novel topical liposomal gel (lipogel) improved pain compared with placebo in a recent small study [45].

An alternative delivery of topical NSAIDs is via medicated plasters. Early NSAID plasters used methyl salicylate, but indomethacin plasters have also been developed. In a crossover trial of 168 participants with knee OA [18], both methyl-salicylate and indomethacin plasters significantly improved Japanese Knee Osteoarthritis Measure scores (measuring pain, stiffness and function) over placebo, though no significant difference between the two active comparators were found. The potential indication of IA NSAIDs would be to limit systemic toxicity, and a non-placebo randomized trial, reported that an IA preparation of NSAID ketorolac had comparable efficacy in improving pain and function to that of IA triamcinolone in treating hip and knee OA [19].

IA CSs is an established knee OA treatment, though analgesic benefits are short-lived. Longer-acting preparations could therefore provide prolonged benefits, although cost implications need to be considered. FX006 is a long-acting triamcinolone acetonide extended-release (TA-ER) drug developed using microsphere technology, prolonging its presence in the joint [46]. A phase 3 study randomized 484 participants to TA-ER 32 mg, immediate-release triamcinolone 40 mg or placebo [20]. The study showed a significant improvement in average-daily-pain intensity compared with placebo at 12 weeks (primary end point). IA TA-ER 32 mg is licensed by the FDA for knee OA. Bilateral TA-ER injections are also associated with relatively lower systemic concentrations compared with triamcinolone crystalline suspension [47].

TLC599 is a novel long-acting IA dexamethasone sodium phosphate preparation in a liposomal formulation. This was investigated in a phase 2a study of 75 participants with symptomatic knee OA who received TLC599 12 mg, 18 mg or placebo [21]. TLC599 12 mg demonstrated significantly greater reduction in WOMAC pain at all specified time points up to week 24, which was also

Table 1 Recent trials of OA therapies

Drug	Route and dose	OA sites	Latest study phase	Number of participants	Primary end point time point	Outcomes
Prednisolone [9]	Oral 10 mg	Hand	2	92	6 weeks	Significantly greater VAS finger pain improvement at 6 weeks *vs* placebo but effect reduces on tapering
Triamcinolone acetonide [10]	Intra-articular 40 mg	Hip	2	199	6 months	Triamcinolone acetonide and 1% lidocaine combined with best current treatment confers significant improvement in hip pain NRS over 6 months *vs* BCT alone but not *vs* BCT plus 1% lidocaine only
HCQ [11]	Oral 200–400 mg	Hand	2	153	52 weeks	No significant improvement in Australian Canadian Osteoarthritis Hand Index (AUSCAN) hand pain or radiographic scores *vs* placebo at 52 weeks
MTX [12]	Oral 10 mg	Hand	2	64	3 months	No significant difference in VAS pain score improvement and functional improvement at 3 months and 12 months, respectively
MTX [13]	Oral 25 mg	Knee	2	155	6 months	Significant improvement in average NRS knee pain, WOMAC stiffness and physical function at 6 months, but not WOMAC pain
Tocilizumab [14]	I.v. 8 mg/kg	Hand	2	91	6 weeks	No significant improvement in VAS pain at 6 weeks Side effects: Infections (particularly upper airways)
Colchicine [15]	Oral 0.5 mg	Hand	2	64	12 weeks	No significant difference in VAS score improvement *vs* placebo at weeks 6, 12 and 16 Side effects: nausea, diarrhoea, vomiting, bloating and reflux
Zoledronic acid [16]	I.v. 5 mg	Knee	2	223	24 months	No significant difference in tibiofemoral cartilage volume or WOMAC pain change over 24 months Side effects: acute reactions (appear and resolve within 3 days); include fever, eye, musculoskeletal, gastrointestinal or other symptoms
Long-acting diclofenac gel (AMZ001) [17]	Topical 3.06%	Knee	2	444	4 weeks	Once daily dose improved WOMAC pain *vs* placebo at week 4 but twice daily did not
Indomethacin plasters [18]	Topical 70 mg	Knee	2	168	3 weeks	Significant improvement over placebo in Japanese Knee Osteoarthritis Measure scores after 2 weeks
Ketorolac [19]	IA 30 mg	Knee and hip	2	110	3 months	No significant difference in KOOS or HOOS scores at 1 week, 1 month and 3 months
Triamcinolone acetonide extended release (FX006) [20]	IA 32 mg	Knee	3	484	12 weeks	Significant improvement in average daily pain intensity compared with placebo at 12 weeks
Long-acting dexamethasone (TLC599) [21]	IA 12 mg, 18 mg	Knee	2	75	12 weeks	Significantly greater reduction in WOMAC pain *vs* placebo at weeks 12, 16, 20 and 24 with TLC599 12 mg

