THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Review

Latest insights in disease-modifying osteoarthritis drugs development

Shengfa Li*, Peihua Cao*, Tianyu Chen and Changhai Ding

Ther Adv Musculoskelet Dis

2023, Vol. 15: 1–24

DOI: 10.1177/1759720X231169839

***Abstract*:** Osteoarthritis (OA) is a prevalent and severely debilitating disease with an unmet medical need. In order to alleviate OA symptoms or prevent structural progression of OA, new drugs, particularly disease-modifying osteoarthritis drugs (DMOADs), are required. Several drugs have been reported to attenuate cartilage loss or reduce subchondral bone lesions in OA and thus potentially be DMOADs. Most biologics (including interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibitors), sprifermin, and bisphosphonates failed to yield satisfactory results when treating OA. OA clinical heterogeneity is one of the primary reasons for the failure of these clinical trials, which can require different therapeutic approaches based on different phenotypes. This review describes the latest insights into the development of DMOADs. We summarize in this review the efficacy and safety profiles of various DMOADs targeting cartilage, synovitis, and subchondral bone endotypes in phase 2 and 3 clinical trials. To conclude, we summarize the reasons for clinical trial failures in OA and suggest possible solutions.

Keywords: clinic trial, DMOADS, new trends, novel therapeutics, therapy selection

Received: 29 June 2022; revised manuscript accepted: 29 March 2023.

Correspondence to:
Changhai Ding
Clinical Research Center, Zhujiang Hospital, Southern Medical University, 261 Industry Road, Guangzhou 510515, China.

Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

Clinical Research Center, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
changhai.ding@utas.edu.au

Shengfa Li
Peihua Cao
Clinical Research Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China

Tianyu Chen
Clinical Research Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China

Department of Orthopedics, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China

*These authors contributed equally to this work.

Introduction

Osteoarthritis (OA) is the most common articular disease, characterized by chronic joint pain and disabling symptoms.[1,2] As the population ages and risk factors increase, the prevalence of OA is expected to increase globally.[3,4] Approximately 303.1 million cases of OA are estimated to exist worldwide, according to the Global Burden of Disease (GBD) project.[5] OA has been classified as a severe disease with unmet medical needs due to the lack of specific therapies.[6,7] In addition to its impact on individuals and the economy, OA represents a significant public health challenge in the years to come.[8]

Despite the high socioeconomic costs of OA, most patients fail to receive appropriate treatment.[9] Multiple pathogeneses have been implicated in OA development, including mechanical, genetic, metabolic, and inflammatory pathways.[10] Due to an improved understanding of OA pathophysiology, several potential therapeutic targets have been identified that may reduce the pain and slow the progression of OA.[11] OA is a whole joint disease that leads to structural changes in the periarticular muscles, capsule, synovium, subchondral bone, hyaline articular cartilage, and ligaments.[12] Recent research on the pathogenesis of OA suggests that the disease may even be viewed as a syndrome rather than a single entity.[1,13] Various mechanistic phenotypes are probably involved in OA development, including mechanical overload,[14] inflammatory component,[15] cell senescence,[16] and metabolic alterations[17] that may overlap and warrant further investigation.

Current conservative treatment of OA entails pharmacological and nonpharmacological approaches; when these options fail to relieve symptoms, surgical treatment is considered.[18] Available OA pharmacological therapy is merely symptom-relieving drugs, including paracetamol,[19] opioid analgesics,[20] non-steroidal anti-inflammatory drugs (NSAIDs)[21] and intra-articular (IA) medications such as hyaluronic acids[22] and steroids.[23] However, these managements cannot modify the OA progression and prevent long-term disability.[24–26] In the recent guidelines, non-pharmacological approaches such as weight loss if overweight or obese and

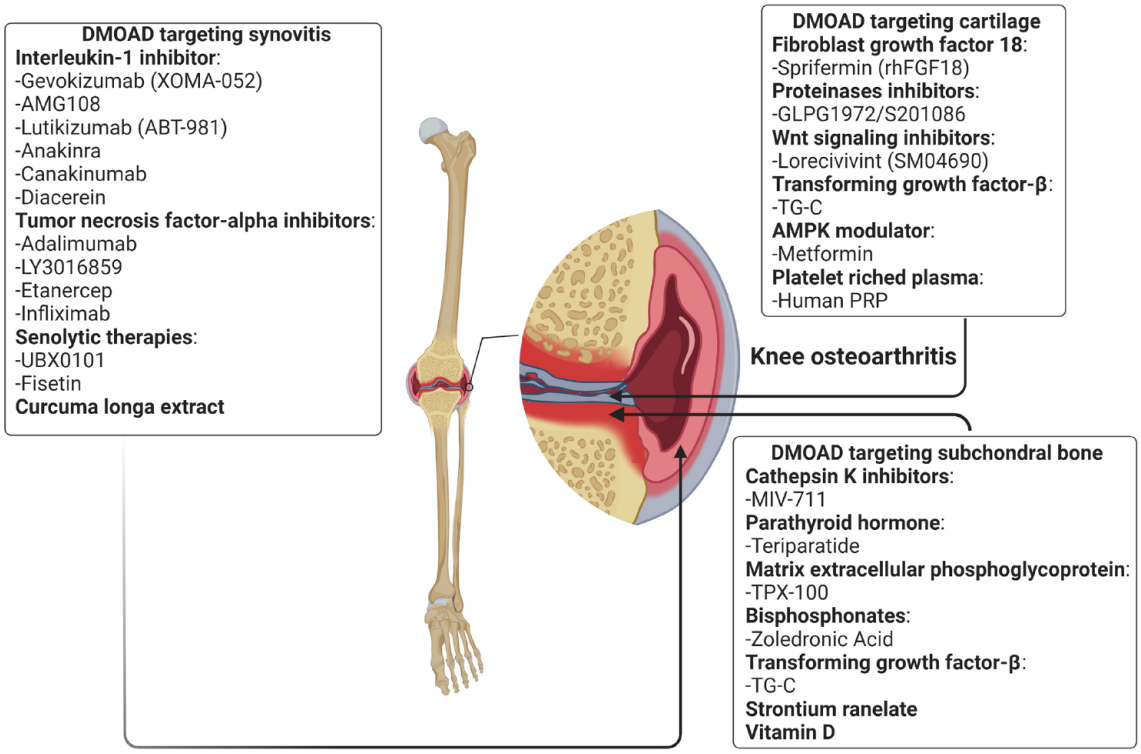

Figure 1. Potential pharmacological therapies for OA.

self-management, exercise, education and walking aids are widely recommended and regarded as first-line management.[27–29] As a last resort, surgical decisions are typically indicated only for patients with end-stage OA.[1,21]

OA is characterized by the progressive loss of structural, mechanical, and biochemical properties and joint functions. This includes subchondral bone remodeling, cartilage damage, osteophyte development, and synovial inflammation.[30] Thus, the disease can be considered a chronic joint failure that affects the whole joint and has an unmet need for disease-modifying drugs,[31] highlighting the need for new and effective treatments.[7] Pharmaceutical agents, which are expected to modify the underlying OA pathophysiology by arresting joint structural change and alleviating symptoms by reducing pain or improving physical function, are termed disease-modifying osteoarthritis drugs (DMOADs).[2,32] At present, there are no identifiable DMOADs.[33] However, some latest developments have been made for potential disease-modifying OA therapies, such as highly selective inhibitors alleviating progressive cartilage breakdown, which are emerging pharmaceutical therapies for OA.[2,6,34]

This review describes the recent development of DMOADs therapies for OA (Figure 1) and related clinical trials. It will focus on attractive drugs with potential applications in preclinical research over the last 5 years and on promising drugs in ongoing OA clinical trials. As part of our search for ongoing phase 2 or 3 clinical trials on the https://clinicaltrials.gov/, we also conducted electronic and manual database searches in PubMed and Embase via Ovid for published reports of phase 2/3 clinical trials between the inception of these databases and March 31, 2022 using the following MESH or keywords: osteoarthritis AND pharmacological treatment/ OR disease modification/ OR disease-modifying osteoarthritis drugs/ OR DMOAD/ OR structure modification.

DMOADs targeting cartilage

Articular cartilage loss is a central feature of OA, which involves various catabolic and reparative mechanisms at the molecular level.[35] Although only a minor contributor associated with pain symptoms, cartilage defect strongly predicts the risk of future joint replacement in knee OA.[36,37] Therefore, development of DMOADs targeting

cartilage is the most important direction for the treatment of OA. In the future DMOADs' trial design, OA patients with cartilage phenotype (e.g. joint space narrowing of grade 1–3, without osteophytes, bone marrow lesions (BMLs), and synovitis) should be selected as the participants. Second, as change in joint space width (JSW) or joint space narrowing is insensitive to change over a short time (<2 years), cartilage loss measured using magnetic resonance imaging (MRI) is recommended as the primary outcome in cartilage DMOADs trials. Last, novel technologies such as radiomics and proteomics could be used to find sensitive and specific cartilage biomarkers to classify cartilage phenotype and to measure cartilage degradation in the future. The pharmaceutical drugs in phase 2/3 stages of development for DMOADs targeting cartilage are summarized in Table 1.

Fibroblast growth factor 18

As a family of polypeptides, mammalian fibroblast growth factors (FGFs) consist of 18 proteins with size ranges from 15 to 38 kDa.[38,39] Signaling pathways of the FGF family play crucial roles in cartilage development and homeostasis.[40] Several *in vitro* and *in vivo* studies have examined the protective effect of FGF18 on OA development and progression that is mediated by FGF receptor-3 (FGFR-3).[41–43] FGF18 improves the ability of human pluripotent stem cell-derived cartilage to integrate with naturally occurring cartilage.[44]

Sprifermin is a truncated product of recombinant human FGF 18 (rhFGF18).[45,46] In a dose-ascending phase 1 study (NCT00911469), sprifermin showed no measurable systemic effects or safety concerns in patients ($n = 55$) with advanced OA at 24 weeks follow-up.[47] Furthermore, in a later study (NCT01033994) of sprifermin (via IA injection) in knee OA patients ($n = 192$) with Kellgren–Lawrence (KL) grade 2 or 3, the results did not meet the primary efficacy endpoint of improving medial tibiofemoral cartilage thickness evaluated by quantitative MRI (qMRI) at 12 months. However, sprifermin was associated with a dose-dependent reduction in loss of cartilage thickness and volume in the lateral femorotibial compartment, as well as reducing narrowing of the JSW.[48] A 5-year, multicenter randomized clinical trial (NCT01919164) named FORWARD (FGF-18 Osteoarthritis Randomized Trial with Administration of Repeated Doses) was conducted to evaluate the effects of IA sprifermin on changes of total femorotibial joint (TFTJ) cartilage thickness in symptomatic knee OA patients ($n = 549$, KL grade 2 or 3).[46] FORWARD was finished in 2019 with the primary endpoint using MRI cartilage thickness and secondary endpoints using minimum JSW and change from Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), including total WOMAC, WOMAC knee pain, WOMAC knee function, and WOMAC knee stiffness scores. Sixty-nine percent of patients ($n = 378$) completed the 5-year follow-up. A 2-year primary analysis with IA sprifermin revealed a dose-dependent promoting effect of cartilage thickness in the TFTJ, medial and lateral subregion of TFTJ, and JSW.[46] In a *post hoc* analysis, long-term structural modification of articular cartilage was maintained with sprifermin *versus* placebo over a 3.5-year to 4-year post-treatment period. A patient sub-group (161 out of a total of 549, 29%) at risk of disease progression received similar structural improvements over this time. In addition, potential translation to clinical benefits such as reducing OA symptoms was also observed in the subgroup at risk.[49]

Proteinases inhibitors

Proteinases are enzymes with essential roles in pathological and physiological processes such as the destruction, digestion, homeostasis, and repair of tissues.[50] Furthermore, microenvironment proteinase-mediated signaling has a crucial effect on arthritis.[51]

Disruption of signaling pathways, explicitly activating pro-inflammatory pathways, increases the activity of matrix-degrading enzymes and contributes to cartilage degeneration.[12] At the early stage of OA, collagens and aggrecan are critical structural components of the cartilage extracellular matrix (ECM), and their degradation is a significant event.[52] Matrix metalloproteinases (MMPs, specifically MMP-13) as well as a disintegrins and metalloproteinases with thrombospondin motifs (ADAMTS) facilitate the degradation of type II collagen and aggrecan, respectively, contribute significantly to the imbalance between matrix synthesis and degradation in OA patients' joints.[53,54] A reasonable strategy to limit cartilage damage is to inhibit the activity of matrix-degrading enzymes such as collagenases and aggrecanases.

