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REDEFINING OSTEOARTHRITIS CLINICAL DEVELOPMENT: THE EMERGING ROLE OF DISEASE-MODIFYING OSTEOARTHRITIS DRUGS

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Osteoarthritis (OA) is the most prevalent form of arthritis and represents a major and growing global health challenge.[1] In 2020, OA affected more than 600 million individuals worldwide, and its prevalence is projected to rise continually, reaching approximately 1 billion by 2050.[2] Characterized by progressive destruction of articular cartilage and the development of chronic pain, OA is responsible for substantial healthcare and socioeconomic burdens.

There are several joint-specific interventions available, including non-pharmacologic, pharmacologic, and surgical options. These interventions are designed to alleviate chronic pain, but do not alter the course of disease. Consequently, more than half of patients with moderate to severe OA report continued reductions in function and inadequate pain relief with available treatments.[3] Even total knee replacement, which can be an option for advanced cases, may not fully relieve pain and restore function. These limitations underscore a large unmet need for new and effective treatment options capable of repairing or regenerating articular tissues, treating the underlying mechanism of these diseases instead of merely attempting to manage symptoms.

RECENT ADVANCES IN OA TREATMENT: DISEASE-MODIFYING OSTEOARTHRITIS DRUGS

While pain relief can support short-term management of OA, it does not halt disease progression or prevent future worsening of symptoms. Disease-modifying osteoarthritis drugs (DMOADs) represent a new pharmacological approach to disease management with the potential to not only relieve pain, but also slow disease progression or even reverse damage that has already occurred, offering new hope to both treating physicians and their patients.

The goal of DMOAD development is to create drugs that will directly target OA mediators, such as cytokines, which contribute to the pathogenesis of OA by promoting inflammation, disrupting chondrocyte regulation, and promoting oxidative stress.[4] Progress has been made in our understanding of the underlying pathophysiology of OA, which is found to be increasingly complex. Despite these advances, no DMOADs have been approved by regulatory agencies thus far, indicating the need for continued research and innovation.

Advances in our knowledge of OA pathogenesis have led us to the understanding that many different joint tissues are involved, including subchondral bone, synovium, articular cartilage, ligaments and tendons, and the infrapatellar fat pad. Recent drug development has mainly focused on cartilage preservation or regeneration; however, despite promising preclinical findings, published clinical trial results have been disappointing thus far, and none have been approved for clinical use.[5]

These clinical trial setbacks are likely due to the numerous challenges that arise when designing and executing OA clinical trials, including:

1. **Inadequate Animal Models**

   Many preclinical studies evaluating potential DMOADs in OA animal models have demonstrated promise, but these often do not translate to clinical trial success. OA is a heterogenous disease with a complex etiology. The development of an animal model that accurately represents human OA has historically fallen short. OA is now recognized as a disease of the entire joint, yet animal models have traditionally focused on pathology in one or two tissue types, namely articular cartilage.

   Numerous animal models using different species and OA constructs (e.g., surgically or chemically induced OA, naturally occurring OA, etc.) have been developed, none of which have proven to be a truly accurate reflection of its human counterpart. For example, a chemical model of OA such as the collagenase-induced model (CIOA) has been shown to be easily reproducible and less invasive than surgically induced models, but the cartilage degradation that occurs is typically unilateral and progresses more rapidly than human OA. While naturally occurring animal OA may be a more accurate representation, this approach is more costly and time consuming.

   The ideal animal species and gender for OA research is also not well elucidated. Small animals are frequently utilized, as they reach skeletal maturity faster and are cheaper and easier to handle compared to larger animals. However, in comparison, larger animals possess joint anatomy more similar to humans. Animal age, gender, and pain-perception also vary among species and influence outcomes differently than in human counterparts. Lastly, accurate pain measurement techniques in animal models are lacking. Although more objective pain analysis in animals is emerging, they are not yet standardized for use in clinical trials.[6]

   It is well known that human OA patients frequently have a number of metabolic and cardiovascular comorbidities. To date, there are few animal models that adequately represent these comorbidities.

