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Disease modification in osteoarthritis; pathways to drug approval

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SUMMARY

Objective: To summarize proceedings of a workshop convened to discuss advances in disease modifying osteoarthritis (OA) drugs and regulatory challenges in bringing these drugs to market.
Design: Summary of a one day workshop held in Washington, DC in May 2019.
Results: Attendees presented data documenting the prevalence, cost and disability burden of OA; recent documentation of disease modification without concomitant clinical benefit in trials of disease modifying drugs; regulatory considerations pertinent to disease modifying therapy; and methodologic approaches to addressing these regulatory considerations.
Conclusions: The research, pharmaceutical and regulatory communities must continue to collaborate on defining pathways for approval of disease modifying osteoarthritis drugs that document effects on clinical endpoints (such as pain, function or joint replacement) as well as on bone, cartilage and other structures.

Osteoarthritis is a highly prevalent and disabling condition that is managed symptomatically because there are no commercially available agents proven to arrest or reverse progression of the disease. In the last decade, several agents have been developed that hold promise as structure modifying therapies. However, understanding and defining disease progression and clinical benefit in this setting as is expected by regulatory agencies poses a number of challenges. The Osteoarthritis Research Society International (OARSI) convened a workshop in May 2019 to bring various stakeholders together to discuss the burden of OA, recent developments in treatment and in assessing change, and regulatory challenges and potential approaches to addressing these challenges. This paper summarizes the workshop presentations and discussions. It begins with an overview of the burden of OA and therapeutic challenges in treating this disorder and then discussed regulatory considerations in approval of medications to treat OA, particularly structure modifying therapy. We close by suggesting methodological approaches to addressing these regulatory issues.

1. Burden

Osteoarthritis (OA) affects over 300 million individuals worldwide – 15% of the adult population – and is a leading cause of disability internationally[1]. Symptomatic knee OA is particularly prevalent and disabling, with 40% of men and 47% of women developing knee OA in their lifetimes[2]. Osteoarthritis accounts for over one million hospitalizations annually in the US, primarily for total joint replacement[3]. Thus, the burden of OA is enormous and the need for treatments that reduce pain and attendant disability for persons with OA is critical.

Osteoarthritis is frequently accompanied by comorbid conditions. In fact, 59–87% of people with OA have at least one other chronic condition, especially cardiovascular disease, diabetes mellitus and high blood pressure, and over 30% of people with OA have at least five chronic comorbid conditions [4,5]. Persons with symptomatic radiographic knee OA have 20% higher all-cause mortality than the general population [6],

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which is related, at least in part, to reduced levels of physical activity, comorbid medical conditions and chronic use of analgesic medications, particularly nonsteroidal anti-inflammatory drugs and opioid analgesics. These observations indicate that the burden of OA extends beyond the domains of pain, function and musculoskeletal disability and includes increased risk of cardiovascular morbidity and mortality.

1.1. Therapeutic challenges

Despite the enormous burden of OA, there are no medications approved by either the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) that have been demonstrated to arrest, slow or reverse progression of structural damage in the joint. Several reasons appear to explain the failures of efforts to establish disease-modifying therapies for OA. One is the heterogeneity of the disease process. Osteoarthritis arises from a combination of genetic factors, mechanical, inflammatory, metabolic and other processes affecting cartilage, bone, synovium, meniscus and other tissues. This heterogeneity has made it difficult to target pathways for pharmacologic intervention accurately. Structural outcome assessment has posed additional barriers. Plain radiography is the traditional method of assessing structural change. However, the accuracy of radiographs is vulnerable to subtle variations in knee positioning. Even when positioning is optimal, radiographs have low sensitivity to structural change. Although semi-automated methods of measuring joint space width improve the sensitivity of plain radiographs, progression cannot be detected reliably on plain radiographs for one to two years[7].

Recent work in OA imaging and OA pathogenesis has begun to break down these barriers. From an imaging perspective, magnetic resonance imaging (MRI) has afforded a more sensitive and reliable approach to documenting changes in structural features of osteoarthritis than plain radiography. MRI can assess abnormalities of a range of tissues (bone, cartilage, meniscus, synovium, ligament, others) involved in OA pathogenesis, providing an opportunity to assess mechanistic targets of specific therapies. Changes in MRI parameters also have proven predictive validity: MRI assessments of cartilage thickness loss over two years have been associated with progression to total knee replacement and development of severe pain[8–11]. The shape of the femur and tibia change over the course of OA; these changes can be quantified accurately by MRI with machine learning-based technology. These bone shape measures are more responsive to change than radiographic joint space narrowing [12] and afford another powerful predictor of outcomes that matter to patients, such as progression to total knee replacement and severe pain in OA [13,14].

