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Osteoarthritis today: Lost in translation?

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A B S T R A C T

Osteoarthritis (OA) is a highly prevalent joint disease that is associated with pain, loss of function, and high direct and indirect economic costs. The current therapeutic options are inadequate, providing only a moderate symptom relief without the possibility of disease modification. While treatment options and personalized medicines are increasing for many complex diseases, OA drug development has been impeded by the advanced state of disease at the time of diagnosis and intervention, heterogeneity in both symptoms and rates of progression, and a lack of validated biomarkers and relevant outcome measures. This review article summarizes the OA landscape, including therapies in development as potential OA treatments, potential biomarkers undergoing evaluation by the US Food and Drug Administration, and a summary of current OA treatment guidelines, with a particular focus on the knee OA.

Aging-related diseases

Advancements in science and medicine have significantly altered the global burden of disease (BOD). Whereas communicable diseases historically drove BOD, the COVID-19 pandemic aside, non-communicable diseases now account for the majority of burden, at 60% [1]. Aging-related diseases account for the highest proportion of current BOD, but the impact is reduced in many conditions by the evolution of treatment paradigms, leading to improved outcomes. For example, cardiovascular disease

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(CVD) is now identified prior to myocardial infarction by biomarkers that guide subsequent treatment decisions [2,3]. Furthermore, in oncology, improved diagnostics using biomarkers allow for personalized medicine and improved outcomes when a specific biomarker can be paired with a targeted treatment [4].

In contrast, osteoarthritis (OA) is increasing its share of BOD by both an increase in prevalence (rising to 9.6% between 1990 and 2017) and impact of disability, costing 1–2.5% GDP [5]. OA is the third most rapidly rising condition associated with disability, behind diabetes and dementia. OA is associated with an increase in both all-cause and cardiovascular disease-associated mortality [6]. The current treatment guidelines highlight a lack of treatment options that are sufficient for symptom modification, and there are currently no disease-modifying OA drugs approved by the FDA.

OA has previously been considered a disease of cartilage wear and tear, but it is now broadly understood to be a disease of the whole joint, impacting not only articular cartilage but also bone, fibrocartilage, and synovium (Fig. 1) [7]. The difficulty in developing treatments is impacted by its heterogeneous etiology and the typically advanced level of disease at the time of diagnosis. The treatment challenges are further exacerbated by a lack of biomarkers to identify an earlier disease, to predict prognosis, to match specific pathology to a patient to personalize medicine, or to assess response. Biomarkers of risk/susceptibility, diagnosis, prediction, and prognosis are needed to characterize the disease further and identify potential gateways for drug intervention [8] (See Fig. 2).

It is interesting to contrast the difficulty in treating OA with the successes observed in a parallel disease such as osteoporosis. Both conditions begin clinically silently and manifest over years. However, the pathologies are quite different, with osteoporosis pathologically characterized in the subchondral trabecular bone by loss of horizontal plates and intact maintenance of rods, whereas in OA, the horizontal plates remain and rods are lost. Osteoporosis can now be identified early as screening is universally recommended for females > 65 years and males 70 years, as well as earlier for those with known risk factors. Osteoporosis can, therefore, be treated prior to initial fracture by monitoring bone mineral density and circulating biomarkers.

In contrast, knee OA is not usually identified until the disease is well established. Clinical signals often begin as stiffness and intermittent pain, with the symptoms becoming more constant, severe, and debilitating [9]. Diagnosis may be complicated by heterogenous sources of pain as the initial activity elicited peripheral pain, sometimes leading to central sensitization. For most chronic diseases, including CVD, osteoporosis, and rheumatoid arthritis, earlier identification and intervention have led to improved outcomes. The threshold of early OA symptoms evolving into “illness,” i.e., impacting the quality of life, still needs to be defined. Similar to other chronic diseases, earlier intervention with yet-to-be-developed disease-modifying drugs, ideally at a presymptomatic stage, may render OA more amenable to treatment prior to irreversible structural changes and eventual joint replacement. Note that conservative lifestyle interventions, such as programs prescribing weight loss and physical activity, have been shown to positively impact OA symptoms and quality of life [10]. The field needs to identify progressors earlier, and, to accomplish this, the identification of biomarkers is crucial.

