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Challenges for Osteoarthritis Trials

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Abstract

At a time when advancing understanding of osteoarthritis (OA) has created opportunities for new treatments, development of treatments has remained considerably behind advances in other rheumatic diseases. We suggest elements of trial design and measurements that have inhibited success and offer suggestions that may help break the logjam. Among the problems for pain outcomes include a reliance on a single non-optimal pain outcome, an overestimation of likely effects of treatments on pain, and the failure to identify patient subgroups most likely to respond to specific treatments. Even using MRI to evaluate cartilage loss, demonstrating structure modification is likely to be supremely challenging. First, many OA patients have advanced disease unlikely to respond to treatments that prevent cartilage loss. Further, prevention of cartilage loss and pain reduction correlate weakly at best and, for at least some patients, reduction in pain may actually increase joint damage, making it impossible to demonstrate dual treatment effects on structure and pain in such scenarios. For structure outcomes, treatment effects on pain sensitive structures such as bone and synovium may be more achievable than preventing cartilage loss. We suggest that some of these changes may increase the chance that new exciting and effective OA treatments may become available.

INTRODUCTION

Despite the recent approval of a long-acting triamcinolone intraarticular injection preparation for the treatment of knee osteoarthritis (OA), the development of new effective pharmacologic treatments for this common disabling disease, particularly structure-modifying ones, remains a great source of frustration. Studies of joint biology and clinical studies using MRI have identified numerous structural and molecular treatment targets that offer promise in terms of alleviating pain and slowing disease progression in OA, yet none of these is at the cusp of generating new approved treatments both for those that modify the disease process and those that relieve osteoarthritic joint pain. There could be new treatments that specifically focus on pain sensitization or other biological factors that contribute to pain. Modifying the mechanopathology of OA which is better understood than in the past could also provide new opportunities for OA treatment.

With a focus on trial design and methods, the goal of this editorial is to explore reasons why treatment development has been so slow in OA and has remained behind treatment advances

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in other rheumatic diseases. While the suggested changes in the methodology or approach to trials may not yield any different results than previous ones, we will make the case that changes in approaches to evaluating treatment efficacy will increase the chance of demonstrating efficacy of promising treatments for OA. These might include ones that are already being evaluated, those being currently used for other diseases, or ones under development.

The challenge of treatment development in OA is formidable for at least two reasons. First OA pathogenesis combines mechanopathology and the biologic response to mechanically induced injury, both of which appear to synergize in causing both joint damage and pain. Treatment may fail in some persons if one or the other of these critical causal elements is not addressed. Second, the relation of pain relief and structural improvement is not linear. In some instances, pain relief may lead to structural worsening creating an additional challenge for treatments whose goals are to improve both. Thus, while we will suggest changes in the approach to treatment development, even the changes that we suggest may be insufficient. While advances in treatment may be possible now, especially with our better understanding of causes of both pain and joint damage, progress will still not come easily.

The impact and challenges of OA are enormous. Osteoarthritis is the most common form of arthritis, and its ranking in the global burden of disease studies has been increasing year by year (1) with aging of populations throughout the world and increasing rates of obesity. Rates of total knee replacement (TKR) have been rising exponentially in the United States, with projected numbers of knee replacements in the year 2030 being over 3 million annually from the current rate of just over 700,000 per year (2). This high rate of knee replacements can be ascribed in large part to the inadequacy of non-surgical treatments, both with respect to pain relief, long-term adherence, and delay of disease progression. Development of treatments that relieve pain and delay the need for knee replacement is a high priority in clinical practice and in the public health sphere.

Before even embarking on human trials of new treatments, making decisions about which compounds to move forward to human trials can be fraught. For example, preclinical models chosen for testing may not necessarily be ideal for adequately reflecting efficacy in human OA. Potentially promising compounds may not advance because of toxicity issues despite promising efficacy signals, yet additional work to modify compounds to optimize the efficacy:safety signal may not be pursued.