1. The potential benefits of collagenases such as MMP (especially MMP-13) inhibitors in

Table 1. Registered phase 2/3 clinical trials of potential DMOADs targeting cartilage.

Type of drug	Drug name	ClinicalTrials.gov identifier	Company/ institution	Structure	Targeted tissue	Mechanism of Action	Stage of development	Route
Fibroblast growth factor 18	Sprifermin (rhFGF18)	NCT01919164	Merck KGaA (Germany)	Recombinant human fibroblast growth factor 18 (rhFGF18)	Cartilage regeneration and repair	Stimulating chondrogenesis and cartilage matrix production through fibroblast growth factor receptor-2 and 3	Phase 2 (knee OA)	IA
Proteinases inhibitors	GLPG1972/ S201086	NCT03595618	Galapagos and Servier		Cartilage	Inhibiting the action of aggrecanases, matrix-degrading proteinases	Phase 2 (knee OA)	Oral
Wnt signaling inhibitors	Lorecivivint (SM04690)	NCT02536833, NCT03122860, NCT03706521, NCT03727022, NCT03928184, NCT04385303, NCT04520607	Samumed LLC (USA)	*N*-(5-(3-(7-(3-Fluorophenyl)-3 H-imidazo(4,5-C) pyridin-2-yl)-1 H-indazol-5-yl)-pyridin-3-yl)-3-methylbutanamide	Cartilage catabolism	Induction of protease production, especially matrix metalloproteinases	Phase 2 (knee OA), Phase 2 (knee OA), Phase 2 (knee OA), Phase 2 (knee OA), Phase 3 (knee OA), Phase 2 (knee OA), Phase 2 (knee OA).	IA
Transforming growth factor-β	TG-C	NCT03291470, NCT03203330, NCT01221441	TissueGen, Inc (Duncansville, PN, USA)	Allogeneic human chondrocytes modified to express TGF-β1	Cartilage regeneration	Stimulating the regeneration of damaged cartilage or regrowing lost cartilage	Phase 3 (knee OA), Phase 3 (knee OA), Phase 3 (knee OA)	IA
		NCT02072070	Kolon Life Science (South Korea)	Allogeneic human chondrocytes modified to express TGF-β1	Cartilage regeneration	Stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage	Phase 3 (knee OA)	IA
AMPK modulator	Metformin	NCT04767841	Sadat City University	1,1-Dimethylbiguanide	Cartilage regeneration	activate AMPK	Phase 2	Oral
Human platelet-rich plasma	hPRP	NCT03491761	NorthShore University HealthSystem (Evanston, IL, USA)	Human PRP from patient whole blood samples	Cartilage regeneration and repair	Directing the local mesenchymal cells to migrate, divide, and increase collagen and matrix synthesis	Phase 2 (knee OA)	IA

AMPK, AMP-activated protein kinase; IA, intra-articular; OA, osteoarthritis; hPRP, human platelet-rich plasma; TG-C, Tissue Gene-C.

preserving the OA joint have been investigated.[55] However, the available data on the role of MMP-13 inhibitors in OA treatment are limited. As a broad-spectrum MMP inhibitor, PG-116800 (NCT00041756) showed reversible musculoskeletal toxicities in a dose-dependent manner without clinical benefits in mild to moderate knee OA patients ($n = 401$).[56] It is unclear how the adverse effects occur. The broad-spectrum MMP inhibitors may interfere with other matrix proteins in tissues besides cartilage, according to one hypothesis.[57] However, in a multicenter, randomized, double-blind, placebo-controlled trial, researchers reported proteoglycan aggrecan turnover (846 epitopes) increased in the cartilage of osteoarthritic patients ($n = 35$) after 3 weeks of oral administration of a broad-spectrum MMP inhibitor BAY 12-9566 with a daily dose of 100 mg.[58] In preclinical trials, highly selective MMP-13 inhibitors such as PF152[59] and ALS1-0635[60] have shown advantages in reducing collagen degradation in animal OA models, and further human clinical trials are needed.

2. Since a charge-based repulsion mechanism can clear aggrecan, aggrecanase inhibition such as ADAMTSs (ADAMTS-4 and ADAMTS-5) may be a safer medication than collagenases. Aggrecan can be cleared by a diffusion driven by charge repulsion, consisting of only highly negatively charged molecules without proteolysis, and prevents cartilage from accumulating newly formed aggrecan.[61] Targeting ADAMTSs may be a safer measure than targeting collagenases. GLPG1972/S201086 is a highly selective inhibitor of ADAMTS- 5 that has been demonstrated to have a protective effect on the cartilage in animal OA models.[62,63] GLPG1972/S201086 has been investigated in a worldwide, 52-week, and phase 2 clinical study in patients with knee OA (NCT03595618). This trial was completed in 2020, but the results have not yet been published. As a reversible, non-hydroxamate, zinc-binding selective inhibitor of ADAMTS-4 and ADAMTS-5, AGG-523 can attenuate elevated aggrecanase activity in a rat joint injury model.[64] It previously entered the clinical phase I study (NCT00427687 and NCT00454298), but these trials were discontinued for unknown reasons.

As an ADAMTS-5 monoclonal antibody, CRB0017 administered twice in 3 months could delay cartilage breakdown along with ameliorating disease progression in a spontaneous murine model of OA.[65] In addition, a humanized ADAMTS-5-selective monoclonal antibody, GSK2394002, was reported to have structural modification and analgesic effects in animal OA models.[66,67] Moreover, M6495, a novel anti-ADAMTS-5 inhibiting nanobody with a single domain antibody fragment containing the properties of heavy chain–only antibodies, showed a protective effect on cartilage degradation and inhibited aggrecan turnover *ex vivo* in a dose-dependent manner.[68,69] Preliminary results of a phase I study (NCT03583346) were completed in 2019 to assess tolerability, safety, pharmacokinetics, immunogenicity, and pharmacodynamics of single ascending doses injections of M6495 in knee OA patients, but final data have not yet been reported.

Wnt signaling inhibitors

Wnt signaling is regulated by *Wnt* genes and receptor subunits, regulating canonical β-catenin-dependent and non-canonical β-catenin-independent signaling pathways.[70] Canonical β-catenin signaling pathway has been strongly associated with the development and homeostasis of bones and joints.[71] In OA, increased Wnt signaling has been found in bone, cartilage and synovium from patients[72,73] and has been considered to promote MSCs to an osteogenic lineage fate and induce the generation of MMPs can cause cartilage degradation. Wnt signaling pathway activation induced the production of proteases such as MMP and inflammation by synovial tissue and chondrocytes as a response to injury, which is the main triggering factor of OA pathogenesis.[74,75]

Lorecivivint (LOR; SM04690) is a Wnt signaling pathway inhibitor at the transcriptional level.[76,77] Through inhibition of the intranuclear kinases CLK2 and DYRK1A,[77] locrecivivint seemed to incite chondrogenesis and inhibit joint destruction in a model of OA in rats.[76] A 24-week phase 1 study (NCT02095548) was completed in 2015 to evaluate IA LOR's safety, tolerability, pharmacokinetics, and pharmacodynamics in knee OA patients ($n = 61$). Despite no evidence of systemic exposure, LOR proved safe and well-tolerated.[78] Furthermore, exploratory efficacy analyses showed that total WOMAC score, WOMAC

function, WOMAC pain, Physician Global Assessment (PGA), pain, OMERACT-OARSI response, and VAS (Visual analogue scale) score were improved from baseline with JSW improvement in IA LOR cohort.[78] Moreover, a phase 2a randomized trial (NCT02536833) was completed in 2017. In this trial, patients with symptomatic knee OA ($n = 455$, KL grade 2 or 3) did not meet its primary endpoint which was the change in knee pain from baseline.[79] There was a phase 2b, 24-week, randomized trial of IA LOR (NCT03122860) to evaluate the safety and efficacy for the treatment of knee OA ($n = 695$).[80] This trial was completed in 2021, and results showed that pain NRS (Numeric rating scale), WOMAC pain, and function subscores were significantly improved by IA LOR, especially at 0.07 mg dose.[80] Nevertheless, although WOMAC pain score, and WOMAC function score were considerably improved in the IA LOR group, no overall effect on JSW was observed.[79,81] A phase 3, 56-week clinical study ($n = 510$, NCT03928184) was completed in 2021 to evaluate the safety and efficacy of a single injection of LOR (0.07 mg dose) with moderately to severely symptomatic knee OA. This trial evaluated clinical and radiographic outcomes; the complete data have not been reported.

Transforming growth factor-β

Transforming growth factor-β (TGF-β) stimulates differentiation, growth, and synthesis of ECM proteins in cells.[81,82] The TGF-β signaling in aging and OA chondrocytes is dysregulated, increasing procatabolic activin receptor-like kinase 1 (ALK1)–SMAD1–SMAD5–SMAD8 signaling, while with a decrease in proanabolic ALK5–SMAD2–SMAD3 signaling.[83,84] In addition, TGF-β is likely to contribute to osteophyte formation and synovial fibrosis in OA joints.[83] TGF-β1 is essential to the development and maturation of cartilage and the maintenance of chondrocyte phenotypes.[82,85] However, the effect of TGF-β is contradictory on different joint tissue. So, conditional knockout (CKO) or transgenic animal model was used to try to achieve cartilage-specific interventions. In transgenic mice models of TGF-β mutation, it has been demonstrated that whole-body overexpression of TGF-β1 leads to changes in the knee joint of mice, including hyperplasia and formation of osteophytes.[86,87] Furthermore, in a CKO mice model, knee joints showed OA-like pathologies with TGF-β receptor deletion in chondrocyte.[87]

As a cell-mediated gene therapy to specifically intervene in cartilage repair, Tissue Gene-C (TG-C) is a cell and gene product that delivers allogeneic human chondrocytes GP2-293 cells and non-irradiated allogeneic human chondrocytes in a 1:3 ratio, retrovirally transduced to promote TGF-β1 transcription.[88,89] A preclinical study demonstrated IA injection of TG-C was safe and able to induce cartilage repair.[89] Initial phase 1 trial was performed to evaluate TG-C's safety and biological activity in advanced knee OA patients ($n = 12$).[88] The results have shown no significant safety issues related to TG-C administration, and knee scoring analyses indicated a possibility that TG-C might contribute to improving OA symptoms.[88] A significant improvement in knee pain, function, and physical ability was found following treatment of IA TG-C in late-stage knee OA patients ($n = 27$).[90] Results from a phase II randomized controlled trial (NCT01221441) indicated IA treatment with TG-C over 12 months in moderate to advanced knee OA patients ($n = 57$) showed minor progression of cartilage damage compared with placebo on a whole knee as well as the fewer progression of infrapatellar fat pad synovitis and effusion-synovitis.[91–93] A double-blind phase 3 clinical trial (NCT02072070) reported symptomatic improvement with a trend of structural benefits and statistically significant improvements in knee joint function and pain in OA patients ($n = 163$, KL grade 3).[94] A phase 3 trial (NCT03203330) was recently registered to determine the effectiveness and efficacy of TG-C in knee OA patients with KL grade 2 or 3 but is currently on hold. Another similar phase 3 trial (NCT03291470) was in unknown recruitment status.

