Current status and future prospects for disease modification in osteoarthritis

Zhengping Huang¹, Changhai Ding¹,²,³, Tianwang Li¹ and Shirley Pei-Chun Yu⁴

Abstract
OA is a chronic, progressive and disabling joint disease, leading to a poor quality of life and an enormous social and economic burden. Current therapies for OA patients remain limited, which creates an area of huge unmet medical need. For some time, researchers have been looking for approaches that can inhibit the structural progression of OA. A variety of potential disease-modifying OA drugs have been developed, targeting cartilage, inflammatory pathways or subchondral bone. In addition, non-pharmacological therapies, including joint distraction and weight loss, draw increasing attention, with some showing disease-modifying potential. Thus we performed a comprehensive review to discuss the current status of disease-modifying therapies in OA and appraise the potentials of emerging novel agents.

Key words: osteoarthritis, disease-modifying osteoarthritis drugs, cartilage, therapeutic targets, non-pharmacological treatments

Introduction
OA is the most prevalent joint disorder, resulting in degradation of articular cartilage, subchondral bone remodelling and varying degrees of synovial inflammation [1]. It is associated with chronic pain, joint function impairments and disabilities, causing a poorer quality of life and significant socio-economic burden worldwide [2]. Along with the wave of aging and obesity sweeping over the world, there is an urgent need for a large increase in health services to deal with the rising epidemic of OA [3].

However, OA is a condition that is lacking in cost-effective interventions and has no cure [4]. The current treatments mainly focus on symptom relief and improvement of joint disabilities rather than modifying the disease progression. The current dilemma in OA treatment has driven investigations into new approaches to slow or reverse joint structural destruction and thus prevent the occurrence of late-stage OA and reduce the socio-economic burden. Along with an increasing knowledge of pathological processes and the development of imaging techniques and soluble biomarkers, more standardized clinical trials have been conducted and some potential disease-modifying therapies have been discovered [5–7]. Some existing approaches, mainly used for symptom relief, have been further tested for their potential disease-modifying effects. A number of new agents have been developed and several have been tested in clinical trials, providing the promise of controlling the structural progression of OA by targeting cartilage metabolism and catabolism, inflammation and subchondral remodelling (Fig. 1).
In this narrative review we discuss therapies with potential disease-modifying effects on OA, including existing treatments, as well as an update on recent developments of novel agents (Table 1). Clinical trials of both disease-modifying OA drugs (DMOADs) as well as non-pharmacological approaches will be appraised.

**Currently available agents**

**Glucosamine and chondroitin sulphate**

Glucosamine (GS) and chondroitin sulphate (CS) have been shown to be associated with the anabolic/catabolic balance of human articular chondrocytes [8, 9], which indicated potential disease-modifying effects of these agents. Some randomized controlled trials (RCTs) demonstrated that single use of GS or CS might have small to moderate structural protective effects in OA patients when using joint space width (JSW) or cartilage volume loss (CVL) as outcome measures [10-13]. Fransen et al. [14] revealed that the JSW protection effect was achieved only in the combination use of GS and CS rather than single treatment with each of them. However, Sawitzke et al. [15] failed to find any statistically significant difference in mean JSW loss in either the single treatment group with GS or CS or the combination group. Similarly, Martel-Pelletier et al. [16] demonstrated that the combination of GS and CS did not slow the radiological deterioration of JSW in knee OA patients; instead, the combination significantly reduced CVL in some subregions.

**Diacerein**

Diacerein has been shown to regulate cartilage homeostasis and subchondral bone metabolism in OA by reducing the synthesis of resorptive factors (e.g. IL-1β, MMP-13 and TNF-α) as well as inhibiting the osteoclast differentiation process and the survival of mature osteoclasts [17]. Evidence to date demonstrates potential structure-modifying effects of diacerein in hip OA rather than knee OA [18]. In an RCT with hip OA patients, joint space loss was significantly reduced in the diacerein group compared with the placebo group [19]. However, because of its side effects of liver toxicity and diarrhoea, diacerein is not marketed in the USA and has been under restriction in Europe since 2014 [20].

