Drug Design, Development and Therapy

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REVIEW

The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date

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Abstract: Osteoarthritis (OA) is a complex heterogeneous articular disease with multiple joint tissue involvement of varying severity and no regulatory-agency-approved disease-modifying drugs (DMOADs). In this review, we discuss the reasons necessitating the development of DMOADs for OA management, the classifications of clinical phenotypes or molecular/mechanistic endotypes from the viewpoint of targeted drug discovery, and then summarize the efficacy and safety profile of a range of targeted drugs in Phase 2 and 3 clinical trials directed to cartilage-driven, bone-driven, and inflammation-driven endotypes. Finally, we briefly put forward the reasons for failures in OA clinical trials and possible steps to overcome these barriers.

Keywords: osteoarthritis, DMOADs, disease-modifying drugs, intra-articular therapy, phenotype, endotype

Why is the Development of Disease-Modifying Osteoarthritis Drugs (DMOADs) Required?

Disease Burden

Osteoarthritis (OA) is the most prevalent arthritis globally and represents a major challenge for twenty-first century health care systems.[1,2] The Global Burden of Disease 2020 report showed an increase of 9.3% and 8.2% in the age-standardized OA point prevalence and annual incidence rate from 1990 to 2017.[3] The prevalence rises with increasing age; in the USA (United States of America), OA was found in 13.9% of adults aged ≥25 years and 33.6% for those aged ≥65 years respectively in 2005.[4] The lifetime risk of having symptomatic knee OA is about 40% in men and 47% in women, and the risk increases to 60.5% among obese persons.[5] By the year 2040, an estimated 25.9% of the total adult population will have doctor-diagnosed arthritis in the USA.[6]

Globally, 80% of patients with OA suffer from limitations in movement, and 25% from difficulty in performing their major daily activities of life; representing a significant impact of OA on functional impairment and disability.[7] In terms of economic burden, mean per-person earnings losses caused by OA were, on average, 7548 US$ per year from 2008 to 2011.[8] The mean all-cause health care utilization of working-age patients with OA is $14,521 US$ per year.[9] The socio-economic costs of OA were reported to range between 0.25% and 0.50% of a country's GDP.[10] In an individual patient data meta-analysis, the pooled estimate for

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premature mortality revealed a 23% increased risk (95% CI 1.07, 1.42) in patients with knee OA and a 20% increased risk (95% CI 1.04, 1.37) in hip OA.[11]

Unmet Needs for Disease-Modifying Drugs

Current OA treatment options are focused on symptomatic improvement in pain and joint function and include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular medications such as steroids and hyaluronic acids.[14] Surgical treatments are typically indicated only for patients with end-stage OA, as a last resort. Recently, paracetamol and opioids are only conditionally or not recommended by several scientific organisations,[12,13] highlighting the importance of finding new effective treatments for OA. In addition, outcomes for patients with OA are usually suboptimal and patients remain vulnerable to the clinical consequences of the disease on pain and physical function.[14]

OA was previously regarded as a degenerative disorder resulting from cartilage damage;[15] however, the development and utilization of modern imaging methods revealed that it results from the failure of the joint organ with a heterogeneous involvement of the whole joint structures, including cartilage damage, subchondral bone remodeling, synovial inflammation and osteophyte development.[16] Therefore, OA can be defined as a complex heterogeneous syndrome with multiple joint tissue involvement of varying severity. In part as a consequence, it is a huge challenge to develop a single 'one size fits all' therapy that may be suitable and effective for all patients with OA.[17]

Disease-Modifying Osteoarthritis Drugs (DMOADs)

The central hallmark in the pathologic process of OA disease is the progressive deterioration in the biological, structural and mechanical properties and function of the joint tissues, and an effective medical treatment should possess the ability to delay these processes or ideally even halt them completely. Such pharmaceutical agents that will alter the natural history of disease progression by arresting joint structural change and ameliorating symptoms, either by reducing pain or improving physical function are termed as "DMOADs".[18]

Currently, regulatory bodies such as US Food and Drug Administration (FDA)[19] and the European Medicines Agency (EMA)[20] have not approved any drug as an effective DMOAD, as the approval guide requires a potential DMOAD to demonstrate a slowing in the loss of knee or hip joint space width (JSW) on x-ray with associated symptomatic improvement.[17] Therefore, current OA trials for DMOAD development pipeline need to meet both clinically meaningful symptom improvement with concomitant structural benefits according to US FDA's published draft industry guidance on structural endpoints for OA published in 2018.[18]

OA Subtypes: Phenotypes and Endotypes

Because OA is characterised by its extraordinary inter-patient variability in clinical and structural manifestations, identification of patient/disease subtypes appropriate for targeted therapy is probably one of the promising ways forward in drug development research.[21,22] In addition, structural changes in OA result from complex interactions among different pathobiological pathways, which implicate a variety of catabolic factors and cytokines in the different joint tissues (molecular cross-talk).[23] Therefore, a new model of classifying OA based on pathophysiological disease subtypes is needed.

These subtypes can be clinical phenotypes or molecular/mechanistic endotypes.[24] A clinical phenotype can be defined as a group of observable traits (ie aetiologic factors, risk factors) that can identify and characterize a subtype in a defined population.[25,26] In other words, these subgroups of patients have similar clinically observable characteristics for better identifying individuals who are at higher risk of progression (prognostic) or who are more likely to respond to a specific intervention (prescriptive).[27,28]

An endotype is a disease subtype defined by distinct pathophysiologic mechanisms, including cellular, molecular and biomechanical signalling pathways.[29] Therefore, the endotype is distinct from a phenotype, and indicates the presence of a well-defined molecular mechanism. A given clinical phenotype of OA may comprise overlapping molecular endotypes (ie, different mechanisms giving rise to the same manifestation at varying degrees during different phases of the disease).[24]

From the point of view of targeted drug discovery, where identifying and directing the right pathobiological mechanism and structural manifestations of disease is key for success, drug development in OA should be based on the endotypes as the basis of the main drivers of OA disease.[30] In this review, we will, therefore, focus on currently ongoing phase 2 and 3 clinical trials of active drug development (Figure 1) related to three main