(continued)

Table 1 Continued

Drug	Route and dose	OA sites	Latest study phase	Number of participants	Primary end point time point	Outcomes
Tanezumab [22]	S.c. 5 mg	Knee and hip	3	849	24 weeks	Tanezumab 5 mg improved WOMAC pain, physical function and PGA-OA *vs* placebo at 24 weeks; tanezumab 2.5 mg improved pain and function in patients but did not reach statistical significance for PGA-OA Side effects: arthralgia, paraesthesia, headaches, peripheral oedema, peripheral neuropathy, hypo- and hyperaesthesia
Fasinumab [23]	S.c. 1 mg, 3 mg, 6 mg, 9 mg	Knee and hip	3	421	16 weeks	Clinically significant improvements in WOMAC pain, function and PGA for all doses *vs* placebo at week 16 Side effects: paresthaesia, arthralgia and upper-respiratory infections
Tropomyosin receptor kinase A inhibitor (GZ389988) [24]	IA 3 ml	Knee	2	104	4 weeks	Significantly greater WOMAC A1 pain improvement *vs* placebo at 4 weeks Side effects: joint inflammatory reaction and arthralgia
Tropomyosin receptor kinase A inhibitor ASP7962 [25]	Oral 100 mg	Knee	2	215	4 weeks	No significant difference between ASP7962 and placebo for any WOMAC subscale at week 4
Tropomyosin receptor kinase A, B and C inhibitor ONO-4474 [26]	Oral 100 mg	Knee	2	110	4 weeks	No significant difference in change of VAS pain over 24 h *vs* placebo at week 4 Side effects: myalgia, arthralgia, dizziness and hypoesthesia
Synthetic capsaicin (CNTX-4975) [27]	IA 1 mg	Knee	2	848	8 weeks	**Unilateral OA injection** • OMERACT–OARSI response rates • 67% in those with no/mild non-index knee pain and 81% in patients with non-index knee single-joint replacement, respectively, at 8 weeks **Bilateral OA injections** • Response rates for index and non-index knees were 73% and 79%, respectively, for those receiving bilateral injections at 8 weeks Side effects: arthralgia
Imidazoline-2 receptor agonist (CR4056) [28]	Oral 100 mg, 200 mg	Knee	2	214	14 days	Significant improvement in WOMAC pain score *vs* placebo at 14 days in males only Side effects: headache
Lutikizumab [29]	S.c. 25 mg, 100 mg, 200 mg	Knee	2	347	16 weeks and 26 weeks	Statistically greater WOMAC pain improvement at 16 weeks at 100 mg *vs* placebo, but not at 25 mg or 200 mg No improvement in slowing cartilage loss or reducing synovitis at week 26
Lutikizumab [30]	S.c. 200 mg	Hand	2	132	16 weeks	No significant improvement in AUSCAN pain *vs* placebo at 26 weeks Side effects: Injection site reactions and neutropaenia

(continued)