Biomarkers

The lack of validated biomarkers is an obstacle to the successful treatment of OA as this adds complexity to the diagnosis, prognosis, and measurement of treatment success. The FDA has a framework to support a systematic approach to biomarker development [8]. The FDA's Biomarkers, Endpoints, and other Tools (BEST) program categorizes these as markers of.

- Susceptibility/risk
- Diagnostic
- Monitoring
- Prognostic
- Predictive
- Pharmacodynamic/response
- Safety

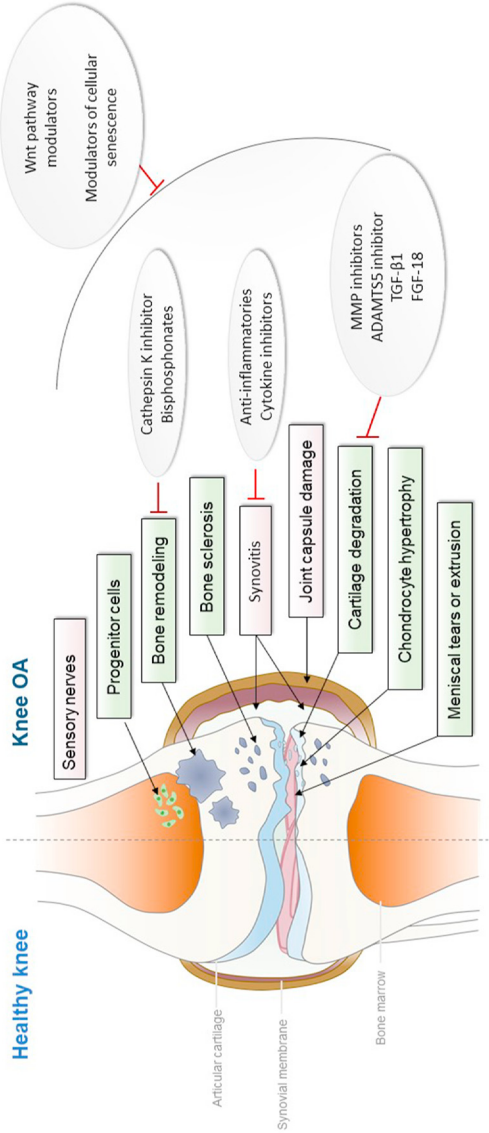

Fig. 1. Osteoarthritis as a disease of the whole joint.

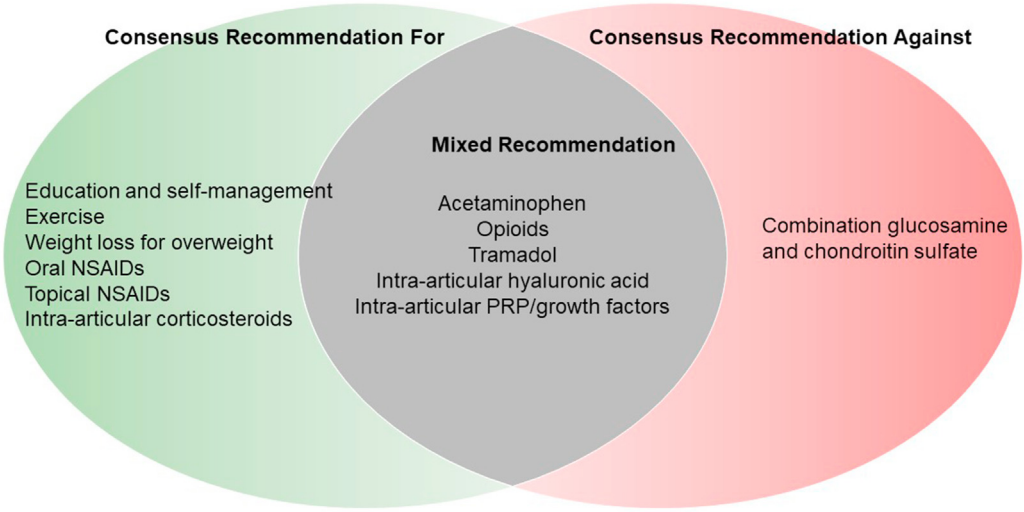

Fig. 2. OA treatment guidline agreement.