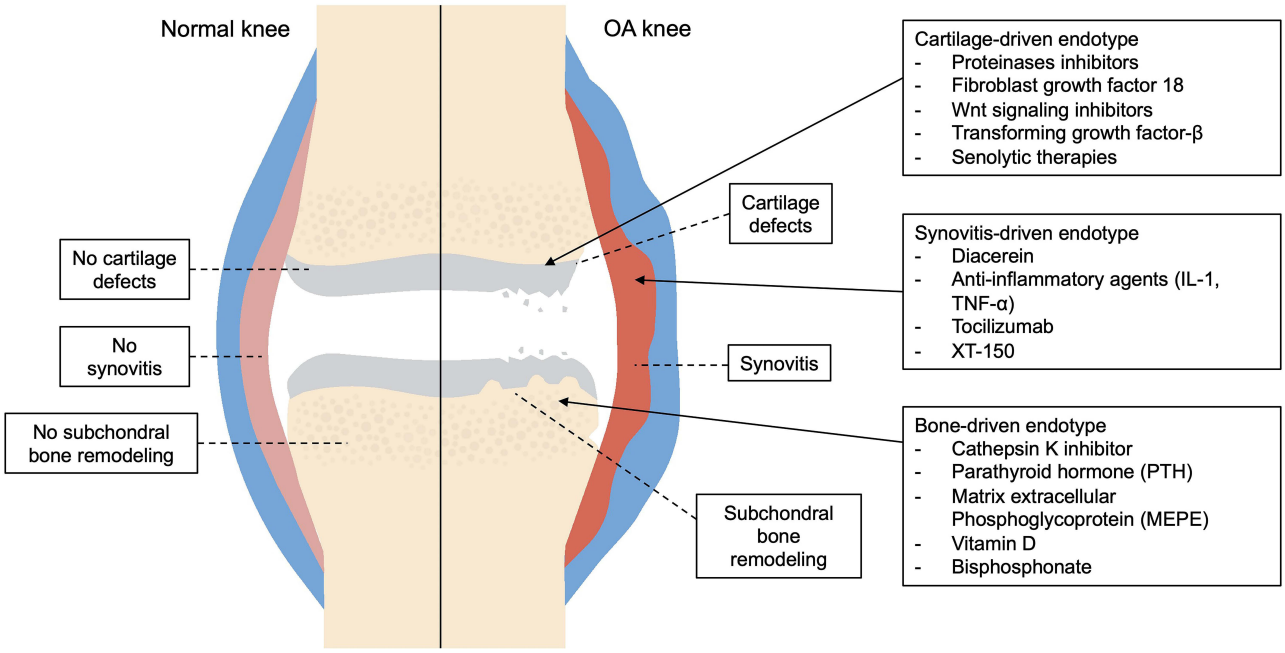

Figure 1 Active drugs related to the three main molecular or mechanistic OA endotypes (phase 2 and 3).

molecular/mechanistic endotypes: 1) Cartilage-driven endotype, 2) Bone-driven endotype, 3) Inflammation-driven endotype. While each drug has been assigned to and is discussed under one endotype based on its predominant activity, a particular therapeutic may have broader endotype-effects and where present, these are duly noted.

One author (WMO) conducted electronic and manual searches on the https://clinicaltrials.gov/ for identifying ongoing phase 2/3 clinical trials in active drug development pipelines, as well as electronic database searches in the PubMed and Embase via Ovid for published reports of phase-2/3 clinical trials results from the inception of these databases to 31st March 2021 using the following MESH or keywords: osteoarthritis OR osteoarthrosis AND DMOAD/ OR structure modification OR disease-modifying osteoarthritis drugs/.

What Developments Have There Been in Clinical OA Trials Currently in Active Phase 2 and 3 Trials?

Cartilage-Driven Endotype

Cartilage damage is considered as a central part of OA disease process, which involves a variety of catabolic and reparative mechanisms at the molecular level. The pharmaceutical drugs in phase 2 and 3 stages of development for cartilage-driven endotype are summarized in Table 1.

Proteinases Inhibitors (PI)

Matrix-degrading enzymes in the joint such as collagenases and aggrecanases are responsible for proteolysis of extracellular matrix components such as type II collagen and aggrecan, which is the most abundant proteoglycan in cartilage.[31] Proteinases such as matrix metalloproteinase 13 (MMP13) and ADAMTS5 (a Disintegrin And Metalloproteinase with ThromboSpondin-motif-5) are involved in cartilage destruction and progression of cartilage damage in OA pre-clinical models.[32,33] The potential benefits of MMP inhibitors in preserving the OA joint have been investigated. However, in patients with knee OA, broad-spectrum MMP inhibitors such as PG-116800 showed reversible musculoskeletal toxicities in a dose-dependent manner without clinical benefits, leading to the termination of further development of this drug.[34]

S201086/GLPG1972 is a potent and highly selective active site inhibitor of ADAMTS5. It possesses an excellent selectivity profile in animal models and high stability in dog and human liver microsomes and hepatocytes.[35] Phase-1 clinical studies revealed favorable pharmacokinetics as well as a strong and consistent target engagement in both healthy subjects and OA patients (n=171).[36] In a phase-2 study (Roccella study) which investigated the efficacy and safety profile of three different once-daily oral doses of GLPG1972/S201086 (n=932), the change in

Table 1 The Registered Phase 2/3 Clinical Trials on Compounds with Potential Disease-Modifying Effects on Cartilage

Drug Class/ Compound	Drug in Development	ClinialTrials.gov Identifier	Company	Structure	Targeted Tissue	Mechanism of Action	Route	OA Site	Stage of Development
ADAMTS-5 inhibitors									
	GLPG1972/ S201086	NCT03595618	Galapagos and Servier		Cartilage	Inhibiting the action of aggrecanases, matrix- degrading proteinases	Oral	Knee	Phase 2 (Completed in July 2020) (n=938)
Fibroblast Growth Factor (FGF-18)									
	Sprifermin (AS902330)	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	IA	Knee	Phase 2 (active, not recruiting; estimated completion date in 2019)
Gene Therapy									
	TissueGene-C	NCT01221441	TissueGen, Inc. (USA)	Allogeneic human chondrocytes modified to express transforming growth factor (TGF)-β1	Cartilage regeneration	Stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage	IA	Knee	Phase 2 (completed in 2014))
		NCT02072070	Kolon Life Science (South Korea)						Phase 3 (completed in 2015)
		NCT03291470	TissueGen, Inc. (USA)						Phase 3 (Not yet recruiting and estimated to be completed in Sept 2021) (n=510)
		NCT03203330	TissueGen, Inc. (USA)						Phase 3 (Active, not recruiting and estimated to be completed in Oct 2024) (n=510)

Wnt/ß-catenin signalling pathway inhibitors									
	Lorecivivint SM04690	NCT02536833 (results in webpage)	Samumed LLC (USA)	N-(5-(3-(7-(3-Fluorophenyl)-3H-imidazo(4,5-C)pyridin-2-yl)-1H-indazol-5- yl)-pyridin-3-yl)-3-methylbutanamide	Cartilage catbolism	Induction of protease production, especially matrix metalloproteinases	IA	Knee	Phase 2 (completed in April 2017) (n=455)
		NCT03122860							Phase 2 (completed in April 2018) (n=700)
		NCT03706521							Phase II (active and estimated to be completed in Dec 2021) (n=13)
		NCT03727022							Phase2 (active and estimated to be completed in Sept 2021) (n=100)
		NCT03928184							Phase 3 (active and estimated to be completed in Aug 2021) (n=725)
		NCT04385303							Phase 3 (active and estimated to be completed in Sept 2021) (n=726)
		NCT04520607							Phase 3 (Recruiting and estimated to be completed in Sept 2022) (n=500)

(*Continued*)

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Table 1 (Continued).