Metformin

Metformin is the first-line medication to treat type 2 diabetes mellitus (T2DM).[95] Some studies have indicated that metformin is generally well tolerated and beneficial for several age-related diseases, including OA.[96] In addition, metformin has been shown to activate AMP-activated protein kinase (AMPK) and had a chondroprotective effect on decelerating OA development and progression in mice OA models.[97,98] A matched-cohort study evaluated patients with OA and T2DM ($n = 968$) during 10 years of follow-up in Taiwan, and results indicated that patients with OA and T2DM receiving combination COX-2 inhibitors and metformin therapy had lower joint replacement surgery rates

[adjusted hazard ratio (HR) = 0.742, 95% confidence interval (CI) = [0.601–0.915], $p = 0.005$] than patients without combined treatment.[99] Furthermore, this may be attributable to more decreased pro-inflammatory factors associated with combination therapy than patients without metformin therapy.[99] According to a recent study, obese individuals with knee OA were assessed for their risk of total knee replacement over 4 years and metformin use, and the results suggest that those with obesity and knee OA may benefit from using metformin.[96,100] In order to determine whether metformin could be used as a potential DMOADs for obese knee OA patients, randomized controlled trials are needed. Currently, at least two clinical trials (NCT04767841 and NCT05034029) are ongoing to explore the effect of metformin on OA patients.[101]

Human platelet-rich plasma

Human platelet-rich plasma (hPRP) injections are used increasingly to manage OA.[102,103] hPRP is made by centrifugation of autologous blood so that growth factors and cytokines are released from the α-granules found in the platelets.[104,105] With the activation of these growth factors, hPRP potentially results in anti-inflammatory, analgesic, and anabolic effects to alter OA pathogenesis and symptoms.[106] Although hPRP is increasingly used to treat OA, evidence to support the clinical benefits of hPRP is limited. Previous articles reported some benefits for hPRP IA injections on pain and function outcomes compared with saline or hyaluronic acid in knee OA.[103,107,108] They suggested that the benefit was most significant in patients with mild to moderate radiographic disease.[109] Recently, two clinical trials have been finished to demonstrate the efficacy of hPRP on the knee (Australian New Zealand Clinical Trials Registry Identifier: ACTRN12617000853347, named the RESTORE study)[110] and ankle (Netherlands Trial Register: NTR7261)[111] OA.

The RESTORE was a randomized clinical trial conducted in two groups across multiple sites.[112] Volunteers in the community ($n = 288$) had an average of moderate to severe knee pain in most days of the past month and mild to moderate radiographic OA in the tibiofemoral joint. Commercially available hPRP was injected thrice through IA ($n = 144$ participants) at weekly intervals or saline placebo ($n = 144$ participants). MRI measurements of medial tibial cartilage volume and average knee pain scores were assessed after a 12-month follow-up. There was no difference in knee pain scores between hPRP injections and placebo injections after 12 months ($p = 0.17$), while the medial tibial cartilage volume changed by 1.4 *versus* 1.2%, respectively ($p = 0.81$). Based on this study, the authors found that hPRP injections did not significantly differ from saline placebo injections in symptoms or joint structure at 12 months in patients with mild to moderate radiographic knee OA.[110]

Another clinical trial (NTR7261), which included 100 patients with moderate to severe pain and narrowing of the tibiotalar joint space, was conducted at six sites in the Netherlands. The primary outcome was the American Orthopaedic Foot and Ankle Society score (AOFAS) over 26 weeks. The results indicated that, compared with baseline values, the mean AOFAS improved by 10 points in the PRP group (95% CI = [6–14]; $p < 0.001$) and 11 points in the placebo group (95% CI = [7–15]; $p < 0.001$). The adjusted between-group difference over 26 weeks was −1 (95% CI = [–6 to 3]; $p = 0.56$). This study concluded that over a 26-week treatment, IA hPRP injections did not significantly improve ankle symptoms or function in patients with ankle OA.[111]

DMOADs targeting inflammatory signaling

Due to the increasing local production of chemokines, pro-inflammatory cytokines, and mediators of joint tissue damage, synovitis is an essential contributing factor to OA pathogenesis. It may be treated with anti-inflammatory drugs commonly used for inflammatory rheumatic diseases.[113,114] Table 2 summarizes the pharmaceutical drugs in phase 2/3/4 development for DMOADs targeting inflammatory factors.

Interleukin-1 inhibitors

In preclinical studies, interleukin-1 (IL-1) exhibits pro-inflammatory actions, leading to joint inflammation, pain and the initiation and progression of cartilage damage.[115,116] In addition, IL-1β is one of the catabolic cytokines and a major inflammatory in OA pathophysiology.[117] IL-1β can decrease the synthesis of crucial extracellular cartilage matrix components like type Ⅱ collagen and aggrecan.[118,119] However, the quality of evidence for its involvement in OA disease is modest.

Table 2. Registered phase 2/3/4 clinical trials of potential DMOADs targeting inflammatory signaling.

Type of drug	Drug name	ClinicalTrials.gov identifier	Company	Structure	Targeted tissue	Mechanism of action	Stage of development	Route
Interleukin-1 inhibitors	Gevokizumab (XOMA-052)	NCT01683396, NCT01882491.	XOMA (USA)	Immunoglobulin G2, anti-(human interleukin 1beta) (human-Mus musculus XOMA 052 heavy chain), disulfide with human-Mus musculus XOMA 052 kappa-chain, dimer	Synovitis	Neutralizing IL-1β	Phase 2 (hand OA), Phase 2 (hand OA).	SI
	AMG108	NCT00110942	Amgen (USA)	A full human, immunoglobulin subclass G2 monoclonal antibody to IL-1R1	Synovitis	Inhibiting IL-1	Phase 2 (knee OA)	SI
	Lutikizumab (ABT-981)	NCT02087904, NCT02384538.	AbbVie (USA)	A dual variable domain immunoglobulin (DVD-Ig) of the IgG1/k	Synovitis	Neutralizing IL-1α and IL-1β	Phase 2 (knee OA), Phase 2 (hand OA).	SI
	Anakinra	NCT00110916	Amgen Inc	7-[[2-(2-amino-1,3-thiazol-4-yl)2-(2,2-dimethylpropanoyloxy methoxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid	Synovitis	IL-1R antagonist	Phase 2 (knee OA)	IA
	Canakinumab	NCT01160822	Novartis (Switzerland)	Immunoglobulin G1, anti-(human interleukin-1beta (IL-12)) human monoclonal ACZ885; (1Glu > Glp)-gamma heavy chain (221–214′)-disulfide with kappa light chain, dimer (227–227″:230–230″) bisdisulfide	Synovitis	Neutralizing IL-1β	Phase 2 (knee OA)	IA
	Diacerein	NCT02688400	TRB Chemedica International SA (Switzerland)	2-Anthracenecarboxylic acid, 4.5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo(9CI)	Synovitis	Inhibiting the production and activity of IL-1	Phase 3 (knee OA)	Oral
Tumor necrosis factor-alpha inhibitors	Adalimumab	NCT00296894	University Hospital, Ghent	Immunoglobulin G1, anti-(human tumor necrosis factor) (human monoclonal D2E7 heavy chain), disulfide with human monoclonal D2E7 light chain, dimer	Synovitis	Binds specifically to TNF-α and blocks its interaction with endogenous TNF	Phase 2 (hand OA)	SI
		ACTRN12612000791831	Abbott Australasia Pty Ltd and University of Tasmania	Immunoglobulin G1, anti-(human tumor necrosis factor) (human monoclonal D2E7 heavy chain), disulfide with human monoclonal D2E7 light chain, dimer	Synovitis	Binds specifically to TNF-α and blocks its interaction with endogenous TNF	Phase 3 (hand OA)	SI

(Continued)

Table 2. (Continued)

Type of drug	Drug name	ClinicalTrials.gov identifier	Company	Structure	Targeted tissue	Mechanism of action	Stage of development	Route
	LY3016859	NCT04456686	Eli Lilly and Company	High-affinity humanized IgG4 monoclonal antibody	Synovitis	Antibody that binds to key residues in the C-terminal regions of TGF-α and epiregulin, preventing their binding to the EGFR	Phase 2 (knee OA)	IV
	Etanercept	NTR1192					Phase 2 (hand OA)	SI
	Infliximab	NCT01144143	Herbert Lindsley, MD and Centocor, Inc.				Phase 4 (knee OA)	IA
Senolytic therapies	UBX0101	NCT04129944	Unity Biotechnology, Inc.	Small molecule inhibitor of the MDM2/p53 protein interaction	Synovitis and cartilage regeneration	Cartilage regeneration and anti-inflammatory action	Phase 2 (knee OA)	IA
	Fisetin	NCT04210986, NCT04815902	Steadman Philippon Research Institute	3,3′,4′, 7-tetrahydroxyflavone	Synovitis and cartilage regeneration	Potential senolytic and anti-inflammatory action	Phase 2 (knee OA), Phase 2 (knee OA).	Oral
Curcuma longa extract	curcuma longa complexed with phosphatidilcholine	NCT02409381	Ache Laboratorios Farmaceuticos S.A.		Synovitis and cartilage regeneration	Potential senolytic and anti-inflammatory action	Phase 4 (knee OA)	Oral
	Turmeric extract	NCT04500210	University of Copenhagen		Synovitis and cartilage regeneration	Potential senolytic and anti-inflammatory action	Phase 3 (knee and hip OA)	Oral
	Curcuma domestica extracts	NCT00792818	Mahidol University		Synovitis and cartilage regeneration	Potential senolytic and anti-inflammatory action	Phase 3 (knee OA)	Oral
	Turmeric extract	NCT00992004	University of Liege–Bone and Cartilage Research Unit		Synovitis and cartilage regeneration	Potential senolytic and anti-inflammatory action	Phase 2 (knee OA)	Oral

EGFR, epidermal growth factor receptor; IA, intra-articular; OA, osteoarthritis; TNF, tumor necrosis factor; TRB, Théa-R&D-Biotechnology.