The FDA, acknowledging the unmet drug development need for the treatment of knee OA, has accepted 5 "letters of interest" to date supporting the development of biomarkers in OA into their Biomarker Qualification Program (BQP) from different sponsors, as outlined in Table 1. Two of these are focused on imaging, two are composite measures incorporating both imaging and patient-reported outcomes (PROs), and one focuses on a panel of soluble biomarkers; all measures were accepted with a prospective context of use to allow for prognostic enrichment of clinical trials. All these biomarkers require additional studies for validation.

To date, researchers have emphasized on imaging and soluble biomarkers. Historically, radiographic changes in OA joints have been staged by joint space width (JSW), Kellgren–Lawrence (KL) grade, or Osteoarthritis Research Society International (OARSI) joint space narrowing (JSN) grading [11]. These radiographic evaluations have been used to establish the presence and progression of OA. For example, changes in JSW over 3 years have shown some value in predicting total knee replacement, but these are based on retrospective analyses and have limited prognostic value [12]. Newer techniques using machine learning and semi automated software to extract fractal signature analysis of bone texture show promise in predicting OA progression from plain radiographs, with prognostic ability improved by the addition of clinical information [13]. Further validation of these methods is ongoing, with a letter of intent accepted into the FDA BQP to further qualify trabecular bone analysis as a prognostic biomarker.

Over the past decades, there has been an increasing emphasis and interest in the value of MRI outcomes as a biomarker. Semi quantitative measures have attempted to encompass the whole joint, with the Whole Organ Magnetic Resonance Imaging Score (WORMS) and MRI Osteoarthritis Knee Score (MOAKS) incorporating bone marrow lesions (BMLs), osteophytes, cartilage defects, meniscal pathologies, and meniscal extrusion [14,15]. Thresholds for OA progression have been published for MOAKS, and it is another potential biomarker working through the FDA BQP process [16].

Cartilage has been widely studied as a tissue of interest. There has been some evidence that cartilage thickness has concurrent validity for symptomatic (WOMAC pain) and radiographic (JSW) progression, but the association is modest and lacks predictive validity [17,18]. Compositional measurement of cartilage such as T1rho and T2* mapping provides insight into cartilage hydration, proteoglycan content, and collagen organization [19]. The alterations shown by compositional MRI may allow for the detection of cartilage damage prior to morphological changes, but the performance characteristics linking a change in compositional MRI to a change in clinical outcome have not yet been quantified.

In addition to the bone measures extracted from radiographs, 3D bone shape as captured by MRI and analyzed by machine learning has been proposed as a tool to characterize OA pathology [20]. The

Table 1
Proposed OA biomarkers accepted into the FDA Biomarker Qualification Program.