Drug Class/ Compound	Drug in Development	ClinialTrials.gov Identifier	Company	Structure	Targeted Tissue	Mechanism of Action	Route	OA Site	Stage of Development
Senolytic agents									
	UBX0101	NCT04129944	Unity Biotechnology, Inc.	Small molecule inhibitor of the MDM2/p53 protein interaction	Cartilage regeneration	Cartilage regeneration	IA	Knee	Phase 2 (completed in 2020) (n=183)
		NCT04349956 (follow-up of previous trial))							Terminated in Nov 2020 (Inability to achieve primary or secondary study objectives)
	Fisetin	NCT 04210986	Steadman Philippon Research Institute	3,3′,4′,7-tetrahydroxyflavone	Cartilage	Potential senolytic and anti-inflammatory action	Oral	Knee	Phase 2 (recruiting; estimated to be completed in 2022) (n=72)
		NCT04815902							Phase 2 (not yet recruiting; estimated to be completed in 2025) (n=100)

cartilage thickness [in mm (SD)] of central medial tibiofemoral compartment of the target knee via quantitative MRI was −0.116 (0.27) for the placebo group and −0.068 (0.20), −0.097 (0.27) and 0.085 (0.22), for the low, medium and high dose, respectively. There was no statistically significant difference versus placebo in both MRI and clinical outcome measures.[37] Another ADAMTS5-targeting agent, M6495 an anti-ADAMTS5 Nanobody (Ablynx), showed an acceptable safety profile and dose-dependent effects in a phase-1 study.[38]

Fibroblast Growth Factor 18

Sprifermin is a recombinant human fibroblast growth factor 18 (FGF18) which binds to fibroblast growth factor receptor-3 (FGFR-3) in cartilage.[39] It stimulates the proliferation of articular chondrocytes and induces hyaline extracellular matrix synthesis in rat OA models.[40] At the cellular level, intermittent administration may transiently promote an anabolic effect, while continuous administration may stimulate other signalling pathways, leading to a weaker effect.[41]

Lohmander et al reported in 2014 that intra-articular (IA) sprifermin administration did not improve medial tibiofemoral cartilage-thickness over 12 months quantified by MRI (n=168) possibly as follow-ups were too short for detection of the full disease-modifying effect of treatment.[39] However, a significant dose-dependent response was detected in total and lateral tibiofemoral cartilage-thickness and radiographic JSW over 12 months. The authors speculated that the dynamic loading implicated in predominantly medial tibiofemoral involvement seems to impede attempts to prevent cartilage loss or regenerate cartilage tissue. Sprifermin had no major local or systemic adverse events compared with placebo. Conference abstracts published in 2015 and 2016 reported the structure-modifying effects on cartilage thickness and bone marrow lesions (BMLs) on MRI on 12-month follow-up, using post-hoc analyses of the same study.[42,43]

In another clinical trial in which Sprifermin was administered up to 300 µg for advanced knee OA, it was reported in 2016 that no significant benefits were detected for cartilage outcomes on histology, synovitis, effusion, BMLs on MRI and JSW on X-ray. However, the study was underpowered as MRI was only available in 30 out of 52 patients and the follow-up period was only 24 weeks, which may be too short for capturing the structure-modifying effects.[44]

In a 5-year, phase 2 dose-finding, multicenter randomized clinical trial [FGF18 Osteoarthritis Randomized Trial with administration of Repeated Doses (FORWARD) study], the effects of Sprifermin on changes in total femorotibial joint cartilage thickness (n=549) on MRI was evaluated at 2-year follow-up (NCT01919164). Hochberg et al reported in 2019 that three once-weekly IA injection of 100 µg sprifermin provided a significant improvement in total femorotibial joint cartilage thickness [0.05 mm (95% CI, 0.03 to 0.07 mm)] for participants administered every 6 months and [0.04 mm (95% CI, 0.02 to 0.06 mm)] for participants administered every 12 months, compared with the placebo saline injection provided every 6 months (−0.02 mm).[45] No significant improvement in total WOMAC scores was detected, compared with placebo. The most frequently reported treatment-emergent adverse event was arthralgia and showed no difference from the placebo group (43%). An exploratory analysis of the same study at 3 year-follow-up (n=442) reveals significant differences (0.05 mm [95% CI, 0.03–0.07 mm]) in total femorotibial joint cartilage thickness over MRI between Sprifermin (100 µg of Sprifermin every 6 months) and placebo (saline every 6 months).[45] However, the clinical significance of a 0.05-mm increase of cartilage thickness in this study remains unclear in terms of reducing risk for knee replacement, delaying time towards knee replacement, or both.[46] No significant change in total WOMAC scores in this study may be attributed to using intra-articular saline injections as a control since the IA saline injection may act as an active placebo,[47] masking symptomatic benefits. In addition, a large number of patients with low baseline pain and/or high baseline cartilage thickness may result in a potential "floor effect" on symptoms as 32% of this study had <40/100 points on WOMAC pain score at baseline and 50% had medial minimum joint space width (mJSW) >4.0 mm on baseline X-rays. Therefore, analysis of a more selective subgroup, featuring baseline characteristics associated with rapid structural and symptomatic OA progression should be investigated. In a 2019 ACR conference abstract, it was reported that in a "subgroup at risk" (n=161) of structural and symptomatic progression with a baseline medial or lateral mJSW between 1.5 and 3.5 mm and WOMAC pain score of 40–90 out of 100, WOMAC pain was significantly improved on 3 year follow-up [−8.8 (−22.4, 4.9)] in the group administered with the 100 µg Sprifermin (n=34) compared with the placebo (n=33)[48] suggesting that, in this subgroup, the drug effect

reaches the absolute minimal clinically important improvement for the WOMAC pain subscore which ranges 6–9.[49]

In a recent 2020 paper using a post-hoc analysis of the same data from the FORWARD study, thinning/thickening scores and ordered values of femorotibial cartilage thickness change on MRI over 24 months were analyzed by applying location-independent (ie not region-specific) analysis methodology in the knee joint.[50] With administration of 100 µg Sprifermin every 6 months cartilage thickening is more than double [856µm (717 to 996) vs 356µm (313 to 398)] and cartilage thinning almost reduced to [−432µm (−521 to −343) vs −335µm (−381 to −288)] that in healthy reference subjects from the Osteoarthritis Initiative dataset (n=82). The authors concluded that the finding supported the evidence of substantial structure-protective action of Sprifermin. However, as this is a post-hoc analysis, further study will be required to confirm its structure-modifying effect.

Wnt Signalling Inhibitors

At a molecular level, the regulation of Wnt signalling determines osteoblast and chondrocyte lineage specification and their homeostasis.[51] Increased Wnt signaling predisposes MSCs to an osteogenic lineage fate and induces generation of metalloproteinases which can cause cartilage degradation in OA.[52] Increased expression and activation of the Wnt pathway in articular cartilage chondrocytes in OA similarly promotes cartilage degradation, while elevated Wnt signalling in subchondral bone enhances bone formation and sclerosis.[53–55] Therefore, pharmacological modulation of Wnt signaling might have potential benefits in repairing osteochondral dysregulation detected in OA disease process. Moreover, increased Wnt signaling in the synovium may potently lead to the OA progression via increased production of MMPs as well as activation of osteoclast differentiation and enhanced subchondral bone turnover.[56,57]