There is no evidence that IL-1 inhibitors are effective at OA disease-modifying in most clinical trials. These DMOADs trials included subcutaneous injection of gevokizumab (XOMA-052; NCT02293564), subcutaneous injection of AMG108 (NCT00110942),[120] subcutaneous injection of lutikizumab (ABT-981; NCT02087904 and NCT02384538)[121,122] and IA injection of anakinra (NCT00110916).[123,124] However, *post hoc* analyses from the CANTOS trial (NCT01327846)[125] showed that as a monoclonal antibody targeting IL-1β, subcutaneous injection of canakinumab over 3 years in stable post-myocardial infarction patients with increased C-reactive protein levels led to a reduced rate of total knee or hip replacement which suggests that long-term IL-1β inhibition could be protective for the joints.[126] In addition, diacerein as a purified anthraquinone derivative has an inhibitory action on IL-1 and metalloproteases production.[127] Compared with a placebo, a Cochrane review indicated a minimal symptomatic benefit in hip OA with diacerein treatment. In addition, the hip and knee OA structural improvements were minimal or unclear.[128] As reported in 2016, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis found that diacerein showed comparable efficacy to NSAIDs but with slower onset of action and more efficacy than paracetamol.[129]

Tumor necrosis factor-alpha inhibitors

OA synovial fluid contains a variety of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α). It is reported that TNF-α as a pro-inflammatory cytokine produced by synoviocytes and chondrocytes can trigger cartilage catabolism,[130] and biologics inhibiting this cytokine have been proposed as potential DMOADs.[119]

Some clinical trials have been finished to demonstrate the efficacy of subcutaneous injection of TNF-α inhibitors such as adalimumab (NCT00597623)[131–133] and etanercept[134] on OA progression. These trials have also failed to meet their primary and secondary endpoints, suggesting a more complicated interaction among various cytokines than a cytokine in the OA pathogenic process. In a post hoc analysis of data from a clinical trial evaluating the effects of different types of TNF inhibitors on rheumatoid arthritis patients, it was shown that infliximab significantly reduced the risk of progression of OA in distal interphalangeal joints in patients who already had it.[135] Therefore, inhibitors of TNF-α may be considered DMOAD candidates, but more research is needed.

Senolytic therapies

With age being one of the most substantial risk factors for OA, senescent cells (SnCs) are thought to play an essential role in OA-related joint damage.[136,137] Senescence-associated secretory phenotype (SASP) is a robust pro-inflammatory secretome associated with cellular senescence that can alter the structure and function of surrounding cells and tissues.[138] OA is also characterized by inflammation and tissue degradation, mediated by SASP-associated factors.[139] Thus, senolytic therapies provide a potential opportunity to ameliorate OA progression and pathogenesis.[140]

UBX0101 is a novel senolytic agent targeting the Bcl-2 family of antiapoptotic factors.[16,141] UBX0101 has been shown to reduce cartilage damage and joint pain in the anterior cruciate ligament transection model of OA, as well as to induce chondrogenesis in human cartilage explants with OA.[142] To evaluate IA injection of UBX0101's efficacy, tolerability, and safety in knee OA patients, several clinic trials (NCT04229225, NCT04129944, and NCT03513016) were conducted in 2020, but they have not yet been published. In addition, a polyphenol and flavonoid, fisetin, has been shown to relieve joint damage in the mice OA model as a senolytic and anti-inflammatory agent.[143,144] A phase 2 clinical trial (NCT04815902, NCT04770064, and NCT04210986) has been performed to evaluate the effect of oral fisetin on OA pain, bone marrow stem cells (BMSCs), and cartilage breakdown.

Curcuma *longa extract*

Curcuma longa, a rooted plant in the ginger family, has become the potential choice for alternative medicine in OA treatment due to its antioxidant, anti-inflammatory, and digestive properties.[145,146] Curcumin, the main ingredient of *Curcuma longa*, is an effective pain reliever in post-traumatic OA mouse models, as it is also a natural oxygen scavenger and nitrogen provider.[147–149] In addition, a randomized trial (ACTRN12618000080224) has been completed to evaluate the effectiveness of *Curcuma longa* extract for treating symptoms and effusion

synovitis of knee OA ($n = 70$) in 12 weeks. The results have shown that *Curcuma longa* extract was more effective than placebo for knee pain (95% CI = [17.8– 0.4], $p = 0.039$) but did not affect knee effusion synovitis (95% CI = [0.3–6.8]) or cartilage composition (95% CI = [1.1–0.3]).[150] Furthermore, a clinical trial (CTRI/2015/12/006438) reported that *Curcuma longa* extracts reduced knee OA biomarkers of inflammation and oxidative stress over 4 months.[151] A double-blind, multicenter randomized placebo-controlled three-arm study (NCT02909621) was conducted to compare two doses of bio-optimized *Curcuma longa* extract in managing symptomatic knee OA in 2017, and the results have shown that bio-optimized *Curcuma longa* extract can rapidly and significantly reduce the pain in knee OA.[146] In general, *Curcuma longa* extract treatment can reduce OA pain; however, as a potential therapy for DMOADs, multicenter trials with larger sample sizes are needed to assess the clinical significance of these findings and the effects on joint structures.

DMOADs targeting subchondral bone

It is well established that the subchondral change in OA occurs due to a noncoupled remodeling process characterized by the bone formation and resorption.[152] In early OA, the subchondral bone plate becomes thinner and more porous during the initial cartilage degeneration and self-repair period. The loading of subchondral bone falling below a predetermined level leads to excessive osteoclastogenesis and enhanced bone resorption activity with subchondral trabeculae deterioration, resulting in increased trabecular separation and decreased trabecular thickness.[152,153] Therefore, the promoted of parathyroid hormone (PTH) can promote osteogenesis, it could be a potential treatment to retard subchondral trabeculae deterioration in early OA. The structure and composition of the subchondral bone undergo substantial changes that negatively affect the overlying cartilage.[154] Thus, targeting the signaling pathways that control subchondral bone turnover could be useful for DMOADs research. Table 3 summarizes the pharmaceutical drugs in phase 2, 3, and 4 of development for DMOADs targeting subchondral bone.

Cathepsin K inhibitors

Cathepsin K is a cysteine protease involved in bone resorption and cartilage degradation by breaking essential bone matrix proteins.[155–157] It is mainly unknown if inhibition of cathepsin K plays a significant role in OA, although several studies have shown it has structural protection and analgesic effects in animal models of joint degeneration.[157,158]

The cathepsin K inhibitor MIV-711 substantially reduces type Ⅰ collagen C-telopeptides (CTX-Ⅰ) and type Ⅱ collagen C-telopeptides (CTX-Ⅱ), biomarkers of bone resorption.[157,159] It was found that MIV-711 reduced bone remodeling, as measured by bone area on MRI, and reduced cartilage loss over 26 weeks (EudraCT: 2015-003230-26 and 2016-001096-73) in patients with symptomatic knee OA ($n = 244$; KL grade 2 or 3, pain score 4 to 10 on a numerical rating scale). However, MIV-711 did not improve the primary outcome of NRS pain score as a result of being more effective than placebo.[160]

PTH

Recombinant human PTH, teriparatide, is a 1–34 amino-acid fragment derived from human PTH.[161] It has been widely recognized that intermittent administration of PTH has an 'anabolic window'; within this anabolic window, intermittent PTH exhibits promoting effects on bone formation.[162–164] In OA preclinical studies, PTH could attenuate articular cartilage defect,[164,165] stimulate ECM synthesis, and induce chondrocyte proliferation in injury-induced OA models.[166] In PTH clinical research, a phase 2 study (NCT03072147) is investigating the effectiveness of PTH in knee OA participants.

Matrix extracellular phosphoglycoprotein

As a 23-amino acid peptide derived from matrix extracellular phosphoglycoprotein, TPX-100 is a promotor of osteoblast and chondroblast differentiation.[167] A phase 2 clinical study (NCT01925261) has been completed to evaluate the safety and efficacy of IA injections of TPX-100 in mild to moderate patellofemoral OA patients ($n = 104$) involving both knees. A 12-month study with TPX-100-treated knees revealed significant changes in medial and total tibiofemoral cartilage thickness ($p < 0.01$), indicating TPX-100's potential as a DMOAD.[168]

Bisphosphonates

Bisphosphonates have been proposed as possible DMOADs, but their efficacy is poor.[169] In

Table 3. Registered phase 2/3/4 clinical trials of potential DMOADs targeting subchondral bone.

Type of drug	Drug name	ClinicalTrials.gov identifier	Company	Structure	Targeted tissue	Mechanism of action	Stage of development	Route
Cathepsin K inhibitors	MIV-711	NCT02705625, NCT03037489	Medivir (Sweden)	Potent, selective cathepsin K inhibitor	Cartilage and subchondral bone	Inhibiting the proteolytic enzymes in cartilage and bone	Phase 2 (knee OA), Phase 2 (knee OA)	Oral
Parathyroid hormone	Teriparatide	NCT03072147	University of Rochester	Recombinant 1–34 amino-acid fragment of human parathyroid hormone (PTH)	Subchondral bone	Subchondral bone remodeling	Phase 2 (knee OA)	SI
Matrix extracellular phosphoglycoprotein	TPX-100	NCT01925261, NCT02837900	OrthoTrophix (USA)	A 23-amino acid peptide derived from extracellular matrix phosphoglycoprotein	Subchondral bone	Subchondral bone remodeling	Phase 2 (knee OA), Phase 2 (knee OA).	IA
Bisphosphonates	Zoledronic acid	NCT04303026	Martina Hansen's Hospital		Subchondral bone	Subchondral bone remodeling	Phase 3 (hip OA)	IV
Strontium ranelate	Strontium ranelate	ISRCTN41323372	University of Montreal Hospital Research Centre (CRCHUM)		Subchondral bon	Subchondral bone remodeling.	Phase 3 (knee OA)	Oral
Vitamin D	Vitamin D	NCT04739592	CSPC Ouyi Pharmaceutical Co., Ltd.		Subchondral bone	Inducing proteoglycan synthesis and bone mineralization	Phase 4 (knee OA)	Oral
		NCT01176344	Menzies Institute for Medical Research and Monash University		Subchondral bone	Inducing proteoglycan synthesis and bone mineralization	Phase 3 (knee OA)	Oral

IA, intra-articular; OA, osteoarthritis.

addition, the results are inconsistent across the studies, and the outcomes presented a significant heterogeneity.[170–172] Interestingly, the effects of bisphosphonate therapy might be more pronounced in patients with OA and BMLs on MRI scans, which are associated with pain and disease progression in the knee or hand OA.[173–176] However, a 24-month multicenter, double-blind, placebo-controlled randomized clinical trial (ACTRN12613000039785) has been conducted in Australia to evaluate the effect of intravenous zoledronic acid on tibiofemoral cartilage volume among patients ($n = 233$) with knee OA with BMLs. The results indicated that compared with placebo patients with symptomatic knee OA over 24 months, zoledronic acid infusions administered annually did not significantly reduce cartilage loss. It is concluded that using zoledronic acid for treating knee OA is not supported by these findings.[177] Furthermore, cohort studies have demonstrated that the intake of bisphosphonates in knee OA patients is associated with a reduction in the odds (approaching statistical significance but not achieving it) of bone expansion in the periarticular region, specifically in the medial tibial subregion,[178] and the numeric rating scale pain score decreased significantly[179] (data from OAI). Another OAI report has revealed that bisphosphonates are protective of knee OA progression when the patient has low disease severity and is not overweight, but to a lesser extent when the patient has more advanced disease or more weight-bearing joint pressure.[180] A phase 3 study is underway to examine its effects on hip OA (NCT04303026). Clinical heterogeneity of OA is one of the challenging aspects of developing DMOADs, and OA patients with bone remodeling phenotypes could be used in future bisphosphonate clinical trials.[2]