	Proposed biomarker	Context of use	Status
Tufts/McAlindon	End-stage KOA score (esKOA) is defined by 1) a knee with KL grade = 4 with moderate intense pain (Likert WOMAC pain + function >11) or 2) a KL grade <4 with intense or severe pain (WOMAC pain + function >22) and limited mobility or instability	Prognostic biomarker panel for use in clinical trials with subjects with a diagnosis of knee osteoarthritis to identify patients who are likely to experience long-term disease progression to esKOA defined as requiring knee replacement surgery."	LOI accepted December 2019
Tufts/McAlindon	Cumulative Damage score and Disease Activity score Cumulative damage score: A MR-based composite score calculated from measures of articular cartilage damage at pre-specified informative locations distributed across medial and lateral distal femur, proximal tibia, and patella and localized using a 3-dimensional cartilage mapping application. Disease activity score: A MR-based composite score calculated from standardized measures of bone marrow lesion volumes and effusion-synovitis volume	Prognostic enrichment imaging biomarker panels for use in clinical trials with subjects with a diagnosis of knee osteoarthritis to identify patients who are likely to experience long-term disease progression based on Kellgren-Lawrence (KL) grade, the WOMAC pain subscale, and/or radiographic lateral joint space narrowing (JSN)	LOI accepted September 2019
FNIH/Cush	Trabecular bone texture (TBT) biomarkers (n = six) from fractal signature analysis (FSA) curves generated from the tibial subchondral region of plain knee radiographs; the six biomarkers are the vertical filter (VF) intercept, VF linear slope, VF quadratic slope, horizontal filter (HF) intercept, HF linear slope, and HF quadratic slope.	Prognostic enrichment imaging biomarker panel for use in phase 2 and 3 clinical trials to identify individuals with a diagnosis of knee osteoarthritis who are likely to experience disease progression within the subsequent 48 months based on the WOMAC pain subscale and/or radiographic joint space width loss and/or joint replacement.	LOI accepted February 2020
FNIH/Cush	Osteoarthritis prognostic biomarkers as assessed by immunoassays: [urinary = u, serum = s] uCTXII, sPIIANP, and uC2C-HUSA (derived from COL2A1); sNTXI, uNTXI, sCTXI, uCTXIalpha, and uCTXIbeta (derived from COL1A1); and Hyaluronan (PDB name: 3HYA)	Prognostic enrichment molecular biomarkers for use in phase 2 and 3 clinical trials to identify individuals with a diagnosis of knee osteoarthritis who are likely to experience disease progression within the subsequent 48 months based on the WOMAC pain subscale and/or radiographic joint space width loss and/or joint replacement."	LOI accepted February 2020
FNIH, Menetski	11 knee joint magnetic resonance imaging (MRI) markers under five major MRI feature groups be qualified by FDA as prognostic biomarkers for the enrichment/identification of subjects with knee osteoarthritis who are likely to experience long-term (up to 36 months) disease progression in the absence of treatment.	Prognostic enrichment imaging biomarker panel for use in phase 2 and 3 clinical trials with subjects with a diagnosis of knee osteoarthritis who are likely to experience long-term (up to 36 months) disease progression based on the WOMAC pain subscale and/or radiographic lateral joint space narrowing (JSN).	LOI accepted May 2019

shape of the femur changes as OA progresses, developing osteophytic ridges and widening and flattening of the articular surfaces. Conversion of this shape into a single metric value, termed a B-score, may be able to quantify OA status and predict progression, similar to a T-score in osteoporosis.

BMLs, captured in the semi quantitative MRI WORMS and MOAKS scores, may underlie cartilage-bone crosstalk in an OA joint [21]. BMLs may appear prior to overt joint degeneration, thereby serving as an early marker of OA. Furthermore, BMLs collocate with areas of cartilage loss and are associated with structural progression and OA pain. Specificity of BMLs may be a limitation in that not all OA patients will have BMLs on MRI, while some non-OA knees do [22,23]. Further evaluation of BMLs as a potential biomarker for risk/susceptibility is therefore warranted.

It is worth noting that while the synovium likely plays an important role in OA development and progression, imaging of the synovium has been rarely discussed as a biomarker. Synovial hypertrophy and fluid volume can be captured by MRI, but it is best imaged using a contrast agent, creating an additional barrier to routine clinical use. Synovial volume on contrast-enhanced MRI has shown a treatment response to intra-articular (IA) corticosteroid treatment; hence, there is a possibility that synovitis could serve as a pharmacodynamic biomarker of treatment response [24]. Synovitis also has a strong association with both OA symptoms and structural progression, and similar to BMLs, it may occur before other overt signs of OA. As synovitis is a sign of active inflammation, it is possible that biochemical markers of acute inflammation may serve as a proxy. Serum, urine, and synovial fluid have been screened to identify biochemical markers indicative of an inflammatory endotype of OA [25,26]. The use of a panel of these as prognostic biomarkers for clinical trial enrichment is undergoing evaluation through the FDA BQP.