Table 1 Continued

Drug	Route and dose	OA sites	Latest study phase	Number of participants	Primary end point time point	Outcomes
Canakinumab [31]	S.c. 50 mg, 150 mg, 300 mg	Hip Knee	3	10 061	5 years	Reduced rates of total hip and knee replacements in addition to OA-related adverse events compared with placebo over 5 years Side effects: neutropaenia, thrombocytopaenia
Otilimab [32]	S.c. 180 mg	Hand	2	44	6 weeks	No change in 24 h hand pain intensity scores from baseline at week 6 compared with placebo
Sprifermin [33]	IA 30 μg, 100 μg	Knee	2	549	2 years	Dose-dependent increase in overall cartilage thickness with sprifermin *vs* placebo after 2 years No WOMAC subscale significantly improved with any sprifermin dose compared with placebo Side effects: arthralgia
Matrix extracellular phosphoglycoprotein derivative (TPX-100) [34]	IA 20 mg, 50 mg, 100 mg, 200 mg	Knee	2	93	12 months	Clinically meaningful improvements in KOOS and WOMAC scores at 6 and 12 months
Cathepsin K inhibitor (MIV-711) [35]	Oral 100 mg, 200 mg	Knee	2	244	26 weeks	Did not significantly improve NRS pain score *vs* placebo at 26 weeks MRI femoral OA bone disease progression significantly reduced at week 26 in MIV-711 100 mg and 200 mg dose groups *vs* placebo
Lorecivivint [36]	IA 0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg	Knee	2	695	12 weeks	0.07 and 0.23 mg were the most effective doses for improving pain NRS and WOMAC pain, physical function and patient global assessment from weeks 12–24

BCT, best current treatment; HOOS, Hip Disability and Osteoarthritis Outcome Score; KOOS, Knee Osteoarthritis Outcome Score; NRS, numeric rating scale; PGA, patient's global assessment; PGA-OA, patient's global assessment of OA; VAS, visual analogue scale.

considered a durable response. TLC599 18 mg was less effective than 12 mg at improving pain.

There has been concern regarding local effects on cartilage from repeated injections [48]. Other single-centre case series have suggested structural associations include subchondral insufficiency fracture, osteonecrosis, and rapid joint destruction [49]. However, confounding factors exist with such data, and a recent expert consensus group suggested no benefit of pre-injection imaging screening [50]. Local anaesthetic may play a role in developing increased joint damage [51].

Novel mechanisms of action

Modulating peripheral nociceptive pathways

There has been increasing interest in agents targeting peripheral nociceptive pathways of OA pain. Nerve growth factor (NGF) is a neurotrophin that also sensitizes peripheral nociceptors following tissue injury or inflammation. NGF binds to tropomyosin receptor kinase A (TrkA) and the p75 neurotrophin receptors on sensory nerve axons [52] and stimulates nociceptive nerve fibre growth and nociceptive cell surface receptor expression, which are abundant, particularly in the joint capsule, ligaments, periosteum, menisci, subchondral bone and synovium of OA knees [53].

Tanezumab and fasinumab are anti-NGF mAbs, preventing NGF receptor binding, thereby reducing pain [54]. Due to fears of side effects related to rapidly progressive OA (RPOA) and possible sympathetic nerve dysfunction (not borne out subsequently) [55], there have been delays in development of these agents.

A meta-analysis of tanezumab with 10 RCTs (prior to its clinical hold) enrolling 7665 patients with knee or hip OA demonstrated i.v. tanezumab (2.5 mg, 5 mg and 10 mg) had superior efficacy over placebo in improving WOMAC pain, function, and patient's global assessment

(PGA) [56]. S.c. preparations of tanezumab have replaced i.v. formulations in recent trials. A recent phase 3 trial of s.c. tanezumab compared fixed (2.5 mg) doses 8 weeks apart and step-up dosing (2.5 mg at baseline, 5 mg at week 8) *vs* placebo in 696 OA hip/knee patients unresponsive or intolerant to standard analgesia. Both regimes were superior to placebo for WOMAC pain, function and PGA improvement at week 16 [57]. The tanezumab group had more joint replacements, although they were mostly elective and not associated with an adverse effect. Two joint replacements were considered to be due to RPOA (see below). Another subsequent phase 3 RCT with longer safety follow-up investigated tanezumab 2.5 mg or 5 mg every 8 weeks for 24 weeks, with a further 24 month follow-up in 849 participants with hip or knee OA [22]. At 24 weeks, tanezumab 5 mg improved WOMAC pain, physical function and PGA of OA (PGA-OA) *vs* placebo; tanezumab 2.5 mg improved pain and function in patients but this did not reach statistical significance for PGA-OA.