**Hyaluronic acid**

HA is responsible for several structural properties of tissues as a component of the extracellular matrix (ECM), and intra-articular injection of HA has symptomatic effects and may modify structure [21]. In an RCT, less progression of joint space narrowing (JSN) was seen in knee OA patients receiving HA with radiologically milder disease at baseline than those with radiologically more severe disease, suggesting that HA may modify joint structure at an earlier stage.
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<td>Kahan et al. [10]</td>
<td>Knee OA (n = 622)</td>
<td>CS 800 mg QD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 12, 18 and 24 months</td>
<td>A significant reduction (P &lt; 0.0001) in minimum JSW loss was seen in the CS group compared with the placebo group. The CS group had less significant radiographic progression (&gt;0.25 mm compared with the placebo group: 28 vs 41% (P &lt; 0.0005)).</td>
<td>CS showed protective structural effects using JSW as the outcome measure</td>
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<td>Reginster et al. [11]</td>
<td>Knee OA (n = 212)</td>
<td>GS 1500 mg QD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 12 and 36 months</td>
<td>The placebo group had a progressive JSN, with a mean joint space loss after 3 years of -0.31 mm. No significant joint space loss in the GS group: -0.06 mm (-0.22-0.09). Similar results with minimum joint-space narrowing progression.</td>
<td>GS showed structural protective effects using JSW as outcome measure</td>
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<td>Pavelka et al. [12]</td>
<td>Knee OA (n = 202)</td>
<td>GS 1500 mg QD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 12, 24 and 36 months</td>
<td>Progressive JSN with placebo use was -0.19 mm after 3 years. No average change with GS use (0.04 mm; -0.06-0.14 mm), with a significant difference between groups (P = 0.001). Fewer patients treated with GS experienced predefined severe narrowings (&gt;0.5 mm): 5 vs 14% (P = 0.05).</td>
<td>GS showed protective structural effects using JSW as the outcome measure</td>
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<td>Wildi et al. [13]</td>
<td>Knee OA (n = 69)</td>
<td>CS 800 mg QD PO, placebo</td>
<td>Cartilage volume and BMLs were assessed by MRI at baseline and 6 and 12 months</td>
<td>The CS group showed significantly less CVL than the placebo group after 6 months. Significantly lower BML scores found for the CS group at 12 months.</td>
<td>CS showed protective structural effects using CVL as the outcome measure</td>
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<td>Fransen et al. [14]</td>
<td>Knee OA (n = 605)</td>
<td>GS 1500 mg QD; CS 800 mg QD, alone or in combination; placebo</td>
<td>JSW measured with radiographs at baseline and 12 and 24 months</td>
<td>The combination use of GS and CS resulted in a statistically significant (P = 0.046) reduction of 2 year JSN compared with placebo: mean difference 0.10 mm (95% CI 0.002, 0.20), while the single treatment allocations did not.</td>
<td>The combination use of GS and CS showed protective structural effects using JSW as the outcome measure</td>
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<td>GS 500 mg 3 TDS; CS 400 mg TDS, alone or in combination; celecoxib 200 mg QD; placebo</td>
<td>JSW measured with radiograph at baseline and 24 months</td>
<td>The mean JSW loss in the placebo group was 0.166 mm. No significant difference in mean JSW loss in any treatment group compared with the placebo group. Treatment effects on Kellgren-Lawrence grade 2 knees showed a trend toward improvement relative to the placebo group.</td>
<td>GS and CS, alone or in combination, did not slow the radiological deterioration of JSW</td>
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<td>Pham et al. [25]</td>
<td>Knee OA (n = 301)</td>
<td>Hyaluronic acid (NRD101) IA × 3; diacerein 50 mg BD PO; placebo</td>
<td>JSW measured with radiograph at baseline and 12 months</td>
<td>JSW deteriorated, but with no difference between the groups (P = 0.82). Percentages of progressors were 17.7, 18.9 and 20.3% (P = 0.90) in the NRD101, diacerein and placebo groups, respectively.</td>
<td>Neither HA nor diacerein showed structural protective effects using JSW as the outcome measure</td>
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<td>Dougados et al. [19]</td>
<td>Hip OA (n = 507)</td>
<td>Diacerein 50 mg BD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 36 months</td>
<td>Two hundred and thirty-eight patients discontinued the study due to adverse events in the diacerein group (25 vs 12%) and inefficacy in the placebo group (14 vs 7% with diacerein). The rate of JSN was significantly lower with diacerein (0.18 vs 0.23 mm/year with placebo; P = 0.042).</td>
<td>Diacerein showed structural protective effects using JSW as the outcome measure</td>
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HA showed structural protective effects using JSW as outcome measure in patients with JSW $\geq 4.6$ mm at baseline