Strontium ranelate

Strontium ranelate (SrR), approved to treat osteoporosis after menopause, has substantial structural-modifying activity in OA.[181–183] Results indicated that SrR reduced subchondral bone resorption in preclinical studies and stimulated cartilage matrix formation *in vitro* and rat OA model.[184–186] A double-blind, placebo-controlled trial (ISRCTN41323372) has been completed to evaluate the safety and efficacy of oral SrR for treating knee OA.[187] This trial was also called Strontium ranelate Efficacy in Knee OsteoarthritIs triAl (SEKOIA). Results showed that the treatment group ($n = 1124$) with SrR 1 and 2 g/day had a significant effect on structure, such as reduced JSW degradations and a beneficial effect on symptoms for SrR 2 g/day in knee OA patients after a 3-year follow-up.[188] Based on a *post hoc* analysis of the SEKOIA trial, it was determined that patients with OA treated with SrR 2 g/day were significantly less likely to progress BMLs in the medial compartment and cartilage volume loss in the plateau.[188] Generally, SrR may be a potential DMOAD for OA patients, particularly those with bone phenotypes. However, further investigation and clinical trials are needed to evaluate the clinical efficacy and side effects for long-term use of SrR for OA treatment before clinical application.[189]

Vitamin D

Vitamin D potentially slows the progression of OA by directly decreasing bone turnover and cartilage degradation.[190,191] A preclinical study showed that vitamin D increased chondrocyte viability and reduced inflammation by activating the AMPK/mTOR signal pathway.[192] In a prospective cohort study, sunlight exposure and serum levels of 25-hydroxyvitamin D (25 (OH) D) were positively associated with knee cartilage volume. Thus, vitamin D sufficiency may prevent or retard cartilage loss in knee arthritis.[193] It has been reported that a clinical trial involving 146 patients with symptomatic knee OA (NCT00306774) did not result in reduced knee pain or cartilage volume loss in the case group when vitamin D supplementation for 2 years at a dose sufficient to elevate plasma 25 (OH)D levels to higher than 36 ng/ml.[191] Later a multicenter randomized, double-blind, placebo-controlled clinical trial (NCT01176344) in Australia named the 'Vitamin D Effect on Osteoarthritis' (VIDEO) study evaluated the effect of vitamin D supplementation on knee pain and tibial cartilage volume loss among patients ($n = 413$) with symptomatic knee OA and low serum 25-hydroxyvitamin D. Results indicated that vitamin D supplementation did not lead to significant differences in change of tibial cartilage volume or WOMAC knee pain score but improved physical function[194] and reduced joint effusion synovitis[195] over 2 years. In addition, *post hoc* analyses were carried out in the VIDEO study and reported that vitamin D supplementation and maintaining vitamin D sufficiency (25-hydroxyvitamin D > 50 nmol/l) over 24 months might be beneficial for depressive symptoms,[196] foot pain,[197] and tibial cartilage volume loss, effusion-synovitis volume and physical

function[198] in patients with knee OA. Since the outcomes of vitamin D trial for OA is heterogeneous, there is a need for well-designed randomized trials with larger sample sizes to determine their efficacy.

Expert opinion

OA is a chronic, painful, and disabling arthritis involving various tissue pathologies as a whole joint disease.[199] Current pharmacological approaches to treating OA are generally palliative due to the complex mechanisms of disease progression.[1] In the development of OA drugs, there are several challenges, including slow progression, regulatory hurdles, a lack of correlation between structural changes and clinically meaningful endpoints, disease heterogeneity and a wide variety of risk factors, and a lack of agreement between preclinical and human models that limit translation.[200] The complexity of OA has contributed to the poorly effects of conventional medications in relieving pain, improving joint function, and modifying OA structural progression.

In the prior section, we have highlighted several clinical trials in phase 3 or 4. It is also essential to learn lessons from previous failures. There are some critical reasons for DMOADs trial failures, including no progressors in the trial period, side effects, animal to human translation, wrong structural endpoint (e.g. plain X-ray), structure and symptom discordance (bilateral *versus* unilateral disease), and magnitude of the placebo effect.[32]

It is essential that DMOADs demonstrate clinically meaningful improvement in symptoms (pain or function) in addition to structural improvement. Also, there do not seem to be universally accepted criteria for arthroplasty, leading to differences in guiding recommendations between medical facilities even within the same geographic area. Moreover, it is necessary for the study design to address the criteria issue of total joint replacement as an endpoint.[201] Unfortunately, at this point, no agent has met the DMOADs hurdles imposed by regulatory agencies.

Considering the anatomical characteristics of the joint combined with the likelihood of systemic toxicity and off-target effects associated with utilizing the systemic route of administration, many DMOADs within the development pipeline are being developed via the IA route. As well as enhancing local drug bioavailability, IA route can produce local therapeutic effects, which have a higher safety profile than systemic exposure.[202] It is still challenging to evaluate symptom efficacy in the presence of IA administration due to the well-known placebo effect.[203] In order to address the short residence time of drugs within the joint, various delivery routes have been demonstrated to prolong residence time and provide stable drug concentrations within the therapeutic window, reducing side effects and improving patient compliance.[204] It is currently unclear how long a particular drug must reside in the joint before it results in meaningful symptomatic relief or structural modification after IA administration.

Multiple phenotypes have been proposed to reflect the extraordinary heterogeneity in OA. These include structural and metabolic factors as well as inflammatory and metabolic factors or imaging features, including medial *versus* lateral femorotibial OA.[205] Implementing private/public datasets such as OAI and the European APPROACH (Applied Public-Private Research Enabling OsteoArthritis Clinical Headway) has identified clinical phenotypes, endotypes, molecular, and imaging biomarkers. However, the precise interaction between these variables and the mechanisms underlying each remain largely unknown.[206] Unfortunately, few clinical trials have been conducted using these phenotype-guided approaches to stratify patients. Multiple OA phenotyping would be valuable for therapy selection and facilitating the advancement of personalized medicine, which can directly address individual clinical characterization, symptom diversity, severity, and genetic characteristics.[207] Therefore, combinations of pharmaceuticals targeting different hallmarks of the OA pathogenic process should be considered.

The natural history of OA is marked by slow progression and involves multi-tissues. Thus, symptomatic efficacy, a long follow-up period, and advanced imaging assessments must be considered in trials evaluating the DMOADs. In addition, alternate preclinical methods that more closely mimic the human condition to assess efficacy in humans are highly desirable.[200] Furthermore, recognizing that OA is a whole organ disease,[208] validating OA disease-modifying therapy's effectiveness in early-stage disease probably needs other more sensitive outcomes than the current measures.

For future DMOADs trials, here are some new trends in clinical trial design. In the first instance, refocusing on eligibility criteria for any DMOAD trial, which is not solely based on radiographic assessment, might enhance the chances of developing a successful treatment. For OA clinical trials, however, quantitative MR image analysis is an advanced tool that should be used.[209,210] In addition, OA is classified into several clinical phenotypes, laboratory parameters, biochemical markers, and imaging criteria. With precision medicine, it will be more important to identify the right patient for a particular treatment approach. Thus, single-cell sequencing, radiomics, and spatial transcriptomics, among others, can be used to find reliable personal classifications. To avoid affecting human homeostasis, it is critical to perform tissue-specific interventions. Several novel precision intervention technologies can contribute to precision treatment, including cell engineering, tissue engineering, novel materials, and gene editing, for example. Finally, it is necessary to conduct multicenter trials with larger sample sizes in order to assess the clinical significance of the findings and their impact on joint structures.

Summary

As a common and severely debilitating disease, there is an unmet medical need for treating OA, especially for drugs to alleviate or prevent OA symptoms and structural progression. Several pharmaceuticals have been shown to prevent cartilage loss or preserve subchondral bone in OA, such as sprifermin and MIV-711. In addition, it remains unclear how the positive structural-modifying effects observed with several DMOADs can contribute to clinical benefits as well as their long-term efficacy and safety. Proteinase inhibitors, bisphosphonates and biologic drugs (including IL-1β and TNF inhibitors) have failed to provide positive results in OA. The OA clinical heterogeneity is one of the significant challenges for developing DMOADs, as different phenotypes could require specific therapeutics. With advances in biomarker technology, imaging, and effective drug delivery systems, OA treatments are making significant progress, despite challenges in disease-modifying drugs and personalized medicine.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Shengfa Li: Conceptualization; Methodology; Writing – original draft.

Peihua Cao: Conceptualization; Validation; Writing – original draft.

Tianyu Chen: Methodology; Writing – review & editing.

Changhai Ding: Conceptualization; Supervision; Validation; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

None.

ORCID iD

Changhai Ding https://orcid.org/0000-0002-9479-730X

References

1. Hunter DJ and Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019; 393: 1745–1759.
2. Latourte A, Kloppenburg M and Richette P. Emerging pharmaceutical therapies for osteoarthritis. *Nat Rev Rheumatol* 2020; 16: 673–688.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 743–800.
4. Peat G and Thomas MJ. Osteoarthritis year in review 2020: epidemiology & therapy. *Osteoarthritis Cartilage* 2021; 29: 180–189.
5. Safiri S, Kolahi AA, Smith E, *et al.* Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global

Burden of Disease Study 2017. *Ann Rheum Dis* 2020; 79: 819–828.

6. Cai X, Yuan S, Zeng Y, *et al*. New trends in pharmacological treatments for osteoarthritis. *Front Pharmacol* 2021; 12: 645842.
7. Administration UFD. *Osteoarthritis: structural endpoints for the development of drugs, devices, and biological products for treatment guidance for industry*. 2018. https://www.fdanews.com/ext/resources/files/2018/08-22-18-OsteoarthritisDraft.pdf?1534955379
8. Hunter DJ, Schofield D and Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014; 10: 437–441.
9. Hunter DJ and Bowden JL. Therapy: are you managing osteoarthritis appropriately? *Nat Rev Rheumatol* 2017; 13: 703–704.
10. Chen D, Shen J, Zhao W, *et al*. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone Res* 2017; 5: 16044.
11. Roos EM and Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol* 2016; 12: 92–101.
12. Glyn-Jones S, Palmer AJ, Agricola R, *et al*. Osteoarthritis. *Lancet* 2015; 386: 376–387.
13. Berenbaum F, Wallace IJ, Lieberman DE, *et al*. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2018; 14: 674–681.
14. Bierma-Zeinstra SM and van Middelkoop M. Osteoarthritis: in search of phenotypes. *Nat Rev Rheumatol* 2017; 13: 705–706.
15. Robinson WH, Lepus CM, Wang Q, *et al*. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016; 12: 580–592.
16. Jeon OH, Kim C, Laberge RM, *et al*. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. *Nat Med* 2017; 23: 775–781.
17. Courties A, Sellam J and Berenbaum F. Metabolic syndrome-associated osteoarthritis. *Curr Opin Rheumatol* 2017; 29: 214–222.
18. Katz JN, Arant KR and Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA* 2021; 325: 568–578.
19. Machado GC, Maher CG, Ferreira PH, *et al*. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ (Clinical Research Ed)* 2015; 350: h1225.
20. Krebs EE, Gravely A, Nugent S, *et al*. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA* 2018; 319: 872–882.
21. Sharma L. Osteoarthritis of the Knee. *N Engl J Med* 2021; 384: 51–59.
22. Singh H, Knapik DM, Polce EM, *et al*. Relative efficacy of intra-articular injections in the treatment of knee osteoarthritis: a systematic review and network meta-analysis. *Am J Sports Med* 2022; 52: 3140–3148.
23. Aresti N, Kassam J, Nicholas N, *et al*. Hip osteoarthritis. *BMJ (Clinical Research Ed)* 2016; 354: i3405.
24. da Costa BR, Pereira TV, Saadat P, *et al*. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ (Clinical Research Ed)* 2021; 375: n2321.
25. Jones IA, Togashi R, Wilson ML, *et al*. Intra-articular treatment options for knee osteoarthritis. *Nat Rev Rheumatol* 2019; 15: 77–90.
26. Arden NK, Perry TA, Bannuru RR, *et al*. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nat Rev Rheumatol* 2021; 17: 59–66.
27. Nelson AE, Allen KD, Golightly YM, *et al*. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. *Semin Arthritis Rheum* 2014; 43: 701–712.
28. Goh SL, Persson MSM, Stocks J, *et al*. Relative efficacy of different exercises for pain, function, performance and quality of life in knee and hip osteoarthritis: systematic review and network meta-analysis. *Sports Med* 2019; 49: 743–761.
29. Block JA. Osteoarthritis: OA guidelines: improving care or merely codifying practice? *Nat Rev Rheumatol* 2014; 10: 324–326.
30. Barnett R. Osteoarthritis. *Lancet* 2018; 391: 1985.
31. Loeser RF, Goldring SR, Scanzello CR, *et al*. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 2012; 64: 1697–1707.
32. Oo WM and Hunter DJ. Disease modification in osteoarthritis: are we there yet? *Clin Exp Rheumatol* 2019; 37(Suppl. 120): 135–140.