Earlier phase 3 studies demonstrated tanezumab monotherapy at 5 mg and 10 mg had greater analgesic efficacy *vs* NSAIDs (celecoxib 100 mg and naproxen 500 mg) and oxycodone 10–40 mg [58, 59]. Yet another phase 3 study investigated s.c. tanezumab 2.5 mg or 5 mg *vs* NSAID (naproxen 500 mg, celecoxib 100 mg, or diclofenac ER 75 mg orally) in an 80-week study of 2996 hip or knee OA patients. Tanezumab 5 mg significantly improved WOMAC pain and function (but not PGA-OA) compared with NSAID at week 16. Tanezumab 2.5 mg was not superior to NSAIDs at 16 weeks and neither of the tanezumab doses was superior to NSAIDs at 56 weeks [60]. Combination tanezumab and NSAID therapy previously demonstrated significantly greater analgesic efficacy over NSAID monotherapy, but not compared with tanezumab monotherapy [59].

Tanezumab (the most widely studied drug) has been associated with a number of adverse effects, although the discontinuation rates in anti-NGF trials are low [56]. Arthralgia was the most commonly reported side effect (8–9% tanezumab-treated patients at 24 weeks). Other side effects include paraesthesia, headaches, peripheral oedema, peripheral neuropathy, hypo- and hyper-aesthesia.

Fasinumab has also been recently investigated in a phase 2 b/3 RCT [23]. The 421 patients with moderate-to-severe knee or hip OA and inadequate response or intolerance to prior analgesics received fasinumab 1 mg, 3 mg, 6 mg, 9 mg or placebo every 4 weeks over 16 weeks until week 36. There were statistically and clinically significant improvements in WOMAC pain, function and PGA for all the doses of fasinumab *vs* placebo at week 16. Improvements were not dose-dependent but lower doses had fewer arthropathies.

Rapidly progressive OA (RPOA)

RPOA is the most serious adverse event reported with the anti-NGFs [23, 61] and presents as rapid reduction in joint space and/or severe progressive atrophic bone [62]. To reduce the risks of RPOA while maintaining therapeutic effect, recent trials have used a maximal 5 mg dose of tanezumab [63]. Modern trials also limit concomitant NSAID use, because combining both drugs confers a much higher risk of RPOA [64].

Single-use IA GZ389988, an inhibitor of TrkA, was investigated in a phase 2 study of 104 knee OA patients [24]. The study achieved its primary end point, significant improvement of WOMAC A1 pain (pain walking on a flat surface) *vs* placebo at 4 weeks.

An oral TrykA inhibitor, ASP7962, was investigated in a phase 2a, double-blind, placebo- and naproxen-controlled, double-dummy, parallel-group study of 215 participants with knee OA [25]. No significant difference was detected between ASP7962 and placebo for any WOMAC subscale. The differences between the two TrykA inhibitors may be due to differences in study population, pharmacological differences and high levels of the placebo effect in both studies [65]. A further oral TryK A, B and C inhibitor, ONO-4474 was investigated in a RCT of 110 knee OA participants and did not show significant reduction in pain after 4 weeks [26].

Chilli peppers contain capsaicin, which binds to the protein transient receptor potential cation channel subfamily V 1 (TRPV1) on Aδ and C nociceptive nerve fibres, causing the burning sensation associated with chillies. CNTX-4975 is a purified, synthetic capsaicin preparation specifically targeting TRPV1-containing pain nociceptors [66]. This may have analgesic effects, as neuronal activation triggers a prolonged refractory state called desensitization [67]. Other sensory fibres such as touch or pressure are unaffected. Topical capsaicin has demonstrated efficacy in relieving OA pain [68]. A dose ranging phase 2 study of 1 mg single IA dose of CNTX-4975 in patients with moderately painful knee OA demonstrated significant improvement in WOMAC A1 pain at weeks 12 and 24 [69]. The most common adverse event was post-procedural pain, which subsided 2 h post injection but did not result in study withdrawals [69]. A phase 3 trial of CNTX-4975 is currently underway, with preliminary data showing high levels of clinical response 8 weeks post-injections [27]. A study examining the efficacy of repeated doses is also in progress [70]. TRPV-1 calcium channel agonists are also currently at an early development stage [71].

