Disease modification in osteoarthritis: are we there yet?

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ABSTRACT
A disease-modifying osteoarthritis drug (DMOAD) is a drug that modifies the underlying OA pathophysiology and potentially inhibits the structural damage to prevent or reduce long-term disability with potential symptomatic relief. The focus of this narrative review is on describing the state of the field for disease-modifying pharmacologic agents that are in late-stage development—specifically phase 2/3.

Introduction
Osteoarthritis is an extraordinary prevalent and disabling disease (1). It can be viewed as the structural and functional failure of the synovial joint and occurs when the dynamic equilibrium between breakdown and repair joint tissues becomes unbalanced. This progressive joint failure (the “disease”) may occur with pain and disability (the “illness”) and it is the symptomatic consequences that drive clinical presentation. Traditionally the management of osteoarthritis has been constrained to symptom modification. The Holy Grail for many within the field is the development of agents that not only assist with symptom management but also modify the structural course of the disease. In recent years, there has been substantial progress made in our understanding of osteoarthritis and the application of new methodology and refined imaging that have made substantial incremental gains in the road towards successful disease modification.

The focus of this narrative review is on describing the state of the field for disease-modifying pharmacologic agents that are in late-stage development—specifically phase 2/3. For readers interested in agents that are in an earlier stage of development, they would be encouraged to read the relevant topic in the current supplement (Malfait and Tortorella: DMOAD and analgesics, the mechanisms/science behind it) (2).

in addition to other recent review papers (3-5). Furthermore, this narrative review may not be comprehensive of every drug development programme; the field is advancing rapidly and a data-search of all individual national clinical trial registries was not conducted.

Overview of disease modification
A disease-modifying osteoarthritis drug (DMOAD) is a drug that modifies the underlying OA pathophysiology and potentially inhibits the structural damage to prevent or reduce long-term disability with potential symptomatic relief (6). However, there exist a number of rate-limiting challenges that have slowed progress including the multifactorial nature and complex pathogenesis of OA disease process and the well-recognised symptom-structure discordance (7). Therefore, patient’s clinical characteristics, OA phenotypes, joint involved, choice of structural endpoints and study duration are critical to capture when investigating efficacy in DMOAD clinical trials (6).

Regulatory guidance from the Food and Drug Administration (FDA) of United States (US) (8) and the European Medicines Agency (EMA) (6) determined that the approval of a DMOAD requires inhibition of loss in knee or hip joint space width (JSW) on plain radiograph with relevant symptomatic benefit. Only a small subset of OA patients undergo radiographic progression on x-rays, which necessitates long term follow-up as well as large sample-sizes in DMOAD trials (9). In addition, determining what change in JSW is clinically relevant to the OA patient is still an area of debate (7). So far, no potential disease-modifying drugs have completed a phase 3 trial and proven to have structural benefits which are clinically meaningful with an acceptable safety profile. Accordingly, no DMOAD has as yet been approved by regulatory bodies such as the EMA or FDA (5).

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Overview of disease-modifying therapies in phase 2/3 development

Data search and selection
We conducted manual and electronic searches on the https://clinicaltrials.gov/ to identify ongoing clinical trials in phase 2/3 stage of drug development. In addition, electronic searches in the PubMed and Embase via Ovid for published phase-2/3 clinical trials of these emerging drugs were also conducted from inception of these databases to 31st May 2019 by using these MESH or keywords: osteoarthritis OR osteoarthritis AND pharmacological treatment/ OR disease modification/ OR disease-modifying osteoarthritis drugs/ OR DMOAD/ OR structure modification. This narrative review will highlight on these ongoing clinical trials related to Fibroblast Growth Factor (FGF-18), Tissue gene, Wnt Inhibitor, parathyroid hormone and Diacerein (Table I).

Fibroblast growth factor (FGF-18) (Sprifermin)
Fibroblast growth factor (FGF-18) uses a chondrocyte-driven principle of cartilage repair and regeneration to halt or reverse OA disease process. FGF-18 is involved in chondrogenesis and promotes extracellular matrix production mediated by fibroblast growth factor receptor-3 (FGFR-3) (10-12). In addition, intra-articular injection stimulates dose-dependent cartilage regeneration in a rat OA model (13). At the cellular level, intermittent exposure may transiently stimulate an anabolic effect, while continuous administration may induce other signalling pathways producing a weak effect (12).