Lorecivivint (SM04690) is a small-molecule CLK/DYRK1A inhibitor that blocks Wnt signalling at the transcriptional level.[58] It showed induction of chondrogenesis and reduction in cartilage degradation in preclinical studies.[58–60] In a 52-week, multicenter, phase-2 trial (n=455) (NCT02536833), the primary end point, a significant improvement in the WOMAC pain score compared with placebo at week 13, was not met, compared with IA placebo saline injection, However, at 52-week follow-up, intra-articular administration of 0.07 mg demonstrated a significant benefit in pain and functional scores [between-group difference versus placebo, −8.73, 95% CI (−17.44, −0.03) and −10.26, 95% CI (−19.82, −0.69)], as well as improvement in mJSW on X-rays [between-group difference versus placebo, +0.39 mm, 95% CI (0.06, 0.72)] in patients with unilateral knee OA. Serious adverse events were reported in 17 (3.7%) patients.[61] The most common SAEs included infections and cardiac disorders and were deemed unrelated to the study drug by the investigators.[62]

Another phase-2 trial evaluated in 700 patients for 24 weeks was completed (NCT03122860) where the 0.07 mg lorecivivint treatment group demonstrated more favorable reductions in both WOMAC indices as compared with placebo.[63] Recently, the investigators reported the safety data after the combined analysis of the two trials, which included 848 Lorecivivint-treated and 360 control subjects in total. The incidence of adverse effects or serious adverse effects was similar in treatment (41.3% and 2.4%) and control groups (38.3% and 1.1%), respectively. The most commonly reported AE in both groups was arthralgia (7.6% vs 7.2%).[64] Two small phase-2 (NCT03727022, NCT03706521) and three phase-3 (NCT03928184, NCT04385303, NCT04520607) trials are still active.

Transforming Growth Factor- β

Transforming growth factor-β (TGF-β) induces extracellular matrix protein synthesis and modulates cartilage development. A variety of TGF-β signalling pathways are crucial for early cartilage growth, maintaining cartilage homeostasis in later life and may also possess anti-inflammatory and immunosuppressive properties.[65] Impaired TGF-β function in cartilage might be related to an increased susceptibility to OA.[66] However, the biological effect of TGF-β is under complex control, and may switch from being protective in normal joints to detrimental in OA as a result of changes in the predominant cell-surface receptors and intra-cellular signalling pathways in various joint tissues (cartilage, bone, synovium).[67] In addition, osteocyte TGF-β signaling could regulate the osteogenic and osteoclastic activity of mesenchymal stem cells and may be associated with the remodeling of subchondral bone in advanced OA.[68]

TissueGene-C (TG-C) uses a cell-mediated cytokine gene therapy approach and includes non-irradiated allogeneic human chondrocytes and irradiated allogeneic human GP2-293 cells in a ratio of 3:1, retrovirally transduced to promote TGF-beta1 transcription (hChonJb#7

cells).[69–71] A recent study reported as a possible mechanism of action that TG-C induced an M2 macrophage-dominant pro-anabolic micro-environment in a rat model, thereby providing a beneficial effect on cartilage regeneration.[72] At one-year follow-up after a single IA administration, there were significant improvements in pain, sports activities and quality of life but structure-modifying effects on the cartilage were insignificant (n=156).[73] In a phase-2 trial (NCT01221441) including 57 patients in the treatment group and 29 patients in the placebo group, the TG-C administration caused less progression (47.9% vs 34.6%; adjusted RR 0.7, 95% CI 0.5–1.1) of cartilage damage than placebo over 12-months.[69] In a phase-3 trial (NCT02072070) which included 163 patients, symptomatic benefit was detected.[74]

The two pivotal phase-3 trials (NCT03203330, NCT03291470) had been on hold in April 2019 while the regulators were investigating chemistry, manufacturing, and control issues related with the potential mislabeling of ingredients.[75] This clinical hold was lifted in April 2020, and trial enrollments have been reinitiated later in 2020.[76] Recently, analysis of the safety data from an observational long-term safety follow-up trial showed that there is no evidence to suggest that injection of TG-C was associated with increased risk of cancer nor generated any long-term safety concerns over an average 10 years.[71]

Senolytic Therapies

Senescence is characterized mainly by altered responses to cellular stress and proliferation arrest of cells.[77] Senescent cells (SnCs) are a newly implicated factor in the OA pathogenic process[78] by promoting pathological age-related deterioration via the production of proinflammatory cytokines, chemokines, extracellular proteases, and growth factors (termed the senescence-associated secretory phenotype (SASP))[79] and altering the function of neighbouring cells (termed secondary or paracrine senescence).[80] Therefore, senotherapeutics which are directed at SnCs are an emerging therapy for treating diseases related to ageing. Senotherapeutics can be classified into of 3 types: 1) senolytics which kill and destroy SnCs selectively; 2) senomorphics which modulate or even reverse the phenotype of SnCs to those of young cells by blocking SASP; 3) senoinflammation, the immune system-mediated clearance of SnCs.[81] Several senolytic pharmaceutical drugs such as Fisetin and UBX0101 are emerging.

Fisetin is a polyphenol extracted from fruits and vegetables and shows potential senolytic and anti-inflammatory activities.[82] Fisetin inhibited IL-1-induced MMP13 and ADAMTS5 expression in human OA chondrocytes in vitro, and reduced cartilage damage along with subchondral bone thickening and synovitis in a mouse OA model induced by destabilization of the medial meniscus (DMM).[83] Two phase-2 clinical trials (NCT 04210986, NCT04815902) are under investigation in patients with knee OA and estimated to be completed in 2022 and 2025, respectively.

UBX0101 is a small molecule inhibitor of the MDM2/p53 protein interaction, which possesses a potent senolytic candidate. In a preclinical study, UBX0101 improved chondrogenesis in human OA tissue in vitro, and in an anterior cruciate ligament transection (ACLT) OA model in mice UBX0101 attenuated SnCs by stimulating apoptosis, and reduced cartilage damage and joint pain.[84] The amount SnCs in human OA synovial tissues positively correlated with knee pain, disease severity and synovitis severity.[85] A phase-1 study (n=48) revealed that a single intra-articular injection of UBX0101 at different doses up to 4 mg had a favorable safety profile and dose-dependent, clinically meaningful improvements in pain on Numeric Rating Scale (0–10) [−3.95 (95% CI, −4.74, −3.16)] and WOMAC function [−1.05 (95% CI, −1.36,-0.74)] compared with placebo injection. Recently, UNITY Biotechnology announced 12-week data from UBX0101 Phase-2 Clinical Study (NCT04129944) which did not detect a significant change in pain and function in 183 patients with painful knee OA.[86] A follow-up observational study of the previous trial (NCT04349956) was terminated in November 2020 due to failure to meet the trial outcomes.

Bone-Driven Endotype

Subchondral change in OA involves an uncoupled remodelling process, which is characterized by both increased osteoblast activation and bone formation but simultaneously macrophage infiltration and osteoclast formation.[87] Activation of osteoclasts can result in pain genesis through developing acidic conditions at the osteochondral junction, thereby activating acid-sensing receptors of sensory neurons.[88,89] Subchondral bone also undergoes remarkable alterations in both composition and structural organization, leading to adverse effects on the overlying articular cartilage.[90] Therefore, targeting the pathways that modify subchondral bone turnover is an attractive option for DMOAD research.[89] The

pharmaceutical drugs in phase 2 and 3 stages of development for bone-driven endotype are summarized in Table 2.