The challenges in studying treatments that relieve OA pain vs. those may delay structural worsening are different with the latter more challenging. We shall indicate below which of these challenges is being addressed. While our suggestions relate clearly to pharmacologic and biologic agents to be developed, they are also relevant to interventions that focus on joint loading such as weight loss, devices and even exercise, though we acknowledge that trials of non-pharmacologic interventions face their own additional challenges often including poor adherence to long term treatment. While examples will be drawn from knee OA trials, the issues identified generalize to OA in all joints so far studied.

The Challenges for Trials Evaluating Effects of Treatments on Pain in OA

Primary Pain Outcomes in Trials

In OA trials, participants usually answer a survey about pain that constitutes the trial's primary outcome. In addition, a variety of information in survey form is collected from patients that is not generally incorporated into the primary outcome even though the findings from these other measures are correlated with that outcome. When WOMAC pain is the primary outcome, other measures assessed typically include WOMAC stiffness and physical function, and even the frequency of rescue medication use. In RA and in cardiovascular disease, composite outcomes have been created which take advantage of the fact that disease improvement is often reflected in multiple related ways and that combining data from correlated outcomes improves the sensitivity of instruments to detecting treatment effects. While there is a hint of this effect in OA trials, it is hard to discern in individual trials given the high correlation between WOMAC pain and other outcomes. Recent evidence (3) suggests that creating a composite outcome combining all WOMAC scales and rescue medication is more sensitive to change than WOMAC pain alone. The OMERACT effort towards identifying relevant domains and instruments to assess those domains may be a first step towards developing a composite outcome for OA trials. As in RA and cardiovascular diseases, the focus on a composite outcome should be accompanied by presentation of results for individual outcomes that contribute to the composite to promote greater understanding of the intervention's specific effects (e.g., pain, function, etc.).

Further, the use of the pain subscale of WOMAC as the primary outcome in trials may not allow for optimal sensitivity to change (4). The WOMAC pain scale sums patient reported pain during 5 selected activities including especially walking and stair climbing. For some patients, pain may improve with activities not captured by WOMAC (and therefore not detected as effects of treatment) and the wording of WOMAC pain questions (e.g., how do you answer a question about pain going up or downstairs if you have pain descending but not going up stairs, or if you don't climb any stairs). Lastly, for interventions targeting specific knee problems (such as knee bracing for patellofemoral disease), a survey that includes activity related pain of questionable relevance (pain on standing) may not be sensitive to treatment effects (4).

Another problem with using pain as an outcome is that improvement in OA symptoms for some patients may not be accompanied by a reduction in pain, but rather an improvement in their ability to do particular activities, leading to increased activity levels. Patients may not report a change in pain severity but may become more active with the same level of pain. Incorporating measures of activity into the assessment of pain, as has been suggested by Lo et al. (5) might enhance the sensitivity of detecting change in OA so as to make it easier to detect treatment effects.

The multiple causes of pain in OA

One challenge in targeting pain in OA is that pain itself is multifactorial. Treatments targeting a single mechanism of pain may be insufficient to deliver a large treatment effect if that mechanism is not operational in the majority of patients. Joint replacement surgery does

relieve pain in almost everyone with disease but at the cost of the removal of all joint tissues that may generate pain. Pharmacologic therapies do not target “the whole joint”. Further, the residual joint pain in 20–30% of persons after knee replacement may suggest that pain mechanisms not addressed by arthrectomy persist. A one-size-fits-all approach to pain treatment is unlikely to address all sources of pain given the numerous contributors to pain beyond structural disease, including psychological factors and pain sensitization. By extension, for clinical trials, the best prediction of treatment response for pain treatment outcomes may require stratification by psychological characteristics (6).

Additionally, identifying particular pain mechanisms may enable improved ability to detect treatment response and patients most likely to benefit from treatment. For example, while in a trial, intra-articular botulinum toxin demonstrated no benefit compared with placebo in the overall sample, there was significant pain improvement in those with nociceptive pain, but not in those with neuropathic or uncertain mechanisms of pain (7). Including a heterogeneous sample of patients in trials may mask differential benefit in a particular subgroup. In another proof-of-concept application of pain phenotyping and stratifying treatment, conditioned pain modulation, which reflects adequacy of descending inhibitory modulation in the central nervous system, predicted efficacy of duloxetine for treatment for diabetic neuropathy (8). In contrast, excluding individuals with widespread pain may enable signal detection, as suggested by a post-hoc analysis of the Phase II Wnt pathway inhibitor SM04690 (9). These types of approaches need to be formally tested in larger well-conducted trials to fully determine their utility. Nonetheless, understanding which pathways are operational in an individual’s pain experience may aid in targeting appropriate therapy.