Sprifermin is a truncated product of recombinant human fibroblast growth factor 18 (rhFGF18). The intra-articular (IA) injection of sprifermin did not meet the primary endpoint of improving medial tibiofemoral cartilage-thickness evaluated by quantitative MRI. However, it showed a significant dose-dependent response on total and lateral tibiofemoral cartilage-thickness on quantitative MRI and radiographic JSW over 12 months (n=168) (14). The study design was not powered to analyse the symptomatic benefit and did not show any separation of symptom effects between placebo and treatment groups. It had a good safety profile with no major local or systemic adverse events compared with placebo. The authors speculated that the dynamic loading implicated in predominantly medial involvement seems to impede attempts to halt cartilage loss or regenerate cartilage (14). There are reports from post-hoc analyses of the same study that demonstrated the improvement of cartilage and bone marrow lesions (BMLs) on MRI over 12 months (15, 16).

Another research group did not find significant improvements in cartilage outcomes on histology, synovitis, effusion, BMLs on MRI and JSW on x-ray even though sprifermin was administered up to 300 μg for advanced knee OA who had planned for knee arthroplasty, perhaps due to the small sample size (MRI is available only for 30 patients and JSW of 52) and the short follow-up period (24 weeks) (17). Currently, a 5-year phase-2 clinical trial (NCT01919164) is expected to be finished in 2019 with the primary endpoint using MRI cartilage thickness, and secondary endpoints using minimum joint space width (mJSW) and WOMAC. The initial data showed significant improvement of cartilage measures on MRI with 50% improvements in WOMAC total score on 2-year follow-up after 6-monthly 100 μg IA sprifermin (n=549) (18). The 3-year follow-up data demonstrated the maintenance of this symptomatic and structural benefit with an acceptable safety profile (19). In a post-hoc analysis in a patient sub-group (161 out of total 549, 29%) at risk of disease progression defined as baseline minimum JSW of 1.5–3.5 mm and WOMAC pain measure ≥40, pain improvement was significantly improved at 3-year follow-up compared to placebo (20).

TissueGene-C
Transforming growth factor-β (TGF-β) signaling pathway is involved in cellular differentiation and growth, extracellular matrix protein synthesis and chondrogenesis (21). Activities of TGF-β signalling pathways are implicated in early cartilage development and maintenance of cartilage homeostasis in later life. Genetic association studies reveal the critical role of TGF-β signalling pathway in OA pathogenesis (22). TissueGene-C (TG-C) is a cell and gene product comprising non-transformed and transduced chondrocytes in a ratio of 3:1, retrovirally transduced to over-express TGF-beta1 transcription. At one-year following a single IA injection, it demonstrated significant symptomatic improvement in pain, sports activities and quality of life although cartilage benefits were not significant (n=156) (23). In a phase-2 trial (NCT01221441) involving 29 patients in placebo group and 57 in treatment, the treatment group showed less progression (47.9% vs. 34.6%; adjusted RR 0.7, 95%CI [0.5–1.1], p=0.077) of cartilage damage compared to placebo on 12-month follow-up (24). A phase-3 trial (NCT02072070) reported symptomatic improvement with a trend of structural benefits (n=163) (25). There are two phase-3 trials (NCT03203330, NCT03291470) which recently registered, but are currently on hold while further investigations from the regulators are conducted on chemistry, manufacturing, and control issues (26).

Wnt Inhibitor
Wnt signalling has played a substantial role in OA disease process, especially remodelling of the subchondral bone and chondrocyte lineage specification (27) and induced protease production such as matrix metalloproteinases (MMP) by synovial tissue and chondrocytes (28) as a response to injury which is the main trigger of OA pathogenesis (29).
SM04690 is an intra-articular (IA) inhibitor of Wnt pathway, and it was evaluated in a 52-week, multicenter, phase-2 randomised placebo-controlled trial in 455 patients having moderate to severe knee OA (NCT02536833). The published 2017 ACR conference abstract reported that 0.07 mg administration demonstrated a significant improvement in pain and functional scores, as well as mJSW, compared with placebo at 26 and 52 weeks in subjects with unilateral knee OA. Serious adverse events, all deemed unrelated to SM04690, were reported in 17 (3.7%) subjects (30).
participants has completed with results pending (NCT03122860) while two other small phase-2 trials were commenced in late 2018 (NCT03727022 and NCT03706521).

**Parathyroid hormone (PTH)**
Recombinant human PTH, teriparatide, is a 1-34 amino-acid fragment derived from human PTH. It has anabolic action on bone formation and is useful for osteoporosis. PTH has demonstrated articular cartilage maintenance (31), stimulation of matrix synthesis and leads to the proliferation of chondrocytes (32) in animal models of injury.