The use of biomarkers to identify specific endotypes (disease subtypes defined by specific molecular mechanistic pathways leading to a clinical phenotype) of OA may be a key development in advancing OA drug development [27]. As the progression of OA is inherently variable, it may be necessary to study the development of different etiologies independently. For example, an analysis from a phase 2 study found that participants with a lower PRO-C2, a marker of type II collagen formation, had a greater response to the cartilage anabolic agent sprifermin, suggesting the potential of a matched endotype and treatment to improve outcomes. Retrospective analyses have suggested decreased total knee replacements associated with patients on metformin for diabetes [28] and canakinumab for CVD (Schieker et al., 2020); these results suggest that modulating metabolic and inflammatory burden might have a protective effect on subsets of OA patients whose comorbidities are driving their OA progression, without improving outcomes in a more heterogenous population [30–32]. However, these associations require formal prospective trials to validate these hypotheses.

Evaluation of OA progression is complicated by individual heterogeneity and the long time span over which it occurs. One potential for enriched progression is the subset of patients with post-traumatic OA (PTOA). PTOA accounts for 12% of all OA and is associated with earlier disease onset [33]. Following a traumatic injury such as anterior cruciate ligament (ACL) rupture, the incidence of OA is estimated to be between 50 and 87% [33,34]. This is a subpopulation of OA that shows defined changes over years instead of decades, with changes as early as 6 months post-injury associated with the markers of cartilage damage at 2 years [35]. Thus, PTOA provides a good clinical model to study OA and define the relationships between specific biomarkers for risk, progression, and ideally positive response to treatment. As the end phenotype of OA looks similar in terms of changes in bone shape and cartilage damage, it is reasonable to believe that these biomarkers may offer value over a longer time scale to model generalized OA as well.

Clinical trial challenges

Operational trial challenges

Without an outcome (monitoring/pharmacodynamic) biomarker, OA clinical trials must focus on the outcomes of how a patient feels, functions, or survives (joint replacement). In measuring how a patient feels, pain is typically the primary outcome measured in OA clinical trials. Pain measurement is inherently problematic as it is complex and subjective. Responses to pain therapeutics will be affected by central and peripheral pain drivers, comorbidities, psychosocial factors, pain qualities, and sleep/

fatigue [36]. There are also differences in responsiveness of single and composite outcome measures. Use of pain measurement as a primary outcome in clinical trials is further complicated as the measures [37] have been developed for short-term use, but OA is a chronic disease. As we evaluate OA over the full spectrum of disease, there is a need for purpose-fit outcome measures. Pain is the hallmark symptom of OA; analgesic compounds are, therefore, a logical OA therapeutic symptomatic drug target. Recent trials targeted blockade of nerve growth factor (NGF), which seemed promising with initial studies demonstrating robust improvements in pain compared with placebo [38–40]. However, despite trial modifications to limit adverse events, these agents were unable to overcome persistent safety signals to achieve regulatory approval. Targeting the NGF receptor, tropomyosin receptor kinase A (TrkA), has yielded mixed results, showing both no effect and modest improvements [41,42]. Pain messaging has also been targeted through ablation of sensory neurons by activation of the transient receptor potential cation subfamily vallinoid member 1 (TRPV1) by either resiniferatoxin or *trans*-capsaicin [43,44]. Local injection administration is appealing as it narrowly targets the pain sensory neurons while leaving motor and proprioception intact; however, intense pain can be induced by these injections and has often required additional substantial management [45,46]. This factor opens another operational challenge for keeping these compounds blinded in a randomized controlled trial (RCT) setting.

Development of pain-targeting OA therapeutics is further hampered by a consistently high placebo response seen across OA clinical trials. In these trials, the IA placebo typically consists of saline or drug vehicle. The effect size of IA placebo on pain in knee OA has been shown to exceed the effect size of the active treatment with acetaminophen [47]. This pain placebo effect has been shown to be robust across knee OA trials, greater in magnitude than minimal clinically important differences, and often durable through 6 months [48,49]. It has been suggested that function as an outcome may be less susceptible to the placebo effect, but other reports suggest that the function placebo effect may last even longer [49,50]. Studies comparing sham with placebo injections have provided evidence that these strong IA placebo effects are in fact contextual or are because of ritual/procedure of the injection rather than because of any physiological benefits of saline or vehicle. These data further show that potential OA therapeutics need to demonstrate statistically significantly better responses compared with placebo in an RCT setting.