However, there is a theoretical risk of structural damage in targeting nociceptive pain relief alone without addressing appropriate joint protection. Thus, a challenge for treatments targeting certain pain mechanisms remains in assuring that necessary nociception remains intact. For treatments primarily targeting structure, there is a yet-to-be-proven theoretical expectation that there may be a downstream pain benefit associated with less structural progression. Whether such treatments are clinically useful if there is no pain benefit is unclear. These issues raise the philosophical question of whether management of OA can realistically be attained with a single treatment, or whether it will require multiple treatments, targeting relevant facets of pain, structure, and biomechanics as appropriate for each individual.

Underpowered Trials

It is natural for investigators planning a trial and enthusiastic about the new treatment being tested to think that this treatment is likely to be highly effective. Unfortunately, treatments in OA are generally only moderately effective with respect to pain relief. For example, a meta-analysis of the effect of intraarticular steroid on pain in knee OA revealed an effect size of 0.33 (a third of the standard deviation) (10). This compares to effect sizes of about 0.6–1.2 for methotrexate in RA (11). Indeed, for many years Brandt et al (12) suggested that non-steroidal anti-inflammatory drugs (NSAIDs) were no more effective than acetaminophen in the treatment of OA based on one trial (13) in which there actually was superiority of NSAIDs, but the effect was modest and failed to reach significance. Subsequent meta-

analyses of trials comparing NSAIDs vs. acetaminophen have definitively shown that NSAIDs are more efficacious but that this effect is modest with an effect size of about 0.3 (14). Expecting large treatment effects in OA is probably unreasonable, and trials designed with that expectation will often fail to show treatment effects when such effects exist. Unfortunately, sample size requirements expand when small treatment effects are sought, making trials more challenging and expensive.

While single centers may be prone to underpower studies given a potentially limited pool of eligible subjects, even large pharmaceutical company efforts have anticipated unrealistically high treatment effects. For example, a major Phase II trial of tanezumab for OA pain (15) estimated an effect size of 0.5 for pain. The good news was that for this treatment at high dose, the effect size was actually higher, but other Phase III trials of NGF inhibitors using lower doses have found a more typical effect size of 0.3–0.4 for pain (16), suggesting that if this treatment had been tested only at low doses, pain effects would likely have been missed.

Challenges for Trials Targeting Structural changes in Osteoarthritis

Joint Space Loss as an Outcome

An important aspect of trial design for treatments targeting structure is identifying the appropriate primary structural outcome. There has been an excessive focus on joint space loss primarily because the Food & Drug Administration (FDA) in the United States has, until recently, required delay of joint space loss in knee and hip OA as evidence that there is a structure modifying effect of a treatment in OA. The recent white paper, “OA: a serious disease”;(https://www.oarsi.org/research/oa-serious-disease) submitted to the FDA in December 2016, aims to support a pathway that establishes the importance of OA as a serious condition according to the FDA definition for which there are currently no satisfactory therapies, thereby lessening the regulatory reliance on joint-space loss alone. There is already a large literature debating the pros and cons of this focus on radiographic joint-space (e.g., Guermazi et al. (17)), but as investigators involved in multiple longitudinal studies in which radiographic joint space loss has been utilized as a structural outcome, we are aware of its many foibles. First, medial joint space loss is reversed in those with lateral joint disease so that pseudo-widening rather than narrowing occurs. Second, we have demonstrated (18, 19) that meniscal extrusion and meniscal disease per se can cause joint space loss without cartilage disease, although the two usually coexist. Thirdly, in severe disease, bone attrition and other bone shape alterations occur which can over time alter apparent joint space on radiographs. Attrition has been demonstrated on MRI in non-end stage disease and its effect on joint space width is unknown but could make it impossible to determine structure modifying efficacy if the latter is defined as preservation of the joint space. Lastly, joint space loss based on the radiograph is seen in two dimensions and three-dimensional assessments either by CT (20) or by MRI (17) are more sensitive to change. The focus on preservation of joint space as a primary outcome measure may have prevented the identification of treatments that may have delayed disease progression such as risedronate (21) and iNOS inhibitors (22).