PG-116800 did not slow the radiological deterioration of JSW

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<td>Jubb et al. [22]</td>
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<td>Sodium hyaluronate, IA 20 mg/2 ml once/week for 3 weeks, placebo</td>
<td>JSW measured with radiographs at baseline and 52 weeks</td>
<td>JSN in the radiologically milder disease group was significantly reduced compared with the placebo group (0.13 vs 0.55 mm; $P = 0.02$), but there was no difference between the radiologically more severe disease group and the placebo group. The 200 mg dose study was discontinued based on an increased frequency of musculoskeletal toxicity. No significant difference in mean JSW in any treatment group compared with the placebo group.</td>
<td>Doxycycline slowed the rate of JSN in the index knee but not in the contralateral knee</td>
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<td>Krzeski et al. [28]</td>
<td>Knee OA</td>
<td>PG-116800 (25, 50, 100 or 200 mg) QD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 12 weeks</td>
<td>Doxycycline reduced the mean rate of JSN at 16 months by 40% (0.15 vs 0.24 mm) and 30 months by 33% (0.30 vs 0.45 mm) compared with the placebo group in the index knee but not in the contralateral knee.</td>
<td>Sprifermin showed structural protective effects using JSW and cartilage thickness as the outcome measure</td>
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<td>Brandt et al. [29]</td>
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<td>JSW measured with radiograph at baseline and 16 and 30 months</td>
<td>Sprifermin caused no significant changes in cartilage parameters (BMLs, synovitis, effusion and JSW) as measured by MRI or X-ray.</td>
<td>Sprifermin did not slow the radiological deterioration of JSW, probably due to short observational periods</td>
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<td>Lohmander et al. [46]</td>
<td>Knee OA</td>
<td>Sprifermin IA 10, 30 and 100 µg once/week for 3 weeks, placebo</td>
<td>Cartilage changes assessed with qMRI and JSW measured with radiograph at baseline and 6 and 12 months</td>
<td>100 mg sprifermin significantly reduced JSW narrowing (0.34 vs -0.18 mm; $P = 0.0118$) in the lateral femorotibial compartment. Sprifermin significantly reduced total and lateral femorotibial cartilage thickness and volume.</td>
<td>Sprifermin showed structural protective effects using cartilage thickness and volume as the outcome measure</td>
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<td>Dahlberg et al. [47]</td>
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<td>Cartilage changes assessed with qMRI and JSW measured with radiographs at baseline and 24 weeks</td>
<td>Sprifermin caused no significant changes in cartilage parameters (BMLs, synovitis, effusion and JSW) as measured by MRI or X-ray.</td>
<td>Sprifermin did not slow the radiological deterioration of JSW, probably due to short observational periods</td>
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<td>Roemer et al. [48]</td>
<td>Knee OA</td>
<td>Sprifermin IA 10, 30 and 100 µg once, placebo</td>
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<td>Less worsening of cartilage damage was observed from baseline to 12 months in the PFJ [0.02 (95% CI -0.04, 0.08) vs placebo [0.22 (95% CI -0.05, 0.49); $P = 0.046$].</td>
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<td>Jo et al. [51]</td>
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<td>Autologous adipose tissue-derived MSCs IA: phase 1: $1.0 \times 10^5$, $5.0 \times 10^5$, $1.0 \times 10^6$ once; phase 2: $1.0 \times 10^5$ once; placebo</td>
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<td>$1.0 \times 10^6$ autologous adipose MSCs significantly reduced cartilage defects in the medial femoral and tibial condyles as well as in the lateral femoral and tibial condyles and increased cartilage volume in the medial femoral and tibial condyles</td>
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<td>Vega et al. [52]</td>
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<td>Manicourt et al. [59]</td>
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<td>Manicourt et al. [59]</td>
<td>Knee OA</td>
<td>Balicatib 25 and 50 mg</td>
<td>Cartilage volume assessed with MRI at baseline and 6 months</td>
<td>Balicatib caused no significant changes in cartilage volume at 6 months</td>
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<td>Raynauld et al. [69]</td>
<td>Knee OA</td>
<td>Licofelone 200 mg BD</td>
<td>Cartilage volume assessed with qMRI and JSW measured with radiographs at baseline and 12 and 24 months</td>
<td>No significant difference in mean JSW between the licofelone group and the placebo group. CVL in the global joint and medial and lateral compartments was significantly less in the licofelone group than in the placebo group.</td>
<td>Licofelone showed structural protective effects using CVL as the outcome measure</td>
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<td>Raynauld et al. [69]</td>
<td>Knee OA</td>
<td>Celecoxib 200 mg QD</td>
<td>Cartilage volume assessed with qMRI at baseline and 12 months</td>
<td>The 95% CI for the mean observed joint medial compartment CVL [6.81% (95% CI 6.01, 7.60)] and mean predicted loss (MCO) [5.65% (95% CI 5.10, 6.19)] were overlapping. The 95% CI for the mean observed joint lateral compartment CVL [5.67% (95% CI 4.94, 6.40)] and mean predicted loss (MCO) [5.11% (95% CI 4.38, 5.83)] were also overlapping.</td>
<td>Celecoxib had no significant effect on the medial and lateral CVL</td>
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<td>Verbruggen et al. [83]</td>
<td>Hand OA</td>
<td>Adalimumab IH 40 mg</td>
<td>Structural damage measured with radiographs at baseline and 26 and 52 weeks</td>
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<td>Adalimumab halted the progression of joint damage in IP joints with palpable soft tissue swelling</td>
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<td>Fioravanti et al. [84]</td>
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<td>Infliximab reduced anatomical lesion progression in both the DIP and PIP joints, but these were not statistically significant</td>
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<td>Cindunistat did not slow the radiological deterioration of JSW</td>
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<td>Register et al. [91]</td>
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<td>Strontium ranelate 1 g QD PO or 2 g QD PO, placebo</td>
<td>JSW measured with radiographs at 12, 24 and 36 months</td>
<td>Treatment with strontium ranelate was associated with smaller degradations in JSW than placebo (1 g/day: −0.23 mm; 2 g/day: −0.27 mm; placebo: −0.37 mm), P = 0.001 for 1 g/day and P = 0.018 for 2 g/day</td>
<td>Strontium ranelate showed structural protective effects using JSW as the outcome measure</td>
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<td>Pelletier et al. [92]</td>
<td>Knee OA</td>
<td>Strontium ranelate 2 g/day</td>
<td>Knee cartilage volume and BMLs measured with MRIs at baseline and 12, 24 and 36 months</td>
<td>Strontium ranelate 2 g/day significantly decreased CVL on the plateaus at 12 (P = 0.002) and 36 (P = 0.003) months compared with placebo</td>
<td>Strontium ranelate showed structural protective effects using CVL as the outcome measure</td>
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<td>Laslett et al. [94]</td>
<td>Knee OA</td>
<td>Zoledronic acid i.v. guttae 5 mg once, placebo</td>
<td>BMLs measured with MRI at baseline and 6 and 12 months</td>
<td>Zoledronic acid significantly reduced the BML area at 6 months (−175.7 mm², P = 0.02) and 12 months (−146.5 mm², P = 0.07)</td>
<td>Zoledronic acid reduces knee area BML size</td>
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<td>Spector et al. [95]</td>
<td>Knee OA</td>
<td>Risedronate 5 mg QD PO or 15 mg QD PO, placebo</td>
<td>JSW measured with radiographs at baseline and 12 months</td>
<td>JSW loss from baseline values was significant only in the placebo group (−0.12 mm, P &lt; 0.05), not in the 5 mg (−0.08 mm) or 15 mg risedronate group (−0.06 mm)</td>
<td>Risedronate had a beneficial effect on the preservation of bone and cartilage using JSW as the outcome measure</td>
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<td>Risedronate did not significantly reduce radiographic progression as measured by decreased JSW or using a dichotomous definition of progression (joint space loss ≥ 0.6 mm)</td>
<td>Risedronate did not slow the radiological deterioration of JSW</td>
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<td>Karsdal et al. (NCT00486434) [101]</td>
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<td>Salmon calcitonin 0.8 mg BD PO, placebo</td>
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<td>No significant difference in mean JSW loss in any treatment group compared with the placebo group</td>
<td>Salmon calcitonin did not slow the radiological deterioration of JSW</td>
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<tr>
<td>Karsdal et al. (NCT00704847) [101]</td>
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BID: twice a day; BML: bone marrow lesions; CVL: cartilage volume loss; DMOADs: disease-modifying OA drugs; GS: Glucosamine; IA: intra-articular injection; IH: hypodermic injection; JSN: joint space narrowing; JSW: joint space width; MSC: Mesenchymal stem cells; OD: once a day; PO: by mouth; qMRI: quantitative MRI; TDS: three times a day.
early stage in the disease process [22]. However, a number of studies failed to find a significant structure-modifying effect of HA compared with placebo [23–25].