33. Oo WM, Little C, Duong V, *et al*. The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): the evidence to date. *Drug Des Devel Ther* 2021; 15: 2921–2945.

34. Yeap SS. Current DMOAD options for the treatment of osteoarthritis. *Clin Exp Rheumatol* 2020; 38: 802.

35. Martel-Pelletier J, Barr AJ, Cicuttini FM, *et al*. Osteoarthritis. *Nat Rev Dis Primers* 2016; 2: 16072.

36. Jones G. Pain in OA: is cartilage loss a major contributor? *Nat Rev Rheumatol* 2020; 16: 541–542.

37. Eckstein F, Boudreau R, Wang Z, *et al*. Comparison of radiographic joint space width and magnetic resonance imaging for prediction of knee replacement: a longitudinal case-control study from the Osteoarthritis Initiative. *Eur Radiol* 2016; 26: 1942–1951.

38. Beenken A and Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009; 8: 235–253.

39. Itoh N and Ornitz DM. Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem* 2011; 149: 121–130.

40. Xie Y, Zinkle A, Chen L, *et al*. Fibroblast growth factor signalling in osteoarthritis and cartilage repair. *Nat Rev Rheumatol* 2020; 16: 547–564.

41. Davidson D, Blanc A, Filion D, *et al*. Fibroblast growth factor (FGF) 18 signals through FGF receptor 3 to promote chondrogenesis. *J Biol Chem* 2005; 280: 20509–20515.

42. Ellsworth JL, Berry J, Bukowski T, *et al*. Fibroblast growth factor-18 is a trophic factor for mature chondrocytes and their progenitors. *Osteoarthritis Cartilage* 2002; 10: 308–320.

43. Moore EE, Bendele AM, Thompson DL, *et al*. Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. *Osteoarthritis Cartilage* 2005; 13: 623–631.

44. Chen X, Yamashita A, Morioka M, *et al*. Integration capacity of human induced pluripotent stem cell-derived cartilage. *Tissue Eng Part A* 2019; 25: 437–445.

45. Eckstein F, Kraines JL, Aydemir A, *et al*. Intra-articular sprifermin reduces cartilage loss in addition to increasing cartilage gain independent of location in the femorotibial joint: post-hoc analysis of a randomised, placebo-controlled phase II clinical trial. *Ann Rheum Dis* 2020; 79: 525–528.

46. Hochberg MC, Guermazi A, Guehring H, *et al*. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *JAMA* 2019; 322: 1360–1370.

47. Dahlberg LE, Aydemir A, Muurahainen N, *et al*. A first-in-human, double-blind, randomised, placebo-controlled, dose ascending study of intra-articular rhFGF18 (sprifermin) in patients with advanced knee osteoarthritis. *Clin Exp Rheumatol* 2016; 34: 445–450.

48. Lohmander LS, Hellot S, Dreher D, *et al*. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2014; 66: 1820–1831.

49. Eckstein F, Hochberg MC, Guehring H, *et al*. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. *Ann Rheum Dis* 2021; 80: 1062–1069.

50. Mehana EE, Khafaga AF and El-Blehi SS. The role of matrix metalloproteinases in osteoarthritis pathogenesis: an updated review. *Life Sciences* 2019; 234: 116786.

51. Oikonomopoulou K, Diamandis EP, Hollenberg MD, *et al*. Proteinases and their receptors in inflammatory arthritis: an overview. *Nat Rev Rheumatol* 2018; 14: 170–180.

52. Rahmati M, Nalesso G, Mobasheri A, *et al*. Aging and osteoarthritis: central role of the extracellular matrix. *Ageing Res Rev* 2017; 40: 20–30.

53. Burrage PS, Mix KS and Brinckerhoff CE. Matrix metalloproteinases: role in arthritis. *Front Biosci* 2006; 11: 529–543.

54. Martel-Pelletier J, Welsch DJ and Pelletier JP. Metalloproteases and inhibitors in arthritic diseases. *Best Pract Res Clin Rheumatol* 2001; 15: 805–829.

55. Cao P, Li Y, Tang Y, *et al*. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. *Expert Opin Pharmacother* 2020; 21: 797–809.

56. Krzeski P, Buckland-Wright C, Bálint G, *et al*. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. *Arthritis Res Ther* 2007; 9: R109.

57. Vandenbroucke RE and Libert C. Is there new hope for therapeutic matrix metalloproteinase

inhibition? *Nat Rev Drug Discov* 2014; 13: 904–927.

58. Leff RL, Elias I, Ionescu M, *et al.* Molecular changes in human osteoarthritic cartilage after 3 weeks of oral administration of BAY 12-9566, a matrix metalloproteinase inhibitor. *J Rheumatol* 2003; 30: 544–549.

59. Schnute ME, O'Brien PM, Nahra J, *et al.* Discovery of (pyridin-4-yl)-2H-tetrazole as a novel scaffold to identify highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. *Bioorg Med Chem Lett* 2010; 20: 576–580.

60. Piecha D, Weik J, Kheil H, *et al.* Novel selective MMP-13 inhibitors reduce collagen degradation in bovine articular and human osteoarthritis cartilage explants. *Inflamm Res* 2010; 59: 379–389.

61. Malfait AM and Tortorella MD. The 'elusive DMOAD': aggrecanase inhibition from laboratory to clinic. *Clin Exp Rheumatol* 2019; 37(Suppl. 120): 130–134.

62. Clement-Lacroix P, Little CB, Smith MM, *et al.* Pharmacological characterization of GLPG 1972/S201086, a potent and selective small-molecule inhibitor of ADAMTS5. *Osteoarthritis Cartilage* 2022; 30: 291–301.

63. Brebion F, Gosmini R, Deprez P, *et al.* Discovery of GLPG 1972/S201086, a potent, selective, and orally bioavailable ADAMTS-5 inhibitor for the treatment of osteoarthritis. *J Med Chem* 2021; 64: 2937–2952.

64. Chockalingam PS, Sun W, Rivera-Bermudez MA, *et al.* Elevated aggrecanase activity in a rat model of joint injury is attenuated by an aggrecanase specific inhibitor. *Osteoarthritis Cartilage* 2011; 19: 315–323.

65. Chiusaroli R, Visentini M, Galimberti C, *et al.* Targeting of ADAMTS5's ancillary domain with the recombinant mAb CRB0017 ameliorates disease progression in a spontaneous murine model of osteoarthritis. *Osteoarthritis Cartilage* 2013; 21: 1807–1810.

66. Larkin J, Lohr TA, Elefante L, *et al.* Translational development of an ADAMTS-5 antibody for osteoarthritis disease modification. *Osteoarthritis Cartilage* 2015; 23: 1254–1266.

67. Miller RE, Tran PB, Ishihara S, *et al.* Therapeutic effects of an anti-ADAMTS-5 antibody on joint damage and mechanical allodynia in a murine model of osteoarthritis. *Osteoarthritis Cartilage* 2016; 24: 299–306.

68. Siebuhr AS, Werkmann D, Bay-Jensen AC, *et al.* The Anti-ADAMTS-5 Nanobody(®) M6495 protects cartilage degradation ex vivo. *Int J Mol Sci* 2020; 21: 5992.

69. Sharma N, Drobinski P, Kayed A, *et al.* Inflammation and joint destruction may be linked to the generation of cartilage metabolites of ADAMTS-5 through activation of toll-like receptors. *Osteoarthritis Cartilage* 2020; 28: 658–668.

70. Nusse R and Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. *Cell* 2017; 169: 985–999.

71. Lories RJ, Corr M and Lane NE. To Wnt or not to Wnt: the bone and joint health dilemma. *Nat Rev Rheumatol* 2013; 9: 328–339.

72. Lambert C, Dubuc JE, Montell E, *et al.* Gene expression pattern of cells from inflamed and normal areas of osteoarthritis synovial membrane. *Arthritis Rheumatol* 2014; 66: 960–968.

73. Nakamura Y, Nawata M and Wakitani S. Expression profiles and functional analyses of Wnt-related genes in human joint disorders. *Am J Pathol* 2005; 167: 97–105.

74. Zhu S, Liu H, Wu Y, *et al.* Wnt and Rho GTPase signaling in osteoarthritis development and intervention: implications for diagnosis and therapy. *Arthritis Res Ther* 2013; 15: 217.

75. Sabha M, Siaton BC and Hochberg MC. Lorecivivint, an intra-articular potential disease-modifying osteoarthritis drug. *Expert Opin Investig Drugs* 2020; 29: 1339–1346.

76. Deshmukh V, Hu H, Barroga C, *et al.* A small-molecule inhibitor of the Wnt pathway (SM 04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 2018; 26: 18–27.

77. Deshmukh V, O'Green AL, Bossard C, *et al.* Modulation of the Wnt pathway through inhibition of CLK2 and DYRK1A by lorecivivint as a novel, potentially disease-modifying approach for knee osteoarthritis treatment. *Osteoarthritis Cartilage* 2019; 27: 1347–1360.

78. Yazici Y, McAlindon TE, Fleischmann R, *et al.* A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. *Osteoarthritis Cartilage* 2017; 25: 1598–1606.

79. Yazici Y, McAlindon TE, Gibofsky A, *et al.* Lorecivivint, a novel intraarticular CDC-like kinase 2 and dual-specificity tyrosine phosphorylation-regulated kinase 1A inhibitor and wnt pathway modulator for the treatment of knee osteoarthritis: a phase II randomized trial. *Arthritis Rheumatol* 2020; 72: 1694–1706.