Cartilage Loss as an Outcome

Even if we jettison radiographic joint space loss as our measure of structural deterioration, there remain important questions about whether cartilage loss should be used as a primary structural outcome in OA. First, healthy cartilage is not innervated and may not be a major source of pain. Pain is by far the predominant concern of patients that drives them to seek care. The correlation between cartilage loss and pain is modest (23–25), and some studies have found no association at all (26, 27). Further, there is no evidence to date that any treatment that delays cartilage loss without also affecting other joint pathology in OA has a favorable effect on pain.

What effect might relieving pain, especially alleviating so-called nociceptive pain, have on cartilage? Ablating nociceptive pain could lead to joint deterioration and cartilage loss. After all, pain has both favorable and unfavorable effects. Pain can modify the way a person walks so as to minimize joint stress and ultimately joint damage. This was demonstrated by Schnitzer et al (28) who showed in patients with painful medial knee OA that pain reduction with NSAIDs led to an increase in the knee adduction moment (a measure of medial loading). This suggests that pain reduction would lead persons to increase their medial load and likely damage the medial joint. Recent studies of NGF inhibitors have suggested rapid deterioration of OA in those with prior joint damage in a subset of patients (29), particularly in combination with NSAIDs. While there is ongoing investigation into potential biologic mechanisms, this may also be due, in part, to the same phenomenon noted in the Schnitzer study, that effective ablation of pain may lead to either activities or ways of walking that cause damage to the joint. In addition, in a randomized trial of hip OA patients examining indomethacin vs. azapropazone, use of the more effective pain reliever, indomethacin, led to earlier joint replacement and more cartilage loss (30). It is ultimately not clear whether pain relief per se can be accompanied by delay in structural progression or whether any effective pain reliever in OA is naturally going to be accompanied by structural deterioration.

Nonetheless, there are efforts to develop structure-modifying treatments that target cartilage with an aim to demonstrate an initial effect of reducing cartilage loss followed later by improvement in pain. It assumes that protecting against cartilage loss in the affected compartment of knees with OA is achievable and will ultimately relieve pain, both unproven assumptions. First, while trials have showed local stabilizing effects on cartilage, these have been primarily in the non-diseased and non-loaded lateral knee compartment in those with medial knee OA (31, 32). Second, attempting to demonstrate a symptom benefit downstream from cartilage preservation has the added challenge of feasibly conducting a trial over several years while maintaining blinding and adherence and minimizing loss to follow-up. It also would require maintaining participants on placebo for several years. Lastly this strategy begs the question of whether an OA treatment which has no effect on reducing pain for up to 3 years will be welcomed by patients and their physicians.

Alternative approaches to structure modification include a focus on pain sensitive structures in the OA joint including bone marrow lesions and synovitis. For both, studies have shown that they predict subsequent cartilage loss or structural deterioration (33, 34) There is also strong evidence that each of them causes pain and that their volumes on MRI fluctuate directly with pain (35, 36). Recent proof-of-concept trials have demonstrated the potential

for targeting BMLs with accompanying symptom relief, though longer term outcomes are not known (37, 38).

Should Rapid Progressors be the Focus?

Given the desire to identify structure modifying drugs for OA, there has been a recent focus on identifying persons with OA who are at high risk of cartilage loss so as to select persons for trials likely to experience the outcome of interest in a short period of time. There are several major limitations to this approach. First, while OA is highly prevalent, recruiting patients for trials is challenging and imposing additional restrictions to identify those at high risk of progression may make recruitment even more so. The second and probably more salient concern is that studies for many years (39), have shown that those with the highest risk of rapid progression are those with advanced structural disease. Specifically, knees with Kellgren & Lawrence grade 3 (0–4 scale) have a much higher risk of radiographic progression than those with less severe OA. Grade 3 is accompanied by considerable cartilage loss and often malalignment, two factors that can lead to ineluctable disease progression, progression that may not be treatable. Indeed, recent attempts to develop an iNOS inhibitor for OA (22) suggested that while those with grade 3 Kellgren & Lawrence disease progressed at a much higher rate than those with grade 2 disease, the therapeutic effect of this inhibitor was not seen in knees with grade 3 disease but rather, there was a delay in joint space loss in knees with grade 2 disease. So, selection of those at higher risk of progression may actually work against selecting patients or knees whose disease progression is preventable with biological agents. This example also may point to likely treatment failure when pharmacological approaches are used alone in late-stage OA joints where potent adverse biomechanical factors contribute to joint destruction.