It should be recognized that the evidence of a structure-modifying effect with these agents is insufficient and weak, thus more high-quality studies are needed to explore their roles as potential DMOADs in OA.

**Therapies for regulating cartilage catabolism and anabolism**

**Cartilage protease inhibitors**

As the main components of articular cartilage, cartilage-specific type II collagen and aggrecan are essential in maintaining the normal structure and function of joints. The proteolysis of collagen and aggrecan correlates with the progression of OA. MMPs and aggrecanase, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), are demonstrated to have emerging roles in the degradation of ECM type II collagen and aggrecan and are thus potential targets for development of OA therapies [26].

MMPs belong to the protease superfamily of metzincins. In an interventional trial with knee OA patients, BAY 12-9566, a broad-spectrum MMP inhibitor, significantly increased the content of 846 epitopes and total type II collagen, indicating an increase in matrix synthesis of knee cartilage [27]. However, another broad-spectrum MMP inhibitor, PG116800, showed no disease-modifying effect with regards to the mean change in minimum JSW of the knee at 1 year in an RCT. The study was discontinued based on an increased frequency of musculoskeletal toxicity [28]. To avoid the musculoskeletal side effects and to increase the efficacy, recent investigational studies have assessed selective MMP inhibitors, including doxycycline, a tetracycline antibiotic. An RCT showed that doxycycline reduced the mean rate of JSN at 16 months by 40% and at 30 months by 33% among obese women with knee OA [29]. However, a Cochrane systematic review argued that doxycycline should not be applied to the treatment of knee or hip OA, due to minimal to non-existent symptomatic benefit and questionable structural benefit, as well as higher rates of adverse reactions [30]. MMP-13 is only expressed in the cartilage of OA patients, not in normal adult cartilage [31], thus selective MMP-13 inhibitors may offer new hope for the treatment of OA. Several MMP-13 inhibitors (e.g. ALS 1-0635, PF152) have shown benefits in slowing disease progression in preclinical studies; however, new selective MMP-13 inhibitors are still under development and the clinical trials remain limited [32–34]. Further exploration of the specific enzymes related to musculoskeletal toxicity will generate highly selective MMP inhibitors with fewer side effects [35].