Imidazoline receptor agonism

Imidazoline-2 (I2) receptors are found in the central and peripheral nervous system and are thought to affect descending pathways of pain control, therefore being a potential target for novel analgesics. CR4056 is a reversible ligand specific for I2 and was investigated in a double-blind, placebo-controlled, parallel-group-design RCT of 214 participants with knee OA [28]. Over 14 days, men received oral CR4056 twice daily or placebo, while women received CR4056 once daily or placebo (based on differing systemic exposures from phase 1 data). The primary end point (of improved WOMAC pain at day 14 compared with placebo) was seen in males only.

Cytokine inhibitors

IL-1 is thought to play a role in OA pathophysiology based on *in vitro* studies demonstrating induction of cartilage-degrading proteases and its upregulation in human OA joint tissues [72]. Anakinra, a recombinant form of IL-1 receptor antagonist, previously failed to improve WOMAC pain *vs* placebo after a single injection in knee OA [73]. Lutikizumab (previously ABT-981) is a novel immunoglobulin agent that targets and inhibits IL-1α and IL-1β [74]. The ILLUSTRATE-K phase 2 trial demonstrated WOMAC pain improvement at 16 weeks with fortnightly s.c. lutikizumab 100 mg *vs* placebo, but not with 25 mg or 200 mg, demonstrating a lack of dose response [29]. The drug also failed to slow cartilage loss or reduce synovitis. A further study of lutikizumab 200 mg in erosive hand OA failed to demonstrate structural or symptomatic improvement over placebo [30].

However the IL-1 story remains intriguing following data from the CANTOS trial, a very large RCT investigating the protective cardiovascular effects of the IL-1β inhibitor canakinumab in participants with a previous myocardial infarction and raised, highly sensitive CRP [75]. In the main trial, s.c. canakinumab 50, 150 or 300 mg every 3 months for up to 5 years were used, with results showing a reduction in cardiovascular events in groups given 150 mg or 300 mg doses. Exploratory analysis also demonstrated substantially reduced rates of total hip and knee replacements and OA-related adverse events over a median follow-up of 3.7 years (though with no clear dose response) [31].

GM-CSF has roles in myeloid cell development and survival. It is also thought to play a role in pain, inflammation and OA progression, based on murine models [76] and the elevated levels found in the synovium of OA patients [77]. Otilimab is an anti-GM-CSF mAb investigated in a very small randomized phase 2a trial [32]. The 44 patients with active inflammatory hand OA received s.c. otilimab 180 mg or placebo once a week from week 0 to week 4 then in alternate weeks until week 10. The study did not achieve its primary end point (reduced hand pain intensity scores) at week 6 compared with placebo.

Recombinant human fibroblast growth factor

Fibroblast growth factor-18 has demonstrated cartilage anabolic effects in OA animal models [78]. Sprifermin is an IA recombinant human fibroblast growth factor-18 targeting FGFR3 receptors in cartilage. A phase 1 study of 168 knee OA participants demonstrated significantly reduced loss of total and lateral femorotibial cartilage thickness at 6 or 12 months, but not the primary end point of reduced loss in the central medial femorotibial compartment [79]. A follow-up 5-year phase 2, dose-ranging trial of sprifermin (FORWARD trial) has recently been completed [33]. Over 18 months, 549 patients were randomized to receive three once-weekly injections of: sprifermin 100 μg 6-monthly or 12-monthly; Sprifermin 30 μg 6-monthly or 12-monthly; or placebo every 6 months. Tibiofemoral quantitative MRI cartilage thickness was the primary end point. After 2 years, there was a dose-dependent increase in overall cartilage thickness with sprifermin *vs* placebo. These data have been confirmed by automated and manual cartilage measurements [80], with benefits also being maintained at 5 years [81]. No symptoms (WOMAC subscales) were significantly improved with any sprifermin dose [81], though this study was designed to assess structural progression and modern pain trial inclusion criteria were not employed. *Post-hoc* analysis using a subgroup with a lower medial joint space width of 1.5–3.5 mm and higher WOMAC pain scores of 40–90, at risk of increased knee OA progression, suggested benefits for the highest dose of sprifermin at year 3 [82].