2. **Heterogeneity of OA Patients**

   The OA patient population is a heterogenous one; this stems from a number of various underlying disease mechanisms and as discussed above, is associated with a number of co-occurring illnesses. Many clinical trials to date have failed to take this disease heterogeneity into account, and in turn, this may have contributed to the failure of several DMOAD clinical trials. An article by Mobasheri and Loeser highlights the benefits of the stratification of OA populations based on well-defined disease subtypes and emphasizes the critical nature of this approach to the success of DMOAD clinical trials moving forward.[7] Z. Jenei-Lanzl, et al. also focus on this topic and further review the concept of defining OA subtypes by discussing phenotypes, endotypes, and theratypes of OA.[8] Although defining subcategories of OA patients remains a work in progress due to the complex nature of the disease, this work is critical to the future success of DMOAD development, as aligning patient selection with a drug's mechanism of action increases the likelihood of demonstrating a statistically significant treatment effect.

3. **Lack of Thorough Outcome Assessments Involving All Joint Structures**

   OA is increasingly recognized as a whole-joint disease involving complex interactions between articular cartilage, subchondral bone, synovium, menisci, ligaments, periarticular muscles, and inflammatory mediators.[9] Nevertheless, many DMOAD studies continue to rely predominantly on conventional radiographic endpoints, particularly joint space narrowing , which remains an indirect and relatively insensitive measure of structural progression. Such approaches may fail to detect early tissue changes or therapeutic effects occurring outside cartilage loss alone.

Magnetic resonance imaging (MRI) has substantially improved the characterization of OA by enabling semiquantitative assessment of multiple joint tissues through scoring systems such as the MRI Osteoarthritis Knee Score (MOAKS).[10] MOAKS allows standardized evaluation of cartilage morphology, bone marrow lesions, osteophytes, meniscal damage and extrusion, synovitis, and effusion, thereby providing a more holistic assessment of disease activity and progression. Importantly, several of these features, particularly bone marrow lesions and synovitis, have been associated with pain severity and future structural deterioration. However, despite their clinical relevance, such MRI-derived parameters are still inconsistently incorporated as primary or key secondary endpoints in many DMOAD trials.

In parallel, compositional MRI techniques, including T2 mapping, T1rho imaging, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), and ultrashort echo time (UTE) imaging, offer the ability to detect early biochemical and ultrastructural cartilage changes before gross morphological damage becomes evident. These techniques may identify alterations in collagen organization, proteoglycan depletion, and water content, potentially enabling earlier detection of therapeutic effects.[11] However, challenges related to standardization, reproducibility, acquisition protocols, and interpretation continue to limit their widespread implementation in multicenter clinical trials.

Another important challenge is the limited integration of patient-reported outcome measures (PROMs) with structural and biological assessments. While PROMs such as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS) pain scores, and quality-of-life instruments remain central for evaluating symptomatic benefit, discordance is frequently observed between symptom improvement and structural modification.[12] This discrepancy likely reflects the multifactorial drivers of OA pain, including inflammation, central sensitization, mechanical instability, and psychosocial factors, which are not fully captured by imaging endpoints alone.

Similarly, biological markers remain underutilized despite their validated potential to improve patient stratification, reduce heterogeneity, and provide mechanistic insight into treatment response. While structural transformations quantified by conventional radiography or MRI accumulate over months or years, biochemical markers capture real-time, high-turnover metabolic alterations within joint tissues. Integrating targeted molecular profiling across distinct pathological pathways can isolate specific OA phenotypes.

Biomarkers reflecting cartilage degradation such as C-terminal telopeptide of type II collagen (uCTX-II), COMP, and serum cartilage oligomeric matrix protein (sCOMP), provide early warning signs of mechanical matrix breakdown. These metrics can successfully isolate “fast progressors” prior to irreversible structural loss. In addition, assessing biomarkers of bone remodeling, synovial inflammation, or systemic inflammatory activity may help identify accelerated joint space narrowing and evaluate the degree of active synovitis to support precision medicine approaches in OA.[13,14,15] The absence of integrated multimodal assessments combining advanced imaging, PROMs, and biological markers therefore represents a major obstacle to accurately evaluating DMOAD efficacy and may contribute to the persistent high attrition rate observed in OA drug development.