Because those with advanced disease tend to experience more rapid structural progression (i.e., cartilage loss) than those without advanced disease, it does not necessarily increase the likelihood of success to find indicators or biomarkers of rapid progression as these would also be markers identifying persons whose disease is so advanced that they are unlikely to respond to biologically targeted agents.

Challenges for Trials Targeting Either Pain or Structure: Opportunities in Stratified Medicine and New Trial Designs

Testing Stratified Medicine Approaches

There is an increasing body of literature that suggests that OA is not one disease but rather consists of subgroups of patients, each representing a different disease pathogenesis. These phenotypes such as inflammatory OA or OA driven by mechanopathology each invokes distinct treatment approaches. While this approach is intuitively appealing, proof will come when trials demonstrate that patients with a particular phenotype respond differently to treatment than those without that phenotype. This has been demonstrated, for example, in randomized trials for the EGFR mutation in lung cancer and was recently demonstrated for eosinophilic COPD (40). Failure to develop OA treatments may be because one treatment may not be effective for all persons with disease and that treatment approaches will have to define a phenotype likely to respond to a specific treatment, a treatment that may not be

effective for those with a different phenotype. Despite multiple efforts to define phenotypes for this disease, there is a paucity of trials testing this approach. For example, knee OA patients with severe malalignment or morbid obesity are not likely to experience benefit from a cartilage anabolic agent. While trials often exclude such patients, the hostile mechanical environment present in many OA joints (as evidenced by, for example, dynamic malalignment or meniscal maceration) may preclude their response to such treatments. Even treatments targeting the aberrant mechanics of knee OA may fail if the phenotype of treated patients includes those with inflammatory subtypes.

New Trial Designs

A related concern is the paucity of trials which have incorporated new approaches to trial design, approaches that might make treatment testing more efficient. Adaptive trial designs have been developed in part to allow for testing not only of novel treatments but also for testing whether specific subgroups of patients are likely to respond better to a given treatment than others (41). We are aware of only one adaptive trial in OA (42) and this did not examine subgroups. Among adaptive trials, enrichment designs might be especially efficient in identifying phenotypes. In these designs initial testing of a treatment in several subgroups is followed by interim analyses after which only subgroups experiencing treatment benefit are randomized and subgroups showing no treatment effect are dropped. Enrichment designs could be used to identify subsets of patients who respond to a given treatment (e.g., an inflammatory phenotype) or could be used to move from a phase 2 trial testing different doses of a treatment to a phase 3 trial in which the doses that did not show efficacy were dropped and those who had been randomized as part of phase 2 were included in the phase 3 results. Another approach that offers promise is the more widespread use of a crossover design (for pain effects or effects on structures where pathology waxes and wanes such as bone marrow lesions), a design which enhances the power to detect modest treatment effects

Also related to trial design are unrealistic expectations about treatment efficacy as noted earlier so that trials anticipating smaller treatment effects are more likely to be successful in detecting efficacy.

CONCLUSIONS

Ultimately, many questions related to the methodology of trials in OA and the approach to the disease itself need to be addressed if new exciting treatments are to show efficacy and obtain regulatory approval for the treatment of OA. Certainly our improved understanding of the biology of OA including findings from animal studies and our better appreciation of sources of pain are increasingly making available ideas that support new treatment options in OA. For those to be realized, new approaches to trial design and outcomes need to be tested.

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Abbreviations

OA	osteoarthritis
RA	rheumatoid arthritis
TKR	total knee replacement
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
NSAIDs	non-steroidal anti-inflammatory drugs

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