ADAMTS-4 (aggrecanase-1) and ADAMTS-5 (aggrecanase-2) are two key aggrecanases from the ADAMTS family that are involved in cartilage degradation. Both play roles in the cleaving of the Glu373–Ala374 bond in the interglobular domain of aggrecan in humans. ADAMTS-4 has also been demonstrated to cleave other CS proteoglycans and cartilage oligomeric matrix protein (COMP), as well as fibromodulin and decorin [36, 37]. Therefore, agents aimed at preventing aggrecan proteolysis by inhibiting aggrecanase activity may slow the progressive cartilage erosion and thereby act as potential DMOADs in the treatment of OA. Several small molecular aggrecanase inhibitors have been developed and were proven to be chondroprotective in models of OA [38, 39]. AGG-523 [40], a selective oral inhibitor of ADAMTS-4 and ADAMTS-5, was the only aggrecanase inhibitor entering into phase 1 studies in humans (NCT00454298, NCT00427687), but the trials were suspended for unknown reasons. CRB0017, a chimeric murine/human IgG4 mAb against ADAMTS-5, is under preclinical development and has been proven to have beneficial structural effects in animal models of OA [41, 42]. These results pave the way for future clinical trials in OA patients.

**Growth factors**

Several growth factors, including fibroblast growth factor 18 (FGF-18) and bone morphogenetic protein-7 (BMP-7), have been demonstrated to stimulate cartilage anabolism and promote cartilage repair in *in vitro* and animal models [43–45]. They pave the way for clinical investigations to further explore the potential of growth factors in cartilage regeneration in human OA.

Sprifermin, a synthetic form of human FGF-18, has exhibited potential disease-modifying effects in OA. In an RCT, intra-articular sprifermin was proven to have no statistically significant effect on the structural primary endpoint of quantitatively MRI-defined central medial tibiofemoral compartment cartilage thickness. However, it was associated with statistically significant dose-dependent reductions in JSW narrowing and loss of total and lateral tibiofemoral cartilage thickness. In addition, sprifermin was proven to be safe, with serious adverse events similar to those in the placebo group [46]. Dahlberg et al. [47] conducted a study of intra-articular sprifermin in patients with advanced knee OA. They showed that with increasing doses of up to 300 μg of sprifermin, no significant changes in cartilage parameters [bone marrow lesions (BMLs), synovitis, effusion and JSW] as measured by MRI or X-ray were reported. The lack of effect may be due to the short observation period and the small sample size. Overall, no local or systemic safety concerns were raised. A recent published study revealed that sprifermin slowed down cartilage damage from baseline to 12 months in the patellofemoral compartments and improved BMLs from 6 to 12 months for whole-knee analyses in knee OA patients, suggesting a structure protective effect of sprifermin [48].

A member of the TGF-β family, BMP-7 (also known as osteogenic protein-1), is an anabolic growth factor, has the clinical potential to repair cartilage by regulating the proliferation and differentiation of chondrocytes as well as synthesis of ECM [49]. Preclinical data have shown effects of intra-articular recombinant human BMP-7 on both joint pain alleviation and cartilage repair. A phase 1 study (NCT01111045) of intra-articular recombinant BMP-7
Mesenchymal stem cells (MSCs)

With the potential of multidirectional differentiation, MSCs provide a promising therapeutic alternative for OA. Intra-articular injection of MSCs for the treatment of OA has suggested positive results with respect to symptom improvement and drug tolerance [51–53]. Meanwhile, MSCs have shown potential effects on cartilage repair and regeneration. In a 1 year RCT, knee OA patients who received intra-articular injections of allogeneic bone marrow MSCs had a decrease in their poor-quality cartilage areas as well as an improvement in cartilage quality in these areas measured by MRI T2 mapping [52]. A proof-of-concept clinical trial demonstrated that intra-articular injection of autologous adipose MSCs reduced cartilage defects in the medial femoral and tibial condyles as well as in the lateral femoral and tibial condyles and increased cartilage volume in the medial femoral and tibial condyles at 6 months [51]. However, current evidence is insufficient and there are no good data in relation to their true effects. Hence, further studies are needed to support their use as DMOADs, especially given the heterogeneity of trials to date with non-standardized ex vivo preparations of MSCs, cell doses and number of injections given.

Platelet-rich plasma

Platelet-rich plasma (PRP) contains several growth factors, including TGF-β and PDGF, VEGF, hepatocyte growth factor and FGF, which stimulate MSC proliferation and synthesis of ECM and collagen. PRP plays a potential role in OA repair partially due to the effects of these growth factors [54]. Several RCTs have shown that intra-articular injections of PRP result in no serious adverse effects and play a role in pain reduction in OA patients. But given the low to moderate methodological quality and discrepancies between studies, no definitive conclusions can be given regarding the effects of PRP in OA [55]. Presently there are still no RCTs investigating the structural effects of PRP in OA.