Cathepsin K Inhibitor

Cathepsin K is a cysteine protease which induces bone resorption and cartilage damage through the breakdown of key bone matrix proteins.[91,92] Cathepsin K knock out mice had attenuated cartilage damage in OA induced by DMM, and inhibition of Cathepsin K in rabbits by daily oral dosing with L-006235 reduced cartilage damage and subchondral bone remodelling in an ACLT model of OA.[93,94]

MIV-711 is a selective cathepsin K inhibitor, and in a 6-month phase 2 clinical trial (NCT02705625) (n=244), significantly reduced femoral bone disease progression and reduced cartilage loss, although there was no improvement in pain outcome.[95] Infrequent musculoskeletal symptoms, infections and rashes were reported. A further 6-month open-level extension study showed the maintenance of structural benefit with symptomatic improvement (n=50).[96] However, as most of the participants in the extension substudy were selected because their symptoms did not worsen, a treatment benefit may be due to positive selection bias.[95]

Parathyroid Hormone (PTH)

Recombinant human PTH, teriparatide, is a 1–34 amino-acid fragment acquired from human PTH). Its anabolic action on bone production is used for osteoporosis management. In OA, it exhibits the ability to maintain articular cartilage health,[97] stimulate the synthesis of extracellular matrix and induce chondrocyte proliferation in pre-clinical injury-induced OA models.[98] PTH can increase subchondral bone mineral density, which could exert a negative effect on OA progression. In this sense, PTH could be an excellent drug in OA patients with osteoporosis and low subchondral sclerosis.[99] Additionally, intermittent parathyroid hormone treatment attenuates OA pain in a DMM model, in association with inhibiting subchondral sensory innervation, subchondral bone deterioration, and articular cartilage degeneration.[100] A phase-2 study is currently ongoing to evaluate the efficacy of PTH in knee OA participants (NCT03072147).

Matrix Extracellular Phosphoglycoprotein (MEPE)

TPX-100 is a novel 23-amino-acid peptide derived from MEPE, a member of the Small Integrin-Binding Ligand, N-linked Glycoprotein (SIBLING) protein family, involved in subchondral bone remodeling.[101] TPX-100 provided symptomatic improvements in patellofemoral OA knees administered with 4 weekly 200 mg injections compared with placebo injection in the contralateral knees (n=93), but only 14% of knees showed changes in cartilage thickness/volume measured on MRI over 12 months with no evidence of structural modification. No drug-related SAEs occurred in this study.[102] Another 2020 OARSI conference abstract reported a statistically significant decrease in pathologic bone shape change in the femur at both 6 and 12 months using 3D femoral bone shape change.[103]

Antiresorptive Drugs: Bisphosphonates and Denosumab

Antiresorptive drugs have shown reduction in bone remodeling and improvement in trabecular microarchitecture and bone mineralization. In clinical trials investigating the structure-modifying effects of bisphosphonates (alendronate, risedronate, zoledronic acid), the results are inconsistent across the studies and their outcomes presented a great heterogeneity.[17,104] In a recent systematic review including preclinical studies (n=26) over the past two decades (2000–2020), these drugs showed better chondroprotective effects at high doses with a dose-dependent manner as well as depending on the timing of treatment initiation in relation to OA stage (time-dependency).[105] Therefore, these agents may still be of potential benefits in certain OA endotypes with high rates of subchondral bone turnover. This phenotype-dependency has been demonstrated in pre-clinical research, where bisphosphonates are differentially effective in reducing pain and not only bone but also cartilage pathology in OA models with high versus low bone turnover.[106–109] Recently, clodronate (n=74)[110] and neridronate (n=64)[111] have been successfully used for the treatment of knee and hand OA, with an interesting efficacy on BMLs, although the sample sizes are small. An individual patient data meta-analysis for examining their efficacy in specific knee OA subtypes is still ongoing.[112]

In a multicentre, randomised controlled trial involving knee OA patients with significant knee pain and MRI-detected BMLs (n = 223), 2 annual infusions with 5 mg of zoledronic acid (the most potent of all bisphosphonates) did not significantly reduce cartilage volume loss, knee pain or BML size although the study was designed for detecting effects on the bone-driven subgroup with BMLs

Table 2 The Registered Phase 2/3 Clinical Trials on Compounds with Potential Disease-Modifying Effects on Subchondral Bone

Drug Class/ Compound	Drug in Development	ClinialTrials. gov Identifier	Company	Structure	Targeted Tissue	Mechanism of Action	Route	OA site	Stage of Development
Cathepsin K inhibitors									
	MIV-711	NCT02705625	Medivir		Subchondral bone	Inhibiting the breakdown of key bone matrix proteins	Oral	Knee	Phase 2 (completed in May 2017 (n=244)
		NCT03037489	Medivir				Oral	Knee	Phase 2 (completed in Nov 2017 (n=50)
Parathyroid hormone (PTH)									
	Teriparatide	NCT03072147	University of Rochester	Recombinant 1–34 amino-acid fragment of human parathyroid hormone (PTH)	Subchondral bone	Subchondral bone remodelling	S/C	Knee	Phase 2 (recruiting; estimated completion at Oct 2022) (n=76)
Matrix extracellular phosphoglycoprotein (MEPE)									
	TPX-100	NCT01925261	OrthoTrophix (USA)	A 23-amino acid peptide derived from extracellular matrix phosphoglycoprotein	Subchondral bone	Subchondral bone remodelling	IA	Knee	Phase 2 (completed in Sept 2016) (n=120)
		NCT02837900	OrthoTrophix (USA)				IA	Knee	Phase 2 (completed in Aug 2017) (n=14)
Anti-resorptives									
	Zoledronic Acid	NCT04303026	Martina Hansen's Hospital		Subchondral bone	Subchondral bone remodelling	IV	Hip	Phase 3 Estimated completion at March 2022 (n=70)
	Denosumab	NCT02771860	University Hospital, Ghent	Humanized monoclonal antibody that binds to RANKL	Subchondral bone	Subchondral bone remodelling	S/C	Hand	Phase 2 Active, not recruiting Estimated completion at May 2021 (n=100)
Vitamin D		NCT04739592	CSPC Ouyi Pharmaceutical Co., Ltd.		Subchondral bone	Inducing proteoglycan synthesis and bone mineralization	Oral	Knee	Phase 4 Estimated completion at July 2024 (n=60)

Abbreviation: RANKL, receptor activator of nuclear factor kappa B ligand.

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which may likely have potential benefits from this therapy.[113] It was noted that more knee replacement procedures were performed in the zoledronic acid group compared with the placebo group (9% vs 2%) in contrast with other population-based studies.[114,115]

Another study involving Osteoarthritis Initiative (OAI) female participants (n=346) showed that bisphosphonate therapy may be protective of radiographic knee OA progression in non-overweight patients with early-stage OA.[116] Currently, a Phase 3 study (NCT04303026) to examine its effects in hip OA is ongoing. A phase 2 study examining the effects of another anti-resorptive, denosumab, in hand OA is expected to finish in 2021 (NCT02771860).

Vitamin D

Vitamin D has a direct impact on cartilage by inducing proteoglycan synthesis in mature chondrocytes,[117] and enhances chondrocyte viability and reduces their inflammatory cytokine synthesis through activating AMPK/mTOR and autophagy.[118] Active vitamin D administration reduced cartilage degradation and inflammation in models of OA in mice and rats induced by meniscal injury/meniscectomy and ACLT.[118–120] Out of two recently published systematic reviews, one review showed the association of vitamin D deficiency with knee OA in patients but inconsistent evidence for its role in the prevention of incidence and progression of radiographic OA,[121] while the other argued that inconsistent results may be attributed to factors such as severity of knee OA, baseline level of serum vitamin D, duration of treatment, and vitamin D dosages.[122] There is a need for multicentric and well-conducted randomized studies using larger samples to determine its efficacy. A small Phase 4 clinical trial is currently active (NCT04739592).