DMOAD DEVELOPMENT EFFORTS TO DATE

Unlike traditional pain management treatments, DMOAD development focuses on the whole-joint pathology of OA and aims to halt or reverse the structural progression of OA by targeting specific pathological and molecular mechanisms. The pathogenesis of OA is complex and involves several pathological processes including cartilage degradation, subchondral bone remodeling, synovial inflammation, altered mechanotransduction, and senescence and metabolic dysfunction.[16, 17, 18] The modulation of molecular pathways such as WNT signaling, inflammatory cytokines, and mechanotransduction are promising therapies to stop or reverse structural joint damage.

WNT Signaling Pathway Modulators	The WNT pathway is a fundamental regulator of chondrocyte differentiation, cartilage homeostasis and bone remodeling.[19] In OA, the Wnt/β-catenin pathway is often dysregulated, leading to the hypertrophy of chondrocytes, the upregulation of Matrix metalloproteinases (MMPs), which contribute to cartilage degradation, reduced joint function and increased pain.[20, 21] Lorecivivint has recently been developed as an intra-articular injected small molecule to modulate the Wnt overactivation through the dual inhibition of tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and CDC-like kinase 2 (CLK2). Importantly, Phase II trials provided promising structural signals for Lorecivivint, while ongoing Phase III programs continue to navigate variable outcomes.[22, 23] Other WNT-targeting candidates remain primarily in preclinical or early-stage development, as the field faces the challenge of balancing local efficacy with systemic safety.
TRPV4 as a Mechanotransduction Target	TRPV4 is a key mechanosensitive ion channel that enables chondrocytes to sense and respond to mechanical loading, playing a critical role in regulating calcium signaling and cartilage anabolism.[24] In addition, studies showed that TRPV4 activation has chondroprotective effects on articular cartilage under inflammatory conditions.[25] Substantial efforts have recently been made to translate these findings into therapeutic strategies targeting TRPV modulation to restore healthy mechanotransduction and maintain joint integrity. However, the field faces significant barriers particularly in translating complex mechanobiological processes into effective clinical pharmacology as the widely distributed characteristics of TRPV channels often cause cross-interactions in vivo and lead to adverse reactions.[26]
Anti-Cytokines Approaches	Low grade inflammation is now recognized as a major contributor to OA progression, often linked to risk factors like obesity, aging, and metabolic syndromes. Dysregulated innate immune system and aberrant activation of chondrocytes and synovial fibroblasts induce the release of pro-inflammatory cytokines causing a vicious cycle of damage.[27] While anti-cytokine therapies, including inhibitors of IL-1β, TNF-α, and IL-6 have been successful in targeting the low-grade inflammation in RA patients, these biologics have largely failed in OA clinical trials. This lack of efficacy is attributed to the less dominant role of inflammation in OA, significant disease heterogeneity, and suboptimal patient selection. Consequently, current strategies are shifting toward identifying and targeting specific inflammatory phenotypes to improve clinical outcomes.[28]
Matrix Degradation Inhibitors	Unbalanced MMPs network plays a critical role in driving OA progression. The mechanical stress and inflammatory process in the synovial cavity drives the expression of MMPs (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-13) and ADAMTS family members (ADAMTS-4 and ADAMTS-5) that drive the joint cartilage destruction.[29, 30] This enzymatic activity shifts joint homeostasis toward a catabolic state, creating a feedback loop of inflammation and irreversible structural damage. Recent Phase II trials for ADAMTS-5 inhibitors, such as GLPG1972 and QUC398, failed to meet primary endpoints because their success in inhibiting biochemical markers did not translate into meaningful reductions in cartilage loss or patient pain. These failures are attributed to potential enzymatic redundancy in humans, where other proteases may compensate for ADAMTS-5, as well as the significant heterogeneity of OA patients who may require more personalized treatment approaches.[31, 32]