Cathepsin K inhibitor

Cathepsin K (CatK), a cysteine protease secreted by osteoclasts, is involved in cartilage and bone degradation [56]. Its inhibition has shown a structural protective effect in animal models [57, 58]. However, balicatib, a CatK inhibitor, has failed to decrease CVL in knee OA patients [59]. Morphea-like skin reactions have been reported in patients treated with balicatib, which were likely dose-related adverse effects and may represent a class effect of CatK inhibitors [60]. MIV-711, a highly selective CatK inhibitor, was measured in an RCT in healthy subjects [61]. It decreased biomarkers of bone resorption and cartilage degradation, including serum carboxy-terminal collagen cross links (CTX-I) levels and urinary levels of CTX-II, CTX-I and amino-terminal collagen cross links (NTX-I, promoting further clinical trials in OA. In addition, it was proved to be safe and well tolerated. A phase 2 study (NCT03037489) of MIV-711 is in progress. By the time this article is published in early 2018, the data from the phase 2a trial may be available.

Wnt signalling pathway inhibitors

The Wnt signalling pathway is associated with joint development and the formation of bone, cartilage and synovium and has drawn increasing attention in OA research. Recent evidence from animal experiments and clinical samples showed that aberrations in Wnt signalling might be involved in OA [62, 63]. Inhibitors targeting the Wnt signalling pathway provide a new potential therapeutic strategy for OA [64]. Chen et al. [65] reported that inhibition of the histone methyltransferase enhancer of zeste homologue 2 delayed OA development through the Wnt/β-catenin pathway in mice. However, it is still a challenge to find inhibitors targeting the Wnt signalling pathway to treat human OA, thus further research is needed to fully examine the effects of Wnt signalling on OA.

Therapies for controlling inflammation

Licofelone

Licofelone is a novel analgesic and anti-inflammatory agent for OA, by inhibiting both cyclooxygenase (COX) and 5-lipoxygenase [66]. It has been shown that licofelone reduces structural changes in OA by its inhibition of leucotriene-B4 and IL-1β synthesis in the synovium [67]. Licofelone also decreased both mRNA expression and protein synthesis of proteolytic enzymes involved in the degradation of cartilage, including MMP-13, CatK, ADAMTS-4 and ADAMTS-5 [68]. In a phase 3 trial, licofelone markedly reduced knee cartilage volume loss assessed by MRI over 12 and 24 months, indicating a protective effect on patients with knee OA [69]. However, more studies need to be conducted before it can be used as a disease-modifying drug in OA.

Celecoxib

Celecoxib is a type of selective COX-2 inhibitor that has been widely used in OA for inflammation and pain relief. Evidence supports that celecoxib has potential disease-modifying properties in OA by regulating a series of inflammatory mediators, including prostaglandin E2 and inducible nitric oxide synthase (iNOS) [70]. Celecoxib prevented glycosaminoglycan release and induced proteoglycan synthesis in healthy human articular cartilage explants under the influence of blood mononuclear cells from RA patients or IL-1β and TNF-α [71]. An observational study showed a chondroprotective effect in patients with end-stage knee OA [72]. However, in an open-label pilot study, celecoxib did not provide any protective effect on CVL in knee OA patients after 12 months [73]. In general, clinical studies of celecoxib in slowing OA disease progression are scarce; more studies, particularly
high-quality RCTs with large numbers of patients and long durations, are needed.

**Inhibitors of pro-inflammatory cytokines**

IL-1β and TNF-α are two major pro-inflammatory cytokines involved in the pathogenesis of OA [74, 75]. Inhibition of these has led to chondroprotective effects both *in vitro* and in animal studies [76–78]. Hence it is a potential way to control structural progression of OA by regulating IL-1β and TNF-α.

Various treatment strategies could be used for specific inhibition of IL-1β production or activity, such as the application of IL-1 receptor antagonist (IL-1Ra), soluble IL-1R and mAb against IL-1β or against IL-1R1 [79]. A pilot study examined the safety and symptom relief effect of intra-articular injections of anakinra (a recombinant human IL-1Ra) in knee OA patients [80], with pain improved by −20.4 mm (P = 0.008) and WOMAC global score by −19.5 (P = 0.005) after 3 months in those who received 150 mg IL-1Ra. In contrast, another RCT demonstrated that anakinra was not associated with improvements in OA symptoms compared with placebo [81]. Similarly, AMG 108, a fully human mAb against IL-1R1, also had no significant effect on pain reduction compared with placebo in an RCT with knee OA patients [82]. However, the effect on joint structure was not assessed in these studies. In addition, phase 2 clinical trials of the other two IL-1β agents, gevokizumab (NCT01683396) and ABT 981 (NCT02087904), have been completed with no published results.

Evidence indicated a possible effect of TNF-α inhibitors in slowing the progression in hand OA. An RCT demonstrated that adalimumab significantly slowed erosive evolution compared with the placebo group in IP joints with palpable soft tissue swelling, suggesting that adalimumab halted the progression of joint damage in this subgroup [83]. In another study, infliximab was shown to reduce the anatomical lesion radiological score, thus signifying a possible disease-modifying effect on erosive hand OA [84]. However, current evidence is limited and controversial, as it did not achieve structural modification in recent trials [85, 86].