Synovitis-Driven Endotype

Synovial inflammation (synovitis) is an important contributing factor to the OA pathogenesis through increased local production of pro-inflammatory cytokines, chemokines, and mediators of joint tissue damage[123,124] which may be amenable to a range of anti-inflammatory drugs commonly used in inflammatory rheumatic diseases. The pharmaceutical drugs in phase 2 and 3 stages of development for inflammation-driven endotype are summarized in Table 3.

Diacerein

Diacerein is a purified anthraquinone derivative. It involves an inhibitory action on IL-1β and its signalling pathway, possesses an anticatabolic effect on OA tissues and reduces generation of metalloproteases.[125] In animal models of OA (sheep meniscectomy, canine ACLT, rabbit ACLT and partial meniscectomy) diacerein has generally shown limited long-term effect on cartilage composition or pathology, but some evidence of reducing synovitis.[126–129] In a 2014 Cochrane review, the authors concluded that diacerein demonstrated only a minimal symptomatic improvement in patients with unclear benefits in JSW on X-rays, compared with placebo. Diarrhoea was the main adverse event with an absolute difference of 26%.[130]

The EMA's Pharmacovigilance Risk Assessment Committee suspended diacerein across Europe in 2013 due to its harms overweighing benefits,[131] and then re-evaluated the drug in 2014, suggesting that 'it remain available with restrictions to limit risks of severe diarrhoea and hepatotoxicity'.[132] In 2016, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) reported that diacerein had efficacy similar to that of NSAIDs with slower onset of action, suggesting that it might have some benefits for patients with contraindication to NSAID.[133]

Recently, results of a phase-3 clinical trial (NCT02688400) were reported where the authors explored the comparative efficacy and safety of diacerein vs celecoxib in patients with moderate and severe knee OA using a non-inferiority trial design [(6-months of diacerein 50 mg once daily for 1 month and twice daily thereafter (n = 187), or celecoxib 200 mg once daily (n = 193)]. Diacerein was non-inferior to celecoxib in reducing pain, stiffness, or functional limitations. The diacerein group had a higher number of emergent AEs (26.3%) compared with the celecoxib group (17.4%), mainly due to higher diarrhoea events (10.2% vs 3.7%). One patient in the diacerein group had three SAEs (abdominal pain, elevated transaminase and gamma-glutamyl transferase, collectively suggestive of hepatitis) which resolved spontaneously following drug withdrawal.[134]

Anti-Inflammatory Agents (Targeting IL-1, TNF-α)

In in vitro and in vivo preclinical studies, interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), IL-6, IL-15, IL-17, and IL-18 exhibit pro-inflammatory actions, leading to the initiation and progression of cartilage damage and joint inflammation.

Table 3 The Registered Phase 2/3 Clinical Trials on Compounds with Potential Disease-Modifying Effects on Inflammation

Drug Class/ Compound	Drug in Development	ClinialTrials.gov Identifier	Company	Structure	Targeted Tissue	Mechanism of Action	Route	OA Site	Stage of Development
Anti-IL-1									
	Gevokizumab (XOMA-052)	NCT01683396	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	Inflammation	Neutralizing IL-1β	S/C	Hand	Phase 2 (completed in Feb 2014) (n=91)
		NCT01882491	XOMA (USA)						Phase 2 (completed in Feb 2014) (n=87)
	AMG108	NCT00110942	Amgen (USA)	A fully human, immunoglobulin subclass G2 (IgG2) monoclonal antibody to IL-1R1	Inflammation	Inhibiting IL-1	S/C	Knee	Phase 2 (completed in Nov 2005) (n=160)
	Lutikizumab (ABT-981)	NCT02087904	AbbVie (USA)	A dual variable domain immunoglobulin (DVD-Ig) of the IgG1/k	Inflammation	Neutralizing IL-1α and IL-1β	S/C	Knee	Phase 2 (completed in Dec 2016) (n=350)
		NCT02384538	AbbVie (USA)				S/C	Hand	Phase 2 (completed in July 2016 (n=132)
	Anakinra	NCT00110916	Amgen Inc	7-[[2-(2-amino-1,3-thiazol-4-yl)-2-(2,2-dimethylpropanoyloxymethoxyimino) acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid	Inflammation	Interleukin-1 receptor antagonist	IA	Knee	Phase 2 (completed in Feb 2005 (n=165)

(*Continued*)

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Table 3 (Continued).

Drug Class/ Compound	Drug in Development	ClinialTrials.gov Identifier	Company	Structure	Targeted Tissue	Mechanism of Action	Route	OA Site	Stage of Development
	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	Inflammation	Neutralizing IL-1β	IA	Knee	Phase 2 (completed in July 2011) (n=169)
	Diacerein	NCT02688400	TRB Chemedica International SA (Switzerland)	2-Anthracenecarboxylic acid, 4.5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo- (9CI)	Inflammation	Inhibiting the production and activity of IL-1	Oral	Knee	Phase 3 (completed in Dec 2019) (n=380)
Anti-IL-6									
	Tocilizumab	NCT02477059	Assistance Publique - Hôpitaux de Paris	Interleukin-6-Receptor Inhibitor			IV	Hand	Phase 3 (completed in Feb 2019) (n=104)
DNA plasmid with IL10 transgene									
	XT-150	NCT04124042	Xalud Therapeutics, Inc.	-	Inflammation	Suppresses proinflammatory cytokine activity	IA	Knee	Phase 2 Recruiting and estimated completed in Feb 2022 (n=270)
Anti-TNF									
	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	Inflammation	Binds specifically to TNF-α and blocks its interaction with endogenous TNF	S/C	Hand	Phase 2 (completed in 2009)

		ACTRN12612000791831	Abbott Australasia Pty Ltd and University of Tasmania						Phase 3 (Completed in Nov 2015) (n=42)
	LY3016859	NCT04456686	Eli Lilly and Company	High-affinity humanized IgG4 monoclonal antibody		Antibody that binds to key residues in the C-terminal regions of TGF-α and epiregulin, preventing their binding to the EGFR	IV	Knee	Phase 2 (recruiting and estimated to be completed in Sept 2022) (n=125)
	Etanercept	NTR1192					S/C	Hand	Phase 2 (completed in 2017) (n=90)
	Infliximab	NCT01144143					IA	Knee	Phase 4 (Completed in Jan 2011) (n=16)

Abbreviations: EGFR, epidermal growth factor receptor; TGF, transforming growth factor.