Growth Factors & Cartilage Regeneration	Growth factors facilitate cartilage regeneration by stimulating chondrocytes to proliferate and synthesize essential matrix components like type II collagen and aggrecan. The dysregulation of this complex network during inflammatory conditions is a key driver of OA progression.[33] A Phase II trial used intra-articular injections in OA patients of a recombinant fibroblast growth factor 18 (FGF18, Sprifermin), a cellular factor essential for bone and cartilage formation.[34] The results showed a long-term increase in total femorotibial cartilage thickness that was sustained through five years of follow-up. While the study failed to demonstrate a significant symptomatic benefit in the general population compared to placebo, post-hoc analyses identified a "subgroup at risk" with more severe baseline characteristics that experienced clinically meaningful pain reduction and a lower rate of total knee replacements.[35]

DMOAD TRIAL CONSIDERATIONS

With the hope of DMOADs to not only relieve pain, but also slow disease progression—or potentially reverse existing damage—continued research is essential to unlock their full potential. However, this requires careful consideration of the unique complexities associated with DMOAD clinical trials. As the field advances, thoughtful trial design plays a critical role in successful trial outcomes. Read on to explore key considerations and strategic approaches in DMOAD trials, including eligibility criteria, patient recruitment, and endpoint protection for patient reported outcomes (PROs).

Eligibility Criteria and Patient Recruitment

As mentioned earlier, selecting the right patient population is a key factor when designing a successful OA clinical trial. Aiming for a more homogenous patient population while also avoiding overly restrictive entry criteria can be challenging. Inclusion criteria can be based upon a number of specific thresholds such as hsCRP values, NRS Pain Scores, K&L grading, synovitis on imaging, prior treatment failures, and disease measures such as the KOOS and/or WOMAC scores; careful consideration should be given when defining these thresholds to avoid targeting a patient population that is too difficult to recruit. Additionally, overly burdensome imaging requirements and drug-washout periods may deter patients from enrolling. It is advisable to incorporate a plan for rescue therapy into the protocol to provide reassurance to patients and investigators that if OA pain worsens throughout the course of the study, they will have treatment options.

Endpoint Protection for Patient Reported Outcomes

PRO data is frequently used in OA clinical trials to support primary and secondary endpoints; however, training and education of both site staff and study participants is often lacking which can lead to data quality issues. Robust training of site staff and study participants can help reduce response variability and improve the overall quality of the data collected, increasing the likelihood of a successful OA clinical trial.

PRO data collected in an inconsistent manner creates a significant risk to the data's quality and calls into question whether meaningful conclusions can be drawn. Despite this risk, site staff training on proper administration of PROs has not been standardized across the industry and surveys of site staff indicate that training related to proper PRO administration is often lacking.[36]

There are several best practices which have been developed with respect to PRO administration in clinical trials. Generally, PROs should be completed as the first assessments at a study visit to ensure that the participants' response to questions isn't inadvertently biased by interactions with the investigator and site staff. PRO administrators should be trained to ensure PROs are administered in a quiet, private location that is free from distractions. This helps alleviate participant concerns that their information could be inadvertently shared, and allows them to focus on providing honest, accurate responses. Finally, site staff should receive training on the use of participant facing materials designed to support proper PRO completion, along with guidance on how to address patient questions.

Patients are more likely to be engaged when the process is transparent, and they can understand their role in the research that may lead to advancements in treatments. The ability to easily submit their data is critical. Medpace has developed processes and technology to support the collection and analysis of this patient-reported data through the TrialPACE® ePRO/eCOA/eDiary system.

Patient Education and Support

Educating participants up front regarding the purpose of PROs and the importance of providing accurate responses is critical to ensuring quality data collection.[37, 38] Without this context, some PRO questions may appear unimportant or unrelated to a participant's condition, increasing the risk of skipped questions or thoughtless responses. Clearly explaining the purpose of the PRO, and reinforcing the importance of honest and accurate responses, helps avoid data quality issues. Participants should also be informed about how the data will be used, offered reassurance that their privacy will be protected, and assured that PRO responses will not adversely impact the care they receive during the trial.