**Inhibitors of iNOS**

iNOS, which is highly expressed in OA cartilage, can lead to cartilage matrix and synovial tissue damage in OA by producing NO and its by-products [54]. Preclinical studies have shown that inhibition of iNOS has the potential to attenuate the disease progression of OA [87]. However, a phase 2/3 study (NCT00565821) of a selective oral iNOS inhibitor, cindunistat (SD-6010), did not slow the rate of JSN vs placebo in patients with symptomatic OA over a 2 year period [88]. Hence, further work is needed to demonstrate the efficacy of iNOS inhibitor in slowing OA progression.

**GM-CSF antibody**

As an inflammatory mediator, GM-CSF causes the increased production of pro-inflammatory cytokines, chemokines and proteases and thereby ultimately leads to articular cartilage destruction. Cook et al. [89] revealed that GM-CSF was essential for the development of experimental OA and its associated pain. Conversely, GM-CSF neutralization by a mAb could completely abolish existing arthritic pain and significantly reduce cartilage damage. Thus it is worthwhile to explore the clinical effect of GM-CSF antibody in OA. Currently a phase 2 clinical study (NCT02683785) is under way to investigate the effectiveness and safety of GSK3196165 (a fully human Human Combinatorial Antibody Library antibody directed against GM-CSF) in patients with inflammatory hand OA.

**Therapies for remodelling subchondral bone**

**Strontium ranelate**

Strontium ranelate is able to dissociate the bone remodelling process and change the balance between bone resorption and formation [90]. An RCT with knee OA demonstrated that besides the beneficial effect on symptoms, treatment with strontium ranelate was associated with smaller degradations in JSW than placebo and less radiological progression was observed over 3 years [91]. In a phase 3 clinical trial in knee OA, treatment with strontium ranelate was found to have beneficial effects on structural changes by significantly reducing CVL in the plateau and BML progression in the medial compartment [92]. However, because of its potential cardiovascular risk, its use in OA needs to be further explored.

**Bisphosphonates**

There has been interest in the possible beneficial effects of bisphosphonates, the most widely used therapeutic agents in osteoporosis, on OA. Preclinical studies have provided evidence for bisphosphonates as a disease-modifying agent in OA [93]. The efficacy of bisphosphonates in human OA was assessed in clinical trials with mixed results. An RCT revealed that a single infusion of i.v. zoledronic acid (5 mg) was effective in reducing knee pain and BML size after 6 months, and with a trend after 12 months, indicating that zoledronic acid may slow the progression of knee OA [94]. Similar effects were achieved with another bisphosphonate in a British phase 2 study demonstrating that risedronate resulted in improvement of symptoms and joint structure in patients with primary knee OA. An observational cohort study investigated the effect of bisphosphonate use on symptomatic and radiographic knee OA in participants from the National Institutes of Health Osteoarthritis Initiative cohort. By year 4, even though the JSW decreased linearly over time in both groups, there was a difference in JSW of 0.35 mm between the bisphosphonate users and non-users. There was a beneficial trend on structural progression, with less JSN in the bisphosphonate users (0.51 vs 0.29 mm; P = 0.06), but it did not reach statistical difference [95]. In the Knee OA Structural Arthritis study, no symptom improvement or slowing of radiographic progression was observed in each treatment dose group.
Non-pharmacological treatments

Joint distraction

Joint distraction is a joint-preserving surgery in which the two bony ends of a joint are slightly separated. An external fixation frame is generally implemented in the procedure to maintain and regulate this distance, thus alleviating the loading stress and enlarging the space of the joint [101]. It was first used in 1979, when patients with various hip diseases received joint distraction. Satisfactory results were achieved in > 70% of patients < 45 years of age, including the potential effect of cartilage repair [102]. Subsequently, joint distraction was aimed at patients with ankle OA. In a 2 year follow-up trial of 17 patients with severe ankle OA, in most cases the JSW significantly increased and remained widened for 2 years as measured by mortise view radiographs. This lead to the conclusion that such structural changes were possibly due to cartilage repair after joint distraction [103]. In a proof-of-concept study, radiographic evaluation showed an increase in JSW and a decrease in subchondral sclerosis among 12 of 17 patients with severe ankle OA after an average 2.8 years of follow-up, suggesting the presence of structural changes [104]. The structural changes could also be seen in knees after joint distraction. Intema et al. [105] reported an increase in the mean and minimum JSN and cartilage thickness and a decrease in denuded bone areas at 1 year follow-up of 20 patients with knee OA. In addition, the collagen type II synthesis/breakdown ratio was increased. Similar findings were seen in another study of knee OA [106]. The potential mechanism to explain the disease-modifying effect of distraction is that the joint distraction attenuates secondary inflammation, cartilage degeneration and subchondral bone remodelling due to the absence of mechanical loading as well as improvement of joint fluid flow and an intermittent increase in intra-articular hydrostatic pressure [107].

Despite of the encouraging results, most of the studies were relatively short term with small sample sizes and a high failure rate occurred in a considerable number of patients during follow-up [108]. Moreover, the potential complications of joint distraction should be a concern, especially the common pin tract infection [107, 109]. Thus further high-quality studies are needed to confirm its long-term efficacy and safety.