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So far, IL-1β and TNF-α have been the most extensively studied cytokines in pre-clinical research.[135,136] Despite this favorable evidence in animal OA models, most clinical trials investigating the disease-modifying effects demonstrated by inhibitors of IL-1 and TNF-α in OA patients failed to meet the primary and secondary endpoints such as in cases of Gevokizumab (XOMA-052),[137] AMG108,[138] Lutikizumab (ABT-981),[139,140] anakinra,[141] adalimumab[142–144] and etanercept.[145] In a meta-analysis evaluating the efficacy of disease-modifying anti-rheumatic drugs in OA, neither IL1-inhibitors nor TNF-inhibitors possess symptomatic benefits irrespective of the joint site affected or the inflammatory phenotype (erosive or non-erosive OA).[146]

These failed trial results may suggest the implication of a more complicated interaction among various cytokines in the OA pathogenic process. One of the reasons for failure may be that the clinical trials were designed to detect an effect on symptoms rather than on joint structure, which is conversely the main outcome evaluated in preclinical studies, or that they are underpowered or have not followed participants for long enough to find meaningful structural effects such as proposed in the recent CANTOS trial.[147] In a recent exploratory analysis of the CANTOS trial involving patients with elevated high-sensitivity C-reactive protein (hs-CRP) levels ≥2 mg/L and a history of myocardial infarction (n=10061), IL-1 inhibition using canakinumab may render a substantial reduction of THR/TKR rates as well as OA-related symptoms on an averaged 3.7 years follow-up.[147] Although the study had some positives such as a large sample size and long-term follow-up, it was not primarily designed to investigate the DMOAD efficacy of canakinumab and many relevant OA outcomes were missing, necessitating further confirmatory studies.

Tocilizumab

IL-6 can increase the risk of radiographic OA and associated with knee cartilage damage,[148] suggesting the potential role of low-level inflammation in the pathogenesis of OA. IL-6R blockage with tocilizumab contributes to cartilage preservation and increases bone volume in a mouse model of ischemic osteonecrosis,[149] and reduced cartilage lesions, osteophyte formation and synovitis in DMM-induced OA in mice.[150] However, male IL-6 knock out mice have increased cartilage damage and age-related OA.[151] In local joint tissues, IL-6 classic signaling produces structure-protective effects, while trans-signaling leads to catabolic effects.[152] This finding might suggest that selective inhibition of IL-6 trans-signaling could be a superior treatment strategy as this may inhibit deleterious IL-6 effects in OA, while maintaining protective IL-6 signaling via the classic pathway.[153] Recently, in a phase-3 trial evaluating the efficacy of tocilizumab in hand OA for 12 weeks (n=104), it revealed no more effectiveness than placebo for pain relief (−7.9 vs −9.9 on VAS score in the tocilizumab and placebo groups).[154]

XT-150

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that potently and broadly suppresses proinflammatory cytokine activity. It also possesses chondroprotective effects, via reduced production of matrix metalloproteases[155] as well as inhibition of chondrocyte apoptosis.[156] Therefore, IL-10 could have potential benefits in OA management, both for pain improvement and suppression of the cartilage-damaging processes. Currently, there is a phase-2 clinical trial evaluating the safety and efficacy of a single injection of XT-150 (a plasmid DNA with a variant of human IL-10 transgene) in patients with knee OA (NCT04124042), and it is estimated to be complete in 2022.

Perspectives

In this section, we briefly put forward the reasons for failures in OA clinical trials and possible steps to overcome these barriers (Figure 2).

Regulatory Approval for DMOADs

The drug will be required to demonstrate symptomatic benefits (pain and/or function) coupled with structural modifications to meet regulatory requirements as a disease-modifying agent.[19,20] To date, no agent has been approved by the regulatory agencies.[17] Some argue that the improvements in structural change (in the absence of any meaningful symptomatic benefits) should be a meaningful target for approval, in and of itself. However, this is unlikely to meet consumers needs as their primary reason for clinical presentation relates to symptomatic complaints.[30]

On the other hand, OA is a slowly progressive disease and only 14% of patients with incident OA have measurable disease progression over a 1-year period (Figure 2).[157] Therefore, structure-modifying effects using targeted therapy would be optimal to delay or even avoid disease worsening and joint replacement. In OA, symptom-structure discordance is often described.[158] Analysis of data from the Osteoarthritis Initiative revealed that changes in bone structure over 2 years do not translate into pain worsening

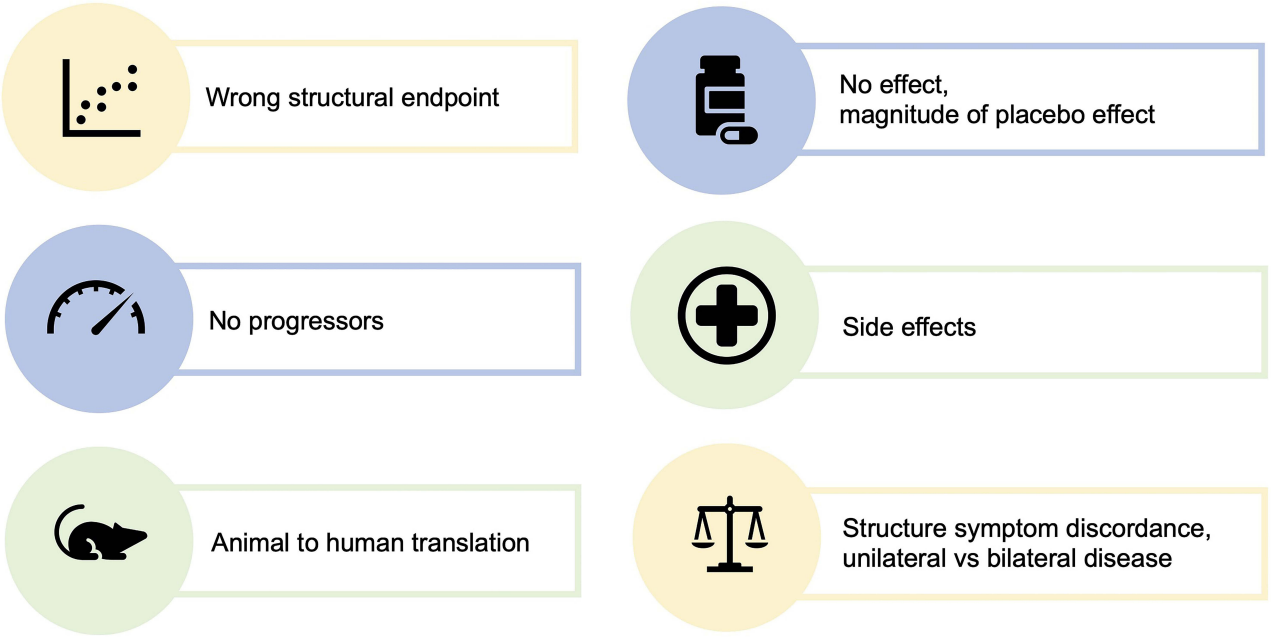

Figure 2 Reasons for DMOAD trial failures.

until 4 years,[159] suggesting that a structure-modifying drug may need longer follow-up to detect symptomatic benefit. In addition, a variety of disease outcomes using different OA subtypes (genotypes, phenotypes and endotypes) are needed to demonstrate the ability of a structure-modifying drug to directly predict for symptomatic benefits to overcome the regulatory hurdles.[18]

In addition, FDA's formal recognition of OA as a serious disease paves the way for using surrogate outcome measures for regulatory approval of DMOADs under accelerated approval regulations. However, two challenges need to be addressed: 1) selection/qualification of appropriate surrogate outcome measures, and 2) appropriate designs for post-marketing confirmatory studies. To overcome the first challenge, the Foundation for NIH (FNIH) OA Biomarkers Consortium initiative was established.[160] For addressing the second challenge, Kraus et al proposed two major study design scenarios: 1) prospective trial continuation which continue all patients on initial drug allocation into the post-marketing approval trial until a failure threshold is achieved; and 2) separate post-marketing approval study which use different study population administered with active treatment only.[161]

Imaging Tools Development

The imaging standard in OA clinical trials has been radiographically measured mJSW which is notoriously unresponsive to change as well as possessing several other drawbacks such as issues with alignment, positioning and assuming JSW as the composite contribution of changes in other structures in this heterogeneous OA with multiple-tissue involvement.[162,163] Therefore, utilization of this insensitive-to-change measure may limit our opportunity to detect any modification in what oftentimes is a slow-moving disease.