Pain and function reporting for OA is further complicated by the high prevalence (60%) of comorbidity and multimorbidity in those with OA [51]. In population surveys, OA occurs in more than one joint in 7–34% and is associated with a greater symptomatic burden [52]. Fibromyalgia may coexist in 35% of OA patients, with both conditions exhibiting altered pain processing and central sensitization, affecting symptomatic burden and efficacy of therapeutics [53]. Other musculoskeletal conditions are also more common in those with OA, such as rheumatoid arthritis (incidence 1.42%, hazard ratio [HR] 3.82 [3.5, 4.17]) and osteoporosis (incidence 5.21%, HR 1.19 [1.15, 1.23]) [51]. Mortality risk with OA is largely connected to comorbid CVD (HR 1.43, 95% CI [1.32, 1.64]), diabetes (HR 2.04 [1.87, 2.23]), and renal diseases (HR 1.14 [1.04, 1.25]) [54]. Systemic comorbidity may also impact the underlying mechanisms of OA, with examples such as metabolic syndrome potentially creating a pro-inflammatory microenvironment associated with the development of OA and estrogen deficiency associated with postmenopausal OA [55,56].

Beyond improvement in OA signs and symptoms, improvement in the health of the joint and changing disease trajectory, disease modification, has become the overarching goal of OA therapeutics. The first challenge toward achieving this is to define what OA disease modification means. To successfully develop a disease-modifying OA drug (DMOAD), the pharmacodynamic changes within the joint that will lead to clinical benefit for a patient must be identifiable and measurable. The question of what constitutes the “clinical benefit” of a DMOAD must also be addressed by drug developers. The FDA defines clinical benefit as providing evidence that a treatment has a positive impact on how a patient “feels, functions, or survives” [8]. Improving pain, the primary symptom of OA, is, therefore, a critical outcome and fundamental to how a patient feels. A beneficial change to a patient's functioning is also appropriate, along with improvements in pain, perhaps with more relevance if earlier intervention is targeted (i.e., prior to the onset of chronic pain). Trial outcomes incorporating objective functional tests and wearable technologies would be useful to measure improvements to this clinical presentation.

Finally, "survival" would be measured by a DMOAD delaying disease progression to end-stage joint disease and joint replacement, also constituting a change in disease trajectory.

Cartilage has been the target of many DMOADs in development. Sprifermin, a recombinant human fibroblast growth factor 18, has demonstrated potential as a cartilage anabolic agent, with a change in cartilage thickness of 0.5 mm seen at 2 years in participants who received 100 μg IA sprifermin every 6 months compared with placebo [57]. Unfortunately, no improvement in pain was detected within the overall trial population, but a post hoc analysis of a "subgroup at risk" did find a signal for improvement in WOMAC pain compared with placebo [58]. Confirmation in a prospective population of this effect is now underway, and, if the initial post hoc result is confirmed, it would be a positive development in support of the importance of cartilage thickness to overall OA outcomes.

Other agents targeting cartilage have been tested. A recent controlled trial (GLPG1975) that targeted the degradative enzyme ADAMTS5 failed to show an improvement in either cartilage thickness or PROs at 1 year [59]. However, the study patient population selected had moderate-to-severe knee OA (KL grades 2 and 3), which may have been a too advanced disease for the drug to demonstrate its effects. Previous trials of metalloproteinase inhibitors have also failed, while targeting of ADAMTS5 through other compounds is ongoing [60,61].

Blood is a source of many growth factors and cytokines that may positively impact knee OA. The appeal of using intrinsic growth factors to treat OA has spurred the widespread clinical use of platelet-rich plasma (PRP) and other progenitor cell cocktails, such as bone marrow aspirate concentrate, adipose-derived "stem cells," and amnion. Overall data are weak and mixed, but the lack of treatment options continues to drive demand, and the market for PRP is expected to reach $1.2 billion by 2050 [62–66]. More rigorous studies with placebo-controlled trials and standardized protocols for the formulation of these products are necessary to evaluate their efficacy in OA treatment.