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### Table I. DMOAD undergoing the phase-2 and phase-3 clinical trials of drug development in osteoarthritis at clinicaltrials.gov

<table>
<thead>
<tr>
<th>Drug Class/ Compound</th>
<th>ClinicalTrials.gov identifier</th>
<th>Company</th>
<th>Targeted tissue</th>
<th>Mechanism of action</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblast Growth Factor (FGF-18)</td>
<td>NCT01919164</td>
<td>Merck KGaA (Germany)</td>
<td>Cartilage regeneration and repair</td>
<td>stimulating chondrogenesis and cartilage matrix production through fibroblast growth factor receptor-2 and 3</td>
<td>Phase II (active, not recruiting; estimated completion date in May 2019) n=549</td>
</tr>
<tr>
<td>Wnt/b-catenin signalling pathway inhibitors</td>
<td>NCT03122860</td>
<td>Samumed LLC (USA)</td>
<td>Cartilage catabolism</td>
<td>induction of protease production, especially matrix metalloproteinases</td>
<td>Phase II (completed in April 2018 with no results posted) n=700</td>
</tr>
<tr>
<td></td>
<td>NCT02536833</td>
<td>Samumed LLC (USA)</td>
<td>Cartilage catabolism</td>
<td>induction of protease production, especially matrix metalloproteinases</td>
<td>Phase II (completed in April 2017 with no results posted) Presented in EULAR 2018 n=455</td>
</tr>
<tr>
<td></td>
<td>NCT03727022</td>
<td>Samumed LLC (USA)</td>
<td>Cartilage catabolism</td>
<td>induction of protease production, especially matrix metalloproteinases</td>
<td>Phase II (Recruiting started November 2018 and estimated to be complete in December 2019) n=100</td>
</tr>
<tr>
<td></td>
<td>NCT03706521</td>
<td>Samumed LLC (USA)</td>
<td>Cartilage catabolism</td>
<td>induction of protease production, especially matrix metalloproteinases</td>
<td>Phase II (Recruiting started in July 2020) n=15 Single group assignment</td>
</tr>
<tr>
<td>Gene Therapy</td>
<td>NCT01221441</td>
<td>TissueGen, Inc. (USA)</td>
<td>Cartilage regeneration</td>
<td>stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage</td>
<td>Phase II (completed in 2014)</td>
</tr>
<tr>
<td></td>
<td>NCT02072070</td>
<td>Kolon Life Science (South Korea)</td>
<td>Cartilage regeneration</td>
<td>stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage</td>
<td>Phase III (completed in 2015)</td>
</tr>
<tr>
<td></td>
<td>NCT03291470</td>
<td>TissueGen, Inc. (USA)</td>
<td>Cartilage regeneration</td>
<td>stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage</td>
<td>Phase III (Not yet recruiting) n=510</td>
</tr>
<tr>
<td></td>
<td>NCT03203330</td>
<td>TissueGen, Inc. (USA)</td>
<td>Cartilage regeneration</td>
<td>stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage</td>
<td>Phase III (recruiting started in October 2018 and suspended due to CMC identity concern in April 2019)</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>NCT03072147</td>
<td>University of Rochester</td>
<td>Subchondral bone</td>
<td>Subchondral bone remodeling</td>
<td>Phase II (recruiting; estimated completion at 2021) n=80</td>
</tr>
<tr>
<td>Interleukin-1 inhibitor</td>
<td>NCT02688400</td>
<td>TRB Chemedica International SA (Switzerland)</td>
<td>Inflammation</td>
<td>inhibiting the production and activity of IL-1</td>
<td>Phase III (Active, not recruiting and estimated to be completed in late 2019) n=380</td>
</tr>
<tr>
<td>Cathepsin K inhibitor</td>
<td>NCT02705625</td>
<td>Medivir (Sweden)</td>
<td>Potent, selective cathepsin K inhibitor</td>
<td>Inhibiting the proteolytic enzymes in bone and cartilage</td>
<td>Phase II (completed in 2017)</td>
</tr>
</tbody>
</table>
induced OA. A phase-2 study is currently recruiting knee OA participants (NCT03072147).

**Diacerein**
Diacerein is a purified anthraquinone derivative (33). It has an inhibitory action on IL-1 and metalloproteases production (33). In a 2014 Cochrane review including 10 clinical trials with a total of 2210 patients, the authors concluded that there was only a minimal symptomatic benefit when diacerein was compared with placebo. Improvement in JSW was also minimal or unclear for hip and knee OA respectively. The main adverse event was diarrhoea with an absolute difference of 26% (34).

In addition, in 2013, the EMA’s Pharmacovigilance Risk Assessment Committee suspended it across Europe due to harms outweighing benefits (35), and then re-examined the drug in 2014, recommending that it remain available with restrictions to limit risks of severe diarrhoea and hepatotoxicity (36). In 2016, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) reported that the diacerein showed the efficacy similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) with slower onset of action, and better efficacy compared with paracetamol, concluding that it may be beneficial in patients with contraindication to NSAID or paracetamol (37). A phase-3 clinical trial is currently recruiting participants with knee OA (NCT02688400).