In parallel with these advances in imaging, after decades of investigation into agents that might modify structural features of OA, at least three agents (sprifermin[15], a cathepsin K inhibitor [16], and lorecivivint [17]) appear to slow the progression of structural damage in early clinical trials. Sprifermin was associated with both dose-dependent reductions in loss of total cartilage thickness loss and actual increases in cartilage thickness over two years compared with placebo[15]. The cathepsin K inhibitor was associated with statistically significant reductions in 3D MRI bone shape change compared with placebo at 26 weeks [16]; and lorecivivint, a Wnt signaling inhibitor showed less radiographic joint space narrowing than placebo over 24 weeks [17].

The clinical importance of these structural changes is not entirely clear as we have not established the amount of change in cartilage thickness or bone shape that is associated with downstream symptom reduction. Indeed, these trials of sprifermin and cathepsin K inhibitor demonstrated structure modification but did not demonstrate significant pain improvement or other clinical outcomes, compared with placebo. Thus, a conundrum arises: we have MRI biomarkers that are associated with clinical outcomes that matter to patients and we have drugs that modify these MRI biomarkers. However, the drugs themselves have not yet been shown to reduce pain due to OA during the 6-24-month timeframes of the existing studies[15–17]. Indeed, given our understanding of the temporal relationship between structural change and symptom onset, symptomatic changes might be expected to take many years to develop.

In addition to MRI imaging biomarkers predictive of structural change, investigators have identified soluble biomarkers in serum and urine associated with key outcomes. CTX-II is measured in urine and reflects degradation of Type II collagen. PIIANP is a serum biomarker that reflects Type II collagen synthesis. Thus, high concentrations of CTXII and low levels of PIIANP would be expected to portend joint destruction. Indeed, clinical studies have demonstrated that these soluble biomarkers have the anticipated relationship with radiographic progression and risk of total joint replacement[18,19].

Thus, both imaging and soluble biomarkers have been shown to be associated with outcomes that matter to persons with OA – pain, functional status and total joint replacement. Further, these imaging and soluble biomarkers are responsive to structure-modifying medications. Study participants given these medications show improvements in these molecular biomarkers as compared with participants treated with placebo controls[15,16,20].

1.2. Regulatory considerations

The question addressed in this workshop is whether improvements in biomarkers known to correlate with clinically relevant outcomes are sufficient to qualify medications for regulatory approval. In the US, drugs must be approved by the FDA before being marketed to the public. The FDA has generally approved drugs based upon evidence from randomized controlled trials demonstrating that the drug is superior to placebo with respect to measures of how a study participant feels, functions, or survives. Thus, for OA treatments, the FDA has traditionally accepted patient-reported outcomes of pain and function as trial endpoints but has not accepted either imaging or biochemical markers. As noted above, this requirement is problematic for approval of disease modifying medications because it is anticipated that changes in structure do not translate immediately to changes in symptoms, but instead give rise to symptom reduction after years.

The FDA recognized that these criteria imply a long process toward drug approval and has an accelerated pathway for approval of drugs used in serious diseases[21]. The pathway is intended for a drug that "treats a serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit." [21] In these disorders, FDA accepts surrogate endpoints (measures that do not themselves represent clinical benefits but have been shown to predict clinical benefit) as outcomes. An example of a surrogate endpoint accepted by FDA for accelerated approval is HIV Viral Load for persons with HIV infection.

As the surrogate marker is only accepted by FDA for 'serious diseases' the designation of 'serious disease' takes on considerable importance. FDA uses the term 'serious disease' to refer to disorders associated with substantial morbidity or mortality and a paucity of available treatments. On the basis of the high prevalence of OA, its associated disability, morbidity and excess mortality, and the lack of therapies that can reverse, slow or arrest the destructive process of OA, the FDA recognized that OA as "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." [22] With OA formally recognized as a serious disease, FDA is open to consider qualified surrogate measures of relevant clinical outcomes as primary outcomes for trials, including imaging or molecular biomarkers associated with cartilage damage or bone remodeling.

The FDA has taken the view that in order for a structural endpoint to serve as a surrogate measure on the accelerated pathway, the measure must have biologic plausibility and there must be evidence showing that treatment associated changes in the measure are associated with changes in outcome. FDA notes in its guidance document[22]:

> "To accept structural endpoints as valid outcome measures for accelerated approval, there should be substantial confidence, either based on empirical evidence from randomized, controlled comparisons from clinical trials and/or based on a comprehensive understanding of the disease process and product mechanism of action, that an effect on the candidate structural endpoint will reliably predict an effect on the clinical outcomes of interest." [22].