In 2015 OARSI published recommendations related to the applications of knee imaging in knee OA trials to set standards and improve quality assurance.[164] Although a range of different MRI approaches have been developed to evaluate changes in overall joint structure,[165–167] further validation studies and evaluation of their clinimetrics are required to gain acceptance by regulatory authorities as a suitable surrogate endpoint which is the focus of the FNIH OA Biomarkers Consortium.[160]

In addition, the emergence of approved surrogate outcomes would allow pharmaceutical companies to examine the efficacy of the DMOADs in a shorter duration of clinical trials and reduce drug development costs. In this way, there is a possibility of instituting accelerated approval based on surrogate imaging endpoints and post-marketing approval studies to prove the longitudinal benefit-to-harm profile and the durability of the potential new therapies.[161]

Issues of Total Knee Replacement as an Endpoint

In the study design for post-marketing approval which uses observational outcomes such as time-to-event of joint replacement surgery, considerable barriers exist in terms of need for large sample sizes due to low annual incidence rates (1.6–11.9%),[14] long study follow-ups (>5 years at least),[46] and the impact of non-disease and other subjective factors on the outcome (ie, comorbidities and/or age of the patient, costs, insurance cover, etc.).[168,169] There is a lack of universal consensus criteria for guiding patient recommendations regarding joint replacement surgery, leading to differences even among treatment centres within the same region. These issues need to be adequately addressed by study design.[161] There is a need for developing a criteria set to define appropriateness for total knee replacement or a virtual total knee replacement.[170]

Drug Delivery System for IA Therapies

Instead of utilizing the systemic route of administration which may produce undesirable systemic toxicity and off-target effects, many of the agents in the development pipeline are focused on an intra-articular route for drug delivery. This can also potentially enhance the local bioavailability, thereby maximizing therapeutic effects locally in the joint with a higher safety profile compared to systemic exposure.[171] On the other hand, the marked placebo effect generated by local intraarticular administration is well-documented in the literature,[172] making the assessment of symptom efficacy more challenging.[30]

Another issue related with the intra-articular therapy is that drugs have a short residence time within the joint.[171,173] To overcome this barrier, a variety of drug delivery systems were proposed to prolong drug residence time while providing a stable concentration within the therapeutic window, leading to a reduction of side effects and better patient compliance.[174] It remains unclear how long particular drugs have to remain in the joint for a meaningful symptomatic relief and/or structure-modification after an intra-articular administration. An ideal drug delivery system should comply with adequate disease modification, biocompatibility, and biodegradability while responding to its physiological environment.[175]

Placebo Effects of IA Saline

In the randomized clinical trials for IA drugs, saline is commonly used as the placebo in the control group. A recent meta-analysis examining the effects of IA saline in 50 clinical trials (n=4076) revealed significant improvement of pain severity on 0–100 VAS up to 6 months [−13.4 (−21.7/−5.1)] and WOMAC function sub-score [−10.1 (−12.2,-8.0)]. The pooled responder rate after saline injections using the OMERACT-OARSI criteria is 48% at 3 months and 56% at 6 months,[47] challenging the concept of saline being a "mere" placebo.[176] However, there is no evidence supporting hypotheses advocating the disease-modifying role of saline injection. Future scientifically robust studies which examined the effects of sham injections compared with saline injections are required to shed new light on this issue.

The IA therapies show a considerably larger therapeutic effect after the adjustment for the effects of IA saline, suggesting an inappropriate underestimating of the true effect of the active medication.[177] Further research is required to determine the underlying mechanisms and the factors influencing the placebo response and ways to overcome it. In addition, the mechanisms of pain genesis in OA are poorly understood and thought to involve a complex interaction among local pathological processes in the OA joint and neuronal mechanisms and alterations of pain processing (ie central sensitization, especially in advanced OA).[178] Further studies should focus on the effects of these interactions on the outcomes in the placebo-controlled clinical trials. It is also necessary to strictly report in each clinical trial what placebo has been used as well as the presence or absence of any additional blinded clinical evaluator, even more, if considering clinical trials with intra-articular therapies.

Combination Therapy

As OA is a heterogeneous disease with a combination of different endotypes in varying degree at different stages of the disease process, a "one size fits all approach" using a single therapeutic agent targeting a single target within a single endotype may be unlikely to succeed in the management of OA.[179] Therefore, as in the oncology therapeutic area, combinations of drugs targeting different hallmarks of OA pathogenic process should be considered. Further research examining the potential synergistic action of combining anabolic therapies with those that downregulate catabolic factors will be required.

Personalized Medicine

OA is well known for marked variations of disease expression,[180] involves a variety of tissue pathologies as

a whole joint disease[16] and presents with different pathobiological manifestations,[181] suggesting the potential value of personalised and precision medicine from the treatment perspective. Personalized medicine is used for treatment focusing on the patient based on their individual clinical characterization, considering the diversity of symptoms, severity, and genetic traits.[182] In precision medicine, the molecular information maximizes the accuracy with which the patients are categorized and treated, typically applying large amounts of data for identification of patient subtypes which possess sharing specific relevant characteristics to predict diagnosis, progression, or treatment response, and to utilize appropriate therapeutic targets.[183] The use of precision medicine in OA remains limited.

The implementation of private/ public initiatives, such as the Osteoarthritis Initiative, the FNIH biomarkers consortium, the European APPROACH ((Applied Public-Private Research enabling OsteoArthritis Clinical Headway)) project have contributed greatly to moving the field forward. Clinical phenotypes, endotypes, and molecular and imaging biomarkers are being identified, but the exact interplay among them and underlying mechanisms of each remain to be elucidated.[24] While these biomarkers may have potential benefits in detecting those patients with the greatest risk for structural progression, their use still needs to be translated into more efficient clinical trial design and widespread clinical application.[184]

Conclusion

There remains an immense unmet need for effective and safe targeted interventions to inhibit both pain and disease progression. The complex overlapping interplay among the pathobiological OA processes and heterogeneity of clinical presentations of patients with OA, call for a universally accepted classification of phenotypes and endotypes for developing targeted disease-modifying therapy and providing the appropriate treatment in clinical setting. Although challenges exist towards the eventual management of OA by applying the concepts of personalized and precision medicine, the lessons learned through failed clinical trials, the ongoing developments of more advanced imaging and sophisticated biomarkers tools and effective drug delivery systems are leading to substantial progress in our field.

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