TPX-100

Another anabolic agent, TPX-100, is a peptide derived from matrix extracellular phosphoglycoprotein and has demonstrated promotion of cartilage proliferation in animal models [34]. The 93 participants in that trial with bilateral moderate-to-severe patellofemoral knee OA received four once-weekly injections of TPX-100 into one knee while the other received placebo. Preliminary data reported that TPX-100 200 mg conferred statistically significant and clinically meaningful improvements in Knee Osteoarthritis Outcome Score and WOMAC scores at 6 and 12 months.

Cathepsin K inhibition

Cathepsin K is a lysosomal cysteine protease highly expressed in activated osteoclasts and is involved in bone resorption by degrading collagen and aggrecan in cartilage. MIV-711 is a novel potent, selective and reversible inhibitor of cathepsin K. Its inhibitory action on osteoclasts is associated with decreased bone resorption and cartilage loss biomarker expression [83]. Cathepsin K inhibition demonstrated reduced fracture risk in post-menopausal osteoporosis, but with increased cardiovascular risks [84]. A three-arm parallel phase 2a study randomized 244 participants with knee OA to receive oral MIV-711 100 mg, 200 mg or matched placebo once-daily for 26 weeks [35]. MIV-711 did not significantly improve pain (the primary outcome), but femoral OA bone disease progression on MRI was significantly reduced at week 26 in both MIV-711 100 mg and 200 mg dose groups compared with placebo. There was also significantly reduced cartilage thickness loss on the medial femur with MIV-711 100 mg *vs* placebo.

Wnt pathway inhibition

The Wnt signalling pathway is involved in cartilage homeostasis, inflammation and OA pathogenesis through effects on chondrocyte, osteoblast and synovial cell differentiation [85, 86]. Altered signalling has been detected in murine and human OA tissues, along with reduced levels of the Wnt inhibitory protein DKK1 [86]. SM04690 (now lorecivivint) is a Wnt signalling pathway inhibitor of the enzymes

CDC-like kinase 2 (CLK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1A, promoting chondrogenesis, chondrocyte function, and reducing inflammation [87]. IA lorecivivint (0.03 mg; 0.07 mg; 0.23 mg and placebo) was investigated in a phase 2a trial of 455 patients with knee OA [88]. No significant difference in WOMAC pain improvement (its primary end point) was detected at week 13. Exploratory analysis of participants with unilateral knee pain showed greater improvements in medial joint space width, WOMAC pain, and function scores in those receiving 0.07 mg *vs* placebo. These differences appeared greater in this group for those without widespread pain. A subsequent 24-week, phase 2 b study investigated lorecivivint at 4 doses: 0.03, 0.07, 0.15 or 0.23 mg. Preliminary data suggested 0.07 and 0.23 mg were the most effective doses for improving pain NRS and WOMAC pain, physical function and PGA from weeks 12 to 24 [36]. Effect sizes were greater when the population was restricted to those with joint space width 2–4 mm receiving 0.07 mg [89]. This has guided inclusion criteria and dose for the ongoing Lorecivivint phase 3 program [90].

Conclusion

Therapeutic options for OA remain limited and there is no dramatic change in current practice, though HCQ should not be used for OA. Some suggestion of analgesic benefits has been demonstrated, especially with new agents targeting peripheral nerve pathways, and perhaps with some agents that have anti-inflammatory actions. Anti-NGF therapy may become an OA therapeutic option in future for knee and hip OA, but patient selection will likely be restricted, because there are important side effects to be considered. OA structure modification of both cartilage and subchondral bone has been reported, but these trials have not demonstrated concomitant symptom reduction. This raises further questions about whether structure modification trials need to be run for longer durations or are underpowered to detect small symptomatic benefits.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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