Developing tools and training materials to facilitate each participant's understanding of the study scales and questionnaires helps ensure proper completion and decreases the likelihood questions will be skipped. Ensuring the participant understands the requested recall period is another critical component, especially with respect to pain reporting. This information can also improve participant engagement, allowing them to feel more connected to the study, which in turn supports participant retention. Strategies may include the development of videos and handouts which can be reviewed by participants prior to completing PRO assessments, keeping key principles top of mind prior to each administration.

Placebo Response Mitigation

Placebo response is another critical concern for studies assessing symptoms of pain and inflammation. Placebo response refers to the overall level of clinical improvement reported by study participants that are assigned to the placebo arm of the study, despite them not receiving an active pharmacological agent. A high placebo response rate can result in a failed trial if there is not enough separation between responses in participants assigned to active vs placebo. Implementing strategies to minimize placebo response will improve the quality of PRO data to study endpoints.

Placebo response can be impacted by expectation bias, previous conditioning, and site staff interactions. For some individuals, just knowing they are going to participate in a clinical trial can have a positive impact on their symptoms, because participation may represent taking a more active role in treating their disease. Previous conditioning can also impact the way a patient perceives their response to taking an investigational product (IP). The simple act of taking a medication may elicit a perception of symptom improvement if the patient associates taking a medication with feeling better. Similarly, if a patient has participated in other clinical studies in the past and experienced an improvement in their symptoms, this can influence their perceptions about how they should be feeling in a different clinical trial.

Participant responses to treatment can also be impacted by the way site staff interact with a participant. Site staff generally have expectations about how participants should respond to receiving an IP based on what they have been told about the IP at investigator meetings, or from observations from other clinical trials they have worked on with the same or similar compounds. If site staff believe the IP will improve a participant's symptoms, this can impact what they say about the trial and how they interact with study participants, which can in turn impact the way a participant perceives changes in symptoms.

Site staff must be trained in the importance of maintaining a neutral demeanor when interacting with participants to avoid inadvertently influencing the way the participant responds to questions. Information provided to participants should be factual and focused on properly administering an assessment rather than being emotionally invested in responses from the participants. Site staff also need to be aware of their body language, ensuring they appear business like and are not revealing their feelings when interacting with participants. Behaviors such as intense leaning or emphatic eye contact should be avoided.

Participants should similarly be educated about the use of placebos in the trial with frequent reminders that they may be receiving the placebo, which is not designed to improve their symptoms. Utilization of a Placebo Control Reminder Script can help safeguard against participants forgetting that they may not be receiving active treatment. Additionally, explaining to them that staff need to remain neutral can prevent the participant reading into site staff behaviors.

CONCLUSION

With OA affecting more than 600 million individuals worldwide, there remains a significant unmet need for new and effective treatment options. Meaningful progress has been made in understanding the underlying pathophysiology of OA. DMOADs represent a new emerging pharmacological approach to relieve pain, slow disease progression, and potentially reverse joint damage. These new innovations are creating new opportunities to improve outcomes and quality of life for patients with OA.

Despite these advances, no DMOADs have been approved by regulatory agencies to date, underscoring the need for continued high-quality research and innovation. Although there have been several promising clinical trials involving DMOADs, Sponsors face numerous challenges when executing OA clinical trials.

These complexities reinforce the value of partnering with an experienced CRO that can effectively navigate the scientific, operational, and regulatory demands of OA development. Medpace is a leading global CRO for rheumatology with a proven track record of success and deep expertise, including in-house board-certified rheumatologists.

Our global team of medical, operational, and regulatory experts have experience in the administration of intra-articular injection of in vivo and ex vivo cell-mediated gene therapies and expertise in ultrasound guided injections. In addition, Medpace has extensive experience in designing and executing T-cell engager therapy studies across multiple stages of clinical development, and the insights gained are directly translatable to OA and other autoimmune indications.

Partner with Medpace to streamline your OA clinical development program and accelerate your path to approval. Contact our rheumatology experts to learn more.

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