Bone has also been a frequent target of DMOAD trials. Bisphosphonates showed efficacy in symptoms and structure (JSW) in pilot studies, but these failed to be replicated in larger, controlled studies [67–69]. More recent trials have focused on studying potentially a better-targeted population for bone agents by focusing on OA subjects with BMLs on MRI. Unfortunately, these trials failed to show a positive effect on either structure or PROs [70]. Cathepsin K, an enzyme mediating bone turnover, has also been targeted for inhibition, with a small phase 2 study showing a positive effect on change in bone shape at 6 months, however, without signals for clinical benefit [71]. Larger and longer clinical trials will be needed to replicate the effects on bone and to demonstrate whether this may lead to clinical benefit in the long term.

Regarding the synovium, many anti-inflammatory compounds have been tested. The role of inflammation is increasingly recognized to contribute to both pain and structural disease progression [72–74]. The anti-tumor necrosis factor (TNF) therapies, which have been foundational for changing the disease course of inflammatory arthropathies, have not shown similar success in OA. Subcutaneous adalimumab and etanercept have failed to treat painful hand OA, erosive hand OA, and knee OA with active effusion [75–77]. Interleukin-1 (IL-1) is an attractive target for an OA therapeutic because of its role in driving catabolic enzymes and synovitis, but both an IL-1α/β antibody and IL-1 receptor antagonist anakinra have failed trials in hand and knee OA [30–32,78]. These data indicate that inflammation in OA is not primarily driven by the same mechanisms as other inflammatory arthropathies. A potential signal of decreased total joint replacements was seen in a post hoc analysis from a canakinumab (anti IL-1β antibody) trial for 10,000 patients with CVD over an average of 3.7 years [29]. These post hoc data will need validation in prospective trials to establish whether the observed association was real or not. It is important to note that the subjects in the canakinumab trial were required to have elevated hsCRP to be enrolled, supporting that it may be necessary to enrich OA clinical trial populations by etiology and risk factors to decrease participant variability and better detect therapeutic signals [79].

Finally, it is important not to overlook the contribution of soft tissues in the pain and progression of OA. Quadriceps and hamstrings strength are associated with reduced knee joint pain with a possible impact on structural progression as well [80,81]. Furthermore, a recent RCT showed that physical therapy is as efficacious and cost-effective as IA corticosteroids for knee OA [82,83].

Moving from targeting tissues toward targeting pathways, the removal of senescent cells is another potential mechanism to alter the progression of OA. Accumulation of senescent cells has been

associated with many hallmarks of OA, including an increase in inflammatory cytokines and chemokines, increased degradative enzymes, and progenitor cell dysfunction; thus, the removal of these cells has therapeutic potential [84,85]. Initial promising signals were seen preclinically, and in the phase 1 trial UBX0101, a p53/MDM2 inhibitor proposed to modulate and remove senescent cells, but clinical and structural effects were not seen in a phase 2 trial [86–88]. Other senescence targeting therapies in early trials include fisetin and losartan [89–92].

The Wnt pathway is known to affect tissue turnover and homeostasis in many tissues, and the disruption of Wnt pathway signaling has been implicated in OA pathogenesis for its role in chondrocyte health and its effects on progenitor cells [93]. An IA therapy, lorecivivint, a CLK/DYRK inhibitor that is thought to modulate the Wnt pathway, is in clinical trials as a potential treatment for the pain in knee OA [94].

Trials to identify successful DMOADs will need to define an optimal population (what enrichment strategy increases the disease endotype being treated?), the clinical benefit outcome (pain and function improvement and/or delaying disease progression), and appropriate biomarkers for risk, prognosis, and response prediction.