80. Yazici Y, McAlindon TE, Gibofsky A, *et al.* A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis. *Osteoarthritis Cartilage* 2021; 29: 654–666.
81. Zhen G and Cao X. Targeting TGFβ signaling in subchondral bone and articular cartilage homeostasis. *Trends Pharmacol Sci* 2014; 35: 227–236.
82. Fang J, Xu L, Li Y, *et al.* Roles of TGF-beta 1 signaling in the development of osteoarthritis. *Histol Histopathol* 2016; 31: 1161–1167.
83. van der Kraan PM. The changing role of TGFβ in healthy, ageing and osteoarthritic joints. *Nat Rev Rheumatol* 2017; 13: 155–163.
84. van Caam A, Madej W, Garcia de Vinuesa A, *et al.* TGFβ1-induced SMAD2/3 and SMAD1/5 phosphorylation are both ALK5-kinase-dependent in primary chondrocytes and mediated by TAK1 kinase activity. *Arthritis Res Ther* 2017; 19: 112.
85. Zhang M, Meng QC, Yang XF, *et al.* TGF-β1/WISP1/Integrin-α interaction mediates human chondrocytes dedifferentiation. *Eur Rev Med Pharmacol Sci* 2020; 24: 8675–8684.
86. Tang Y, Wu X, Lei W, *et al.* TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med* 2009; 15: 757–765.
87. Wang C, Shen J, Ying J, *et al.* FoxO1 is a crucial mediator of TGF-β/TAK1 signaling and protects against osteoarthritis by maintaining articular cartilage homeostasis. *Proc Natl Acad Sci U S A* 2020; 117: 30488–30497.
88. Ha CW, Noh MJ, Choi KB, *et al.* Initial phase I safety of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients. *Cytotherapy* 2012; 14: 247–256.
89. Noh MJ, Copeland RO, Yi Y, *et al.* Pre-clinical studies of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 (TG-C). *Cytotherapy* 2010; 12: 384–393.
90. Ha CW, Cho JJ, Elmallah RK, *et al.* A multicenter, single-blind, phase IIa clinical trial to evaluate the efficacy and safety of a cell-mediated gene therapy in degenerative knee arthritis patients. *Hum Gene Ther Clin Dev* 2015; 26: 125–130.
91. Guermazi A, Kalsi G, Niu J, *et al.* Structural effects of intra-articular TGF-β1 in moderate to advanced knee osteoarthritis: MRI-based assessment in a randomized controlled trial. *BMC Musculoskelet Disord* 2017; 18: 461.
92. Cherian JJ, Parvizi J, Bramlet D, *et al.* Preliminary results of a phase II randomized study to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-β1 in patients with grade 3 chronic degenerative joint disease of the knee. *Osteoarthritis Cartilage* 2015; 23: 2109–2118.
93. Lee B, Parvizi J, Bramlet D, *et al.* Results of a phase II study to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-β1. *J Knee Surg* 2020; 33: 167–172.
94. Kim MK, Ha CW, In Y, *et al.* A multicenter, double-blind, phase III clinical trial to evaluate the efficacy and safety of a cell and gene therapy in knee osteoarthritis patients. *Hum Gene Ther Clin Dev* 2018; 29: 48–59.
95. Flory J and Lipska K. Metformin in 2019. *JAMA* 2019; 321: 1926–1927.
96. Wang Y, Hussain SM, Wluka AE, *et al.* Association between metformin use and disease progression in obese people with knee osteoarthritis: data from the Osteoarthritis Initiative-a prospective cohort study. *Arthritis Res Ther* 2019; 21: 127.
97. Li J, Zhang B, Liu WX, *et al.* Metformin limits osteoarthritis development and progression through activation of AMPK signalling. *Ann Rheum Dis* 2020; 79: 635–645.
98. Feng X, Pan J, Li J, *et al.* Metformin attenuates cartilage degeneration in an experimental osteoarthritis model by regulating AMPK/mTOR. *Aging (Albany NY)* 2020; 12: 1087–1103.
99. Lu CH, Chung CH, Lee CH, *et al.* Combination COX-2 inhibitor and metformin attenuate rate of joint replacement in osteoarthritis with diabetes: a nationwide, retrospective, matched-cohort study in Taiwan. *PLoS ONE* 2018; 13: e0191242.
100. Zhu Z, Huang JY, Ruan G, *et al.* Metformin use and associated risk of total joint replacement in patients with type 2 diabetes: a population-based matched cohort study. *CMAJ* 2022; 194: E1672–e1684.
101. Ruan G, Yuan S, Lou A, *et al.* Can metformin relieve tibiofemoral cartilage volume loss and knee symptoms in overweight knee osteoarthritis patients? Study protocol for a randomized, double-blind, and placebo-controlled trial. *BMC Musculoskelet Disord* 2022; 23: 486.
102. Vannabouathong C, Del Fabbro G, Sales B, *et al.* Intra-articular injections in the treatment

of symptoms from ankle arthritis: a systematic review. *Foot Ankle Int* 2018; 39: 1141–1150.

103. Dong Y, Zhang B, Yang Q, *et al*. The effects of platelet-rich plasma injection in knee and hip osteoarthritis: a meta-analysis of randomized controlled trials. *Clin Rheumatol* 2021; 40: 263–277.

104. Filardo G, Kon E, Roffi A, *et al*. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc* 2015; 23: 2459–2474.

105. Zhu Y, Yuan M, Meng HY, *et al*. Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: a review. *Osteoarthritis Cartilage* 2013; 21: 1627–1637.

106. Fice MP, Miller JC, Christian R, *et al*. The role of platelet-rich plasma in cartilage pathology: an updated systematic review of the basic science evidence. *Arthroscopy* 2019; 35: 961–976.

107. Hohmann E, Tetsworth K and Glatt V. Is platelet-rich plasma effective for the treatment of knee osteoarthritis? A systematic review and meta-analysis of level 1 and 2 randomized controlled trials. *Eur J Orthop Surg Traumatol* 2020; 30: 955–967.

108. Shen L, Yuan T, Chen S, *et al*. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2017; 12: 16.

109. Patel S, Dhillon MS, Aggarwal S, *et al*. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med* 2013; 41: 356–364.

110. Bennell KL, Paterson KL, Metcalf BR, *et al*. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: the RESTORE randomized clinical trial. *JAMA* 2021; 326: 2021–2030.

111. Paget LDA, Reurink G, de Vos RJ, *et al*. Effect of platelet-rich plasma injections vs placebo on ankle symptoms and function in patients with ankle osteoarthritis: a randomized clinical trial. *JAMA* 2021; 326: 1595–1605.

112. Paterson KL, Hunter DJ, Metcalf BR, *et al*. Efficacy of intra-articular injections of platelet-rich plasma as a symptom- and disease-modifying treatment for knee osteoarthritis – the RESTORE trial protocol. *BMC Musculoskelet Disord* 2018; 19: 272.

113. Sokolove J and Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskelet Dis* 2013; 5: 77–94.

114. Chow YY and Chin KY. The role of inflammation in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2020; 2020: 8293921.

115. Kapoor M, Martel-Pelletier J, Lajeunesse D, *et al*. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; 7: 33–42.

116. Conaghan PG, Cook AD, Hamilton JA, *et al*. Therapeutic options for targeting inflammatory osteoarthritis pain. *Nat Rev Rheumatol* 2019; 15: 355–363.

117. Jenei-Lanzl Z, Meurer A and Zaucke F. Interleukin–1β signaling in osteoarthritis – chondrocytes in focus. *Cell Signal* 2019; 53: 212–223.

118. Wang T and He C. Pro-inflammatory cytokines: the link between obesity and osteoarthritis. *Cytokine Growth Factor Rev* 2018; 44: 38–50.

119. Liao CR, Wang SN, Zhu SY, *et al*. Advanced oxidation protein products increase TNF-α and IL-1β expression in chondrocytes via NADPH oxidase 4 and accelerate cartilage degeneration in osteoarthritis progression. *Redox Biol* 2020; 28: 101306.

120. Cohen SB, Proudman S, Kivitz AJ, *et al*. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. *Arthritis Res Ther* 2011; 13: R125.

121. Kloppenburg M, Peterfy C, Haugen IK, *et al*. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann Rheum Dis* 2019; 78: 413–420.

122. Fleischmann RM, Bliddal H, Blanco FJ, *et al*. A phase II trial of lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. *Arthritis Rheumatol* 2019; 71: 1056–1069.

123. Auw Yang KG, Raijmakers NJ, van Arkel ER, *et al*. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis Cartilage* 2008; 16: 498–505.

124. Chevalier X, Goupille P, Beaulieu AD, *et al*. Intraarticular injection of anakinra in

osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2009; 61: 344–352.

125. Ridker PM, Everett BM, Thuren T, *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377: 1119–1131.

126. Schieker M, Conaghan PG, Mindeholm L, *et al.* Effects of interleukin-1β inhibition on incident hip and knee replacement: exploratory analyses from a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2020; 173: 509–515.

127. Dougados M, Nguyen M, Berdah L, *et al.* Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip. *Arthritis Rheum* 2001; 44: 2539–2547.

128. Fidelix TS, Macedo CR, Maxwell LJ, *et al.* Diacerein for osteoarthritis. *Cochrane Database Syst Rev* 2014; 2: CD005117.

129. Pavelka K, Bruyère O, Cooper C, *et al.* Diacerein: benefits, risks and place in the management of osteoarthritis. An opinion-based report from the ESCEO. *Drugs Aging* 2016; 33: 75–85.

130. Wojdasiewicz P, Poniatowski ŁA and Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2014; 2014: 561459.

131. Aitken D, Laslett LL, Pan F, *et al.* A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis – the HUMOR trial. *Osteoarthritis Cartilage* 2018; 26: 880–887.

132. Chevalier X, Ravaud P, Maheu E, *et al.* Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015; 74: 1697–1705.

133. Verbruggen G, Wittoek R, Vander Cruyssen B, *et al.* Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012; 71: 891–898.

134. Kloppenburg M, Ramonda R, Bobacz K, *et al.* Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018; 77: 1757–1764.

135. Loef M, Kroon FPB, Bergstra SA, *et al.* TNF inhibitor treatment is associated with a lower risk of hand osteoarthritis progression in rheumatoid arthritis patients after 10 years. *Rheumatology (Oxford)* 2018; 57: 1917–1924.

136. Loeser RF, Collins JA and Diekman BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016; 12: 412–420.

137. Childs BG, Gluscevic M, Baker DJ, *et al.* Senescent cells: an emerging target for diseases of ageing. *Nat Rev Drug Discov* 2017; 16: 718–735.

138. Calcinotto A, Kohli J, Zagato E, *et al.* Cellular senescence: aging, cancer, and injury. *Physiol Rev* 2019; 99: 1047–1078.

139. Coryell PR, Diekman BO and Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. *Nat Rev Rheumatol* 2021; 17: 47–57.

140. Kirkland JL and Tchkonia T. Senolytic drugs: from discovery to translation. *J Intern Med* 2020; 288: 518–536.

141. Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, *et al.* Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell* 2016; 15: 428–435.

142. Chang J, Wang Y, Shao L, *et al.* Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nat Med* 2016; 22: 78–83.

143. Yousefzadeh MJ, Zhu Y, McGowan SJ, *et al.* Fisetin is a senotherapeutic that extends health and lifespan. *Ebiomedicine* 2018; 36: 18–28.

144. Zheng W, Feng Z, You S, *et al.* Fisetin inhibits IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through activating SIRT1 and attenuates the progression of osteoarthritis in mice. *Int Immunopharmacol* 2017; 45: 135–147.

145. Zeng L, Yu G, Hao W, *et al.* The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis. *Bioscience Reports* 2021; 41: BSR20210817.

146. Henrotin Y, Malaise M, Wittoek R, *et al.* Bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: a double-blind multicenter randomized placebo controlled three-arm study. *Arthritis Res Ther* 2019; 21: 179.

147. Zhang Z, Leong DJ, Xu L, *et al.* Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. *Arthritis Res Ther* 2016; 18: 128.

148. Qiu B, Xu X, Yi P, *et al.* Curcumin reinforces MSC-derived exosomes in attenuating osteoarthritis via modulating the miR-124/NF-kB and miR-143/ROCK1/TLR9 signalling pathways. *J Cell Mol Med* 2020; 24: 10855–10865.

149. Zhang G, Cao J, Yang E, *et al.* Curcumin improves age-related and surgically induced osteoarthritis by promoting autophagy in mice. *Bioscience Reports* 2018; 38: BSR20171691.

150. Wang Z, Jones G, Winzenberg T, *et al.* Effectiveness of curcuma longa extract for the treatment of symptoms and effusion-synovitis of knee osteoarthritis: a randomized trial. *Ann Intern Med* 2020; 173: 861–869.