1.3. The guidance document goes on to state

> "At this time, the ability of treatment effects on common measures of structural progression to reliably predict treatment effects on direct measures of how patients function and feel, has not been established. Therefore, FDA welcomes efforts to address the above considerations and is open to work with all stakeholders on such programs." [22].

Thus, evidence will be needed showing that the proposed drug is superior to placebo in effecting the change in structural endpoint in a defined sample. It must also be demonstrated that the change in structural endpoint is associated with outcomes that matter (how the study participant feels, functions or survives).

To date, OA investigators have shown that structure modifying medications do indeed improve structural and biochemical biomarkers [15,16]. There is also evidence that changes in these structural and biochemical biomarkers are associated with outcomes that matter, including pain[9,14,19,23]. Whether this evidence will be sufficient to quality MRI measures as surrogate outcomes is not clear at this point. It is anticipated that biochemical measures for now will continue to play a supportive role in drug development but not constitute surrogate outcomes until any one of them can be demonstrated to be directly in the treatment pathway. If a product is approved under an accelerated pathway based on a surrogate endpoint, the company must conduct post marketing studies to demonstrate the benefit on outcomes of clinical importance (such as pain, functional status, morbidity, or joint replacement). Conducting confirmatory studies for products approved under accelerated approval has its own challenges and limitations and may leave residual uncertainties about the true clinical benefit-risk assessment and impact on public health of a marketed product unaddressed.

1.4. Methodological approaches to meeting regulatory standards

Several methodological approaches have been suggested by OA investigators to meet the standard created by the FDA and summarized above[24]. Essentially these designs call for randomization of participants to receive the active medication or control, and to be followed for assessment of both biomarkers (imaging, biochemical) as well as meaningful clinical outcomes. The biomarkers are anticipated to be responsive to therapy earlier than patient-reported measures of pain and function; thus, changes in biomarkers would likely be documented in the first year or two of the study, if the medication is effective. At that point, participants would continue to be followed to document changes in pain and/or function and the need for joint replacement. Such changes in pain or function would need to be documented in order to qualify the biomarker as a suitable surrogate outcome. Subsequent trials of disease modifying medications could use the validated surrogate biomarker as the primary outcome, and the drug could be provisionally approved on the basis of the surrogate marker outcome. Full approval would be granted when the participants in these studies, randomized to the active intervention, demonstrated improved measures of pain or function. However, the drug would be available during the provisional period. Failure to demonstrate a clinically relevant drug response in the post-marketing trial could lead to withdrawal of regulatory approval and the drug from the market.

Clinical development for products intended to modify the structural changes underlying OA poses daunting challenges. Keeping participants in trials for several years is resource intensive. Participants may stop the drug if they feel it is not working. Participants may try a range of concomitant therapies, blunting the effect of the randomized treatment. This challenge will require careful collaboration among patients, OA investigators, industry partners, and regulatory agencies.

This is an exciting moment for OA therapeutics. Agents have now been shown to effect changes in MRI structural biomarkers; and changes in these markers have been shown to be associated with outcomes that matter to patients, including pain relief and total joint replacement. Discussions between academic- and industry-based OA investigators and FDA officials have begun, with all parties committed to bringing safe, effective OA therapies to patients.

Author contributions

- Conception and design – all authors
- Analysis and interpretation of the data – all authors
- Drafting of the article – Dr. Katz
- Critical revision of the article for important intellectual content – all authors
- Final approval of the article – all authors
- Administrative, technical, or logistic support – Dr. Katz
- Collection and assembly of data – all authors.

Dr. Katz (jnkatz@bwh.harvard.edu) takes responsibility for the integrity of the work as a whole.

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Conflicts of interest

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- Dr. Callahan reports consultancy from Abbvie and a grant from NIDR,
- Dr. Block reports consultancies with Zynerba Pharma, Inc., GlaxoSmithKline, Inc. and Medvir Inc.; receiving research grants from Novartis, Pfizer and TissueGene; and royalties from Daiichi-Sankyo, Agios, Omeros and GlaxoSmithKline.
- Dr. Conaghan reports consultancies with AbbVBie, BMS, EMD Serono, Flexion Therapeutics, Novartis, Pfizer and Stryker; and receiving research grants from AbbVBie, BMS, Lilly, Novartis, and Pfizer
- Drs. Simon and Kraus report no competing interests
- Dr. Hochberg reports consultancies with Bone Therapeutics, Bristol Myers Squibb, Eli Lilly, EMD Serono, IBSA Institut Biochimique SA, Novartis Pharma AG, Noven Pharmaceuticals Inc., Pfizer Inc., Regenosine, Samumed LLC, Theralogix LLC, Vertex Pharmaceuticals Inc., and Vizuri Health Sciences; grants from NIH; royalties from Elsevier and Walters Kluwer; and stock options from BriOri Biotech and Theralogix LLC.

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