Standard of care

Several organizations have recently reviewed their treatment guidelines for knee OA, including the American College of Rheumatology, OARSI, and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal disease in 2019; and the American Academy of Orthopedic Surgeons and Veterans Affairs/Department of Defense in 2020 [95]. Conservative non-pharmacological therapies, such as exercise and lifestyle changes, are recommended as first-line treatments in all OA treatment guidelines, with improvements noted in pain, function, and quality of life. Adherence to these programs remains a challenge in clinical practice and real life. These guidelines highlight the continued unmet need for effective pharmacological therapeutics as the only consensus-"recommended" pharmacological therapies are oral NSAIDs for hand, knee, and hip OA, with topical NSAIDs also recommended for knee OA, and IA CS for hip and knee. NSAIDs are recommended despite clinical considerations for individual patient risk and advised for usage for as shorter courses as possible, which is difficult when treating a chronically painful condition such as OA. Many other standard-of-care treatments, such as acetaminophen, tramadol, and duloxetine, received mixed evaluation, with recommendations for and against; the variation in guidelines highlights the need for shared decision-making between the patient and health care practitioner to evaluate patient-specific benefits and risks, such as for patients for whom NSAIDs are contraindicated, not tolerated, or ineffective. IA hyaluronic acid is conditionally recommended for and against, yet it is commonly used in standard clinical practice because treatment is seen as more favorable than no treatment and perhaps the contextual (placebo) benefit is worthwhile for a given patient [96]. Non-tramadol opioids are also conditionally recommended against, although data report that 9%–17% of OA patients are still receiving an opioid prescription, suggesting that this remains a treatment mainstay, frequently even as a first-line option [96–98]. IA steroids also remain standard of care despite providing only short-term symptomatic relief and continued questions regarding safety, particularly for repeat injections [99,100].

Future trends

OA is a peculiar entity. For example, the bone tissues in hand and knee OA behave differently with bony erosions common in hand OA and sclerotic thickening a feature of knee OA. These differences raise the question of whether OA is a single disease or a syndrome of many. It may be necessary to rethink its disease paradigm to achieve successful drug intervention. OA in its current clinical paradigm is considered a single disease treated with pharmacological agents for symptoms only. However, regarding OA as a heterogenous group of many clinical phenotypes, such as erosive hand OA, post-traumatic OA, mechanical OA driven by malalignment, multijoint OA, and others, may help disentangle the many mechanisms involved. Taking this concept further, characterization of endotypic OA processes at a molecular level may lead to understanding how these differing OA phenotypes develop.

Eventually elucidating which endotypic processes predominate within any single OA patient will allow potential treatment intervention at a more personalized level that may positively impact the course of the disease.

Practice points

- There remains a significant unmet clinical need for safe and effective therapies for the treatment of OA. The current standard of care is to treat symptoms only, with remaining need for disease modification, and existing medications in use have safety concerns.
- In the absence of disease-modifying drugs, the control of pain and the maintenance of function remain the main treatment goals for OA patients until joint replacement surgery becomes an appropriate option for end-stage disease of the knees, hips, and shoulders.
- Conservative lifestyle interventions such as weight loss and increasing physical activity have been shown to positively impact the quality of life for OA patients, but are difficult to adhere to over the long term as the disease progresses.
- A renewed focus on treating OA at an earlier stage of disease could improve the life span of the OA joint.

Research agenda

- It is still not definitively known whether OA is a single disease or a clinical phenotype of many underlying molecular endotypic processes. Research into different clinical presentations of OA will increase the fundamental understanding of the paradigm of OA disease.
- Progression of the status of OA treatments beyond symptomatic management and toward drugs that alter the course of the disease is hindered by the advanced stage of OA subjects currently recruited into clinical trials. Efforts to identify early and presymptomatic OA for research purposes will allow earlier intervention by treatments and increase the probability of developing more effective OA drugs.
- Development of validated molecular, imaging, and clinical biomarkers that fall within the categories defined by the FDA BEST biomarker program will enable earlier, targeted OA intervention, as well as earlier prediction of response. Development of these tools is a critical goal of current OA research to advance trial design.
- Tailored/individualized outcome measures that capture what is important to the OA patient need to be developed and validated to allow for a better assessment of relief from the chronic burden of OA within clinical trials settings.

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Declaration of competing interest

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