**Cathepsin K inhibitor**
Cathepsin K is the predominant proteolytic enzyme of osteoclasts stimulating bone resorption by cleaving type I collagen (38). It is also involved in the cleavage of type II collagen and aggrecan of cartilage matrix (39). MIV-711 is a selective cathepsin K inhibitor which is currently being developed as a potential DMOAD. In a 6-month phase 2 clinical trial (NCT02705625) involving 244 patients with KL grade 2 and 3, it revealed a significant reduction in femoral bone disease progression, as well as reduced loss of femoral cartilage thickness although symptomatic improvement was not significant. Generally, it had good tolerability and safety, although there were infrequent musculoskeletal symptoms, infections and rashes (40). In a 2019 OARSI conference abstract, a further 6-month open-level extension study including 50 patients demonstrated the maintenance of structural benefit with symptomatic improvement (41).

**The challenges of disease modification**
The prior section highlighted the fact that we have several trials in late-stage development. Many have learned the lessons from previous trial failures but it is important to continue to recognise them so that they do not get repeated (42) (Fig. 1).

To garner regulatory approval as a disease-modifying agent, the agent will need to demonstrate clinically meaningful benefits on symptoms (pain and/or function) with improvements in structure. To date, no agent has met the hurdles set by the regulatory authorities there are substantial hurdles imposed by the disease itself. Historically, many trials have focused on end-stage disease in which the mechanics of the joint environment, which play a pivotal role in disease pathogenesis are likely to overwhelm any pharmacologic agents efforts to preserve the joint tissue (45). We have repeatedly cured osteoarthritis in preclinical models but have failed to translate that into the human condition, in part because one does not mimic the other; many of our animal models are young, male injured joints whereas the human disease is female predominant, typically in older adults and in the absence of recent injury (46). OA is a chronic slowly progressive disease, and only 4% of OA patients with stable disease and up to 14% with incident OA have measurable progression over a 1-year period (47).

Our measurement tools (both for measuring symptomatic change and joint

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**Fig. 1. Reasons for DMOAD trial failures.**
space width on a plain radiograph) are notoriously unresponsive limiting our opportunity to detect what oftentimes is a slow-moving disease (48-50).

A number of steps are being taken to overcome these hurdles. Alternate preclinical methods that more closely mimic the human condition to assess efficacy in humans are highly desirable (51). It is important to recognise the complexity of osteoarthritis—both in terms of the risk factors for the aetiopathogenesis of the disease as well as the multitude of tissues involved. Stratification of different subtypes of osteoarthritis and tailoring treatment to specific categories of disease is more likely to have therapeutic benefits (52). Recognising that this is a whole organ disease (53) and realising that focusing on reducing damage to cartilage in and of itself is unlikely to lead to meaningful improvements in other joint tissue structures that are meaningfully involved in osteoarthritis (including the synovium, bone, meniscus and muscle) is important. Similarly, simply slowing catabolic processes while not doing anything to accelerate repair undermines our opportunity to see meaningful effects (54).

Many of the agents being developed are focused on an intra-articular route of administration as opposed to systemic pharmacotherapy. This may have advantages in minimising systemic toxicity and an enhanced safety profile by reducing off-target effects. This also potentially enhances the local bioavailability and bypasses conventional barriers associated with systemic delivery. It is however, important to recognise the marked placebo effect from local intra-articular administration (55) making the assessment of efficacy more challenging.

Because of the insights gained from previous trials and their application in modern designs we are making substantial progress. The value of private/public initiatives, such as the Osteoarthritis Initiative, the European AP-PROACH (Applied Public-Private Research enabling OsteoArthritis Clinical Headway) project, the FNIIH biomarkers consortium (56) have contributed greatly to moving the field forward.

Improvements in the precision of technology applied to measurement lead to the successful development of effective therapies for osteoporosis and it is pleasing to say that we now have similarly effective tools in osteoarthritis that are being applied in clinical trials (57).

We hope, with some of the current efforts these markers will reach qualification status by the regulators and further enhance clinical trial efficiency.

Additional steps that are assisting in overcoming some of the prior barriers including recognition of osteoarthritis as a serious disease (58) may have assisted in encouraging the development of more recent guidance by the FDA and was acknowledged; “OA can be a serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability” (7). With this recognition, there is a possibility of instituting accelerated approval based on surrogate endpoints and post-marketing confirmatory studies under new FDA regulations (59).

Conclusion
There remains an immense unmet need for effective and safe therapeutic interventions to manage both pain, in addition to targeting disease progression. Despite the numerous challenges discussed DMOADs are an attractive target; our enhanced ability to diagnose the disease earlier, phenotype those with different types of disease (60), apply sophisticated biomarkers to measure change over shorter intervals and target therapies more accurately are leading to substantial progress in our field. In part by virtue of learning from our previous failures, a number of agents targeting the complex pathology known as osteoarthritis are showing promise in late-stage clinical trials.

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