Weight loss

An increasing number of studies support the potential feasibility of weight loss (WL) for disease modification in OA. A prospective, before-after trial with 64 subjects who were morbidly obese showed that surgically induced WL effectively reversed the radiological signs of early changes in knee OA, with a greater increase in mean JSW [110]. Serebrakian et al. [111] reported that a reduction of > 10% of body weight was associated with significantly smaller increases in cartilage T2 in the medial femoral condyle and overall medial compartment in a 48 month study, suggesting WL might attenuate cartilage matrix degeneration. A 12 month observational prospective cohort study showed that WL in obese people had structure-modifying effects on medial articular cartilage by increasing proteoglycan content and reducing cartilage thickness loss [112]. It was demonstrated that WL is associated with reduced medial tibial CVL and cartilage thickness loss, indicating a potential role of disease modification in knee joint structure [113, 114]. WL was also proven to increase procollagen type II N-terminal propeptide and adiponectin, and decrease leptin and cartilage oligomeric matrix protein (COMP) plasma concentrations, which suggested a structure-modifying effect on cartilage [115]. Conversely, some RCTs failed to demonstrate a disease-modifying effect of WL in OA. In an RCT [116] with 252 knee OA patients, a 5% WL over 18 months showed no effect on structural progression as assessed by medial and lateral JSW. Similarly, another RCT that enrolled 454 overweight and obese older adults with knee pain and radiographic evidence of tibiofemoral OA showed no influence of WL on the rate of structural progression either on X-ray or MRI over 18 months [117].

The role of WL in the structural progression of OA remains controversial and studies have failed to reach agreement due to contrary conclusions. Further investigations are needed to verify these conclusions, taking into account both the effectiveness and tolerance of WL based on the individual’s condition [118].

Physical activity

A number of studies have shown the potential effect of physical activity (PA) in the biochemical composition of cartilage both in people at high risk of developing OA and patients with OA. A 4 month RCT demonstrated that moderate exercise improved joint symptoms and function as well as the glycosaminoglycan content of knee cartilage in patients at high risk of developing OA [119]. Likewise, it has been shown in 87 post-menopausal women with knee OA that a 12 month leisure-time PA
program had a positive effect on the glycosaminoglycan content of tibiofemoral cartilage measured by delayed gadolinium-enhanced MRI [120]. In addition, Racunica et al. [121] reported vigorous PA was associated with an increase in tibial cartilage volume and a reduction in the risk of BMLs, indicating a protective effect of PA on knee cartilage. Crescuillo et al. [122] conducted a 12 month follow-up study of 486 females with symptomatic OA. The study showed that light to moderate PA at a frequency of 1–4 days per week appeared to lead to a slight reversal in the progression of OA or a possible slowing of OA. An RCT with 221 older knee OA patients showed that lower-extremity strength training induced less frequent progressive JSW over 30 months, indicating a disease-modifying effect of PA in knee OA [123]. In addition, an RCT demonstrated that serum COMP significantly decreased after strengthening exercises, also suggesting a potential beneficial role of PA in cartilage structure [124].

However, extreme or improper PA poses a risk of joint injuries. High-impact PA with too much loading on joint cartilage may increase the incidence of OA [125]. Interestingly, there are recent claims that the current available evidence is insufficient to conclude that high-intensity exercise induces greater adverse effects [126]. Thus this highlights the need for more studies to determine the effects of PA in OA, with a focus on the duration, intensity and frequency of PA.

Biomechanical intervention

Knee braces can potentially slow structural disease progression in OA. In an RCT including 126 subjects 40–70 years of age with knee OA, the group allocated to patellofemoral bracing had an overall BML volume 18% less than the group without the brace (P = 0.03) [127]. A meta-analysis of 17 studies (218 participants) found that valgus knee bracing significantly reduced the knee adduction moment, a biomechanical measure that has been related to structural disease progression [128]. Flat flexible shoes have also been reported to result in significantly lower parameters of knee adduction movements [129, 130].

Nevertheless, evidence remains scarce and robust clinical trials are required to evaluate whether these interventions slow structural disease progression in OA.

Conclusion

The rationale for the development of DMOADs is strong. With current management predominantly focusing on symptom control, there is an unmet need for agents that will prevent or control the progression of OA. Some clinical trials suggest that the therapeutic value of current agents may extend beyond symptom relief to act as potential DMOADs. A number of target-specific agents are being tested, some of which have shown beneficial effects of structural modification in clinical trials. In addition, non-pharmacological treatments have attracted greater attention recently and favourable results of disease modifications have been reported. However, most trials have failed to obtain the desired results, probably due to inappropriate clinical design, insensitive outcome measures or uncontrollable side effects. All in all, OA is a complex, heterogeneous, whole-joint disease with multiple aetiologies and different phenotypes, which makes it a challenging task to develop ideal approaches. Thus more high-quality clinical trials are necessary to properly assess the effectiveness of these interventions in delaying the structural progression of OA and to provide adequate support for their application in practice.

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