151. Srivastava S, Saksena AK, Khattri S, *et al.* Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology* 2016; 24: 377–388.

152. Hügle T and Geurts J. What drives osteoarthritis?-synovial versus subchondral bone pathology. *Rheumatology (Oxford)* 2017; 56: 1461–1471.

153. Hu W, Chen Y, Dou C, *et al.* Microenvironment in subchondral bone: predominant regulator for the treatment of osteoarthritis. *Ann Rheum Dis* 2020; 80: 413–422.

154. Zhu X, Chan YT, Yung PSH, *et al.* Subchondral bone remodeling: a therapeutic target for osteoarthritis. *Front Cell Dev Biol* 2020; 8: 607764.

155. Drake FH, Dodds RA, James IE, *et al.* Cathepsin K, but not cathepsins B, L, or S, is abundantly expressed in human osteoclasts. *J Biol Chem* 1996; 271: 12511–12516.

156. Dejica VM, Mort JS, Laverty S, *et al.* Cleavage of type II collagen by cathepsin K in human osteoarthritic cartilage. *Am J Pathol* 2008; 173: 161–169.

157. Lindström E, Rizoska B, Henderson I, *et al.* Nonclinical and clinical pharmacological characterization of the potent and selective cathepsin K inhibitor MIV-711. *J Transl Med* 2018; 16: 125.

158. Nwosu LN, Gowler PRW, Burston JJ, *et al.* Analgesic effects of the cathepsin K inhibitor L-006235 in the monosodium iodoacetate model of osteoarthritis pain. *Pain Rep* 2018; 3: e685.

159. Lindström E, Rizoska B, Tunblad K, *et al.* The selective cathepsin K inhibitor MIV-711 attenuates joint pathology in experimental animal models of osteoarthritis. *J Transl Med* 2018; 16: 56.

160. Conaghan PG, Bowes MA, Kingsbury SR, *et al.* Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: a randomized controlled trial. *Ann Intern Med* 2020; 172: 86–95.

161. Shao LT, Gou Y, Fang JK, *et al.* Parathyroid hormone (1-34) ameliorates cartilage degeneration and subchondral bone deterioration in collagenase-induced osteoarthritis model in mice. *Bone Joint Res* 2020; 9: 675–688.

162. Yan JY, Tian FM, Wang WY, *et al.* Parathyroid hormone (1-34) prevents cartilage degradation and preserves subchondral bone micro-architecture in guinea pigs with spontaneous osteoarthritis. *Osteoarthritis Cartilage* 2014; 22: 1869–1877.

163. Dai MW, Chu JG, Tian FM, *et al.* Parathyroid hormone(1-34) exhibits more comprehensive effects than celecoxib in cartilage metabolism and maintaining subchondral bone micro-architecture in meniscectomized guinea pigs. *Osteoarthritis Cartilage* 2016; 24: 1103–1112.

164. Osagie-Clouard L, Sanghani-Kerai A, Coathup M, *et al.* The influence of parathyroid hormone 1-34 on the osteogenic characteristics of adipose- and bone-marrow-derived mesenchymal stem cells from juvenile and ovarectomized rats. *Bone Joint Res* 2019; 8: 397–404.

165. Macica C, Liang G, Nasiri A, *et al.* Genetic evidence of the regulatory role of parathyroid hormone-related protein in articular chondrocyte maintenance in an experimental mouse model. *Arthritis Rheum* 2011; 63: 3333–3343.

166. Sampson ER, Hilton MJ, Tian Y, *et al.* Teriparatide as a chondroregenerative therapy for injury-induced osteoarthritis. *Sci Transl Med* 2011; 3: 101ra193.

167. Hopwood B, Tsykin A, Findlay DM, *et al.* Microarray gene expression profiling of osteoarthritic bone suggests altered bone remodelling, WNT and transforming growth factor-beta/bone morphogenic protein signalling. *Arthritis Res Ther* 2007; 9: R100.

168. McGuire D, Bowes M, Brett A, *et al.* Study TPX-100-5: intra-articular TPX-100

significantly delays pathological bone shape change and stabilizes cartilage in moderate to severe bilateral knee OA. *Arthritis Res Ther* 2021; 23: 242.

169. Fernández-Martín S, López-Peña M, Muñoz F, *et al*. Bisphosphonates as disease-modifying drugs in osteoarthritis preclinical studies: a systematic review from 2000 to 2020. *Arthritis Res Ther* 2021; 23: 60.

170. Vaysbrot EE, Osani MC, Musetti MC, *et al*. Are bisphosphonates efficacious in knee osteoarthritis? A meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2018; 26: 154–164.

171. Deveza LA, Bierma-Zeinstra SMA, van Spil WE, *et al*. Efficacy of bisphosphonates in specific knee osteoarthritis subpopulations: protocol for an OA Trial Bank systematic review and individual patient data meta-analysis. *BMJ Open* 2018; 8: e023889.

172. Oo WM, Yu SP, Daniel MS, *et al*. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. *Expert Opin Emerg Drugs* 2018; 23: 331–347.

173. Damman W, Liu R, Bloem JL, *et al*. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017; 76: 214–217.

174. Felson DT, McLaughlin S, Goggins J, *et al*. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med* 2003; 139: 330–336.

175. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, *et al*. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. *Ann Rheum Dis* 2016; 75: 117–123.

176. Yusuf E, Kortekaas MC, Watt I, *et al*. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis* 2011; 70: 60–67.

177. Cai G, Aitken D, Laslett LL, *et al*. Effect of intravenous zoledronic acid on tibiofemoral cartilage volume among patients with knee osteoarthritis with bone marrow lesions: a randomized clinical trial. *JAMA* 2020; 323: 1456–1466.

178. Haj-Mirzaian A, Guermazi A, Roemer FW, *et al*. Bisphosphonates intake and its association with changes of periarticular bone area and three-dimensional shape: data from the Osteoarthritis Initiative (OAI). *Osteoarthritis Cartilage* 2018; 26: 564–568.

179. Laslett LL, Kingsbury SR, Hensor EM, *et al*. Effect of bisphosphonate use in patients with symptomatic and radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *Ann Rheum Dis* 2014; 73: 824–830.

180. Hayes KN, Giannakeas V and Wong AKO. Bisphosphonate use is protective of radiographic knee osteoarthritis progression among those with low disease severity and being non-overweight: data from the osteoarthritis initiative. *J Bone Miner Res* 2020; 35: 2318–2326.

181. Murphy CL, Murphy E, Duffy T, *et al*. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann Rheum Dis* 2013; 72: e13.

182. Jones B. Osteoarthritis: evaluating strontium ranelate treatment for knee OA. *Nat Rev Rheumatol* 2012; 8: 693.

183. Han W, Fan S, Bai X, *et al*. Strontium ranelate, a promising disease modifying osteoarthritis drug. *Expert Opin Investig Drugs* 2017; 26: 375–380.

184. Coulombe J, Faure H, Robin B, *et al*. In vitro effects of strontium ranelate on the extracellular calcium-sensing receptor. *Biochem Biophys Res Commun* 2004; 323: 1184–1190.

185. Tat SK, Pelletier JP, Mineau F, *et al*. Strontium ranelate inhibits key factors affecting bone remodeling in human osteoarthritic subchondral bone osteoblasts. *Bone* 2011; 49: 559–567.

186. Yu DG, Ding HF, Mao YQ, *et al*. Strontium ranelate reduces cartilage degeneration and subchondral bone remodeling in rat osteoarthritis model. *Acta Pharmacol Sin* 2013; 34: 393–402.

187. Cooper C, Reginster JY, Chapurlat R, *et al*. Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. *Curr Med Res Opin* 2012; 28: 231–239.

188. Pelletier JP, Roubille C, Raynauld JP, *et al*. Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. *Ann Rheum Dis* 2015; 74: 422–429.

189. Ali MS, Berencsi K, Marinier K, *et al*. Comparative cardiovascular safety of strontium ranelate and bisphosphonates: a multi-database study in 5 EU countries by the EU-ADR Alliance. *Osteoporos Int* 2020; 31: 2425–2438.

190. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81: 353–373.

191. McAlindon T, LaValley M, Schneider E, *et al*. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA* 2013; 309: 155–162.

192. Kong C, Wang C, Shi Y, *et al*. Active vitamin D activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK-mTOR signaling pathway. *Biochem Cell Biol* 2020; 98: 434–442.

193. Ding C, Cicuttini F, Parameswaran V, *et al*. Serum levels of vitamin D, sunlight exposure, and knee cartilage loss in older adults: the Tasmanian older adult cohort study. *Arthritis Rheum* 2009; 60: 1381–1389.

194. Jin X, Jones G, Cicuttini F, *et al*. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. *JAMA* 2016; 315: 1005–1013.

195. Wang X, Cicuttini F, Jin X, *et al*. Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2017; 25: 1304–1312.

196. Zheng S, Tu L, Cicuttini F, *et al*. Effect of Vitamin D Supplementation on Depressive Symptoms in Patients With Knee Osteoarthritis. *J Am Med Dir Assoc* 2019; 20: 1634–1640.

197. Tu L, Zheng S, Cicuttini F, *et al*. Effects of Vitamin D Supplementation on Disabling Foot Pain in Patients With Symptomatic Knee Osteoarthritis. *Arthritis Care Res (Hoboken)* 2021; 73: 781–787.

198. Zheng S, Jin X, Cicuttini F, *et al*. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis. *Am J Med* 2017; 130: 1211–1218.

199. Parry E, Ogollah R and Peat G. Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data. *BMC Musculoskelet Disord* 2017; 18: 80.

200. Little CB and Hunter DJ. Post-traumatic osteoarthritis: from mouse models to clinical trials. *Nat Rev Rheumatol* 2013; 9: 485–497.

201. Kraus VB, Simon LS, Katz JN, *et al*. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. *Osteoarthritis Cartilage* 2019; 27: 571–579.

202. Oo WM, Liu X and Hunter DJ. Pharmacodynamics, efficacy, safety and administration of intra-articular therapies for knee osteoarthritis. *Expert Opin Drug Metab Toxicol* 2019; 15: 1021–1032.

203. Zhang W, Robertson J, Jones AC, *et al*. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008; 67: 1716–1723.

204. Saeedi T, Alotaibi HF and Prokopovich P. Polymer colloids as drug delivery systems for the treatment of arthritis. *Adv Colloid Interface Sci* 2020; 285: 102273.

205. Deveza LA, Nelson AE and Loeser RF. Phenotypes of osteoarthritis: current state and future implications. *Clin Exp Rheumatol* 2019; 37(Suppl. 120): 64–72.

206. Mobasheri A, Saarakkala S, Finnilä M, *et al*. Recent advances in understanding the phenotypes of osteoarthritis. *F1000Res* 2019; 8: F1000 Faculty Rev-2091.

207. Goetz LH and Schork NJ. Personalized medicine: motivation, challenges, and progress. *Fertil Steril* 2018; 109: 952–963.

208. Oo WM, Linklater JM and Hunter DJ. Imaging in knee osteoarthritis. *Curr Opin Rheumatol* 2017; 29: 86–95.

209. Roemer FW, Kwoh CK, Hayashi D, *et al*. The role of radiography and MRI for eligibility assessment in DMOAD trials of knee OA. *Nat Rev Rheumatol* 2018; 14: 372–380.

210. Roemer FW, Jarraya M, Collins JE, *et al*. Structural phenotypes of knee osteoarthritis: potential clinical and research relevance. *Skeletal Radiol*. Epub ahead of print 26 September 2022. DOI: 10.1007/s00256-022-04191-6.