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## OSTEOARTHRITIS WORKSHOP

### Better biomarkers needed to assess OA therapies, but patient voice still missing

By Marie Powers, News Editor

ATLANTA – “It takes a village” to develop biomarkers in osteoarthritis (OA), Chris Leptak, medical officer in the FDA Office of New Drugs, Guidance and Policy Team told participants at the Accelerating Osteoarthritis Clinical Trials Workshop co-sponsored by the Arthritis Foundation and the FDA. Representatives from the FDA and EMA, academic research institutions and industry didn't disagree with that assessment as they engaged in lively discussion about developing drugs that could slow OA disease progression – a challenge in addressing any slow-moving indication.

But it was readily apparent that patients represent key stakeholders whose voices are largely missing from the conversation about how to improve OA treatments. Engaging that group early in the process, experts said, is essential to move drug development in the right direction.

Unlike rheumatoid arthritis, where drug development is flourishing, no drugs are currently approved by the FDA to halt the progression of OA, and findings from X-ray – at best an imperfect tool and at worst a modality that completely misses fundamental changes in physical structure – are the only endpoints currently accepted by the agency to conduct a risk/benefit assessment of OA treatments.

Moreover, the FDA guidance – never finalized – to develop drugs, devices and biological products to treat OA dates back to July 1999. The agency recognizes the shortcoming, telling *BioWorld Today* in a statement from the Division of Pulmonary, Allergy and Rheumatology Products that the 1999 draft guidance “needs to be updated” and noting that FDA “will seek public comment on the revision before the guidance would be finalized.”

Input from the OA workshop is a starting point.

“FDA wants to encourage a renewed focus on the patient in OA drug development and will be interacting with workshop participants to brainstorm about better ways to accomplish this in OA drug development programs,” the agency said in its statement.

During the first day of the workshop, FDA representatives suggested some modifications the agency might consider in evaluating trial designs and applications. Endpoints in OA trials will still need to show clinical benefit in managing symptoms, according to Suzette Peng, an FDA medical officer and member of the Arthritis Foundation's accelerating OA clinical trials

workgroup. She suggested, however, that the agency might be willing to consider the link between structural changes and long-term clinical outcomes and to evaluate trials with enriched populations that may have a greater likelihood of progression and, thus, greater opportunity to show benefit from an intervention.

The FDA also is open to evaluating trials that enroll patients with a history of joint trauma, such as anterior cruciate ligament (ACL) tears, and to look at smaller sample sizes.

“The Holy Grail here is to prevent the progression of OA, prevent the damage that eventually leads to the need for joint replacement or, if that isn't possible, leads to serious disability,” Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, told *BioWorld Today*.

The effort by companies to search for therapies that could slow or halt the progression of OA has been thwarted by the fact that “we don't have good biomarkers to predict who's going to progress very quickly and we don't have biomarkers that are able to predict that you can delay progression,” she added.

Woodcock acknowledged that biomarkers to guide the development of therapies that could alter the course of OA are urgently needed. The problem, she said, is that “you have to study them. Everybody discovers them, but few people study whether or not they predict anything.”

In OA, the trick is to identify biomarkers that provide early signals that an intervention will change the course of the disease.

“We've had lots of candidates, but we don't know whether any of them actually do that, and we've had some disappointments over the years,” Woodcock said.

#### DEVELOPING THE TOOLS

Watching OA patients “progress in front of our eyes” has been frustrating for clinicians, as well, said Virginia Kraus, professor of medicine at Duke University and a presenter at the OA workshop, Kraus also worries about the growing

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number of young adults and children – some as young as grade school – at risk for OA following an injury such as an ACL tear. Fifty percent of individuals with an ACL tear will develop knee OA, she said, but researchers don't know which patients are at risk and how quickly OA may develop. Having the right tools could help clinicians get a better handle on the factors involved in both.

Kraus, an expert in the development of biomarkers, is hopeful that “we could get approval for something like MRI, that sees ligaments, tendons, meniscus, articular cartilage, and some metrics around those structures – even joint swelling, which is very hard to quantify clinically on exam and you certainly can't see it on an X-ray.”

The need to accelerate clinical trials in OA also applies to the process of regulatory study design that could lead to the approval of new therapies, according to Kraus. The workshop comes at an ideal time, as the understanding of the biology of OA has increased exponentially over the past five years, in turn increasing the number of potential targets for intervention. Still, OA, like most chronic disorders, is a heterogeneous disease, so “one size may not fit all,” Kraus cautioned. “We need to develop tools that will be able to distinguish different groups of people.” Workshop participants also debated with FDA representatives whether the use of objective measures such as the equivalent of the six-minute walk test might be used together with subjective measure of patient well-being, which assesses how well OA patients feel, function, survive and thrive.

“We would consider it,” said Sarah Yim, associate director of rheumatology in the FDA's division of pulmonary, allergy and rheumatology products. “But the devil is in the details,” she added, noting that the agency would need to understand how to translate such findings into clinical benefit.

“Patients are in best position to inform us on what treatments help them,” Yim said. “We like patient-reported outcomes a lot.” At one point, regulators and researchers debated whether endpoints in OA trials should focus more on improving a patient's pain and function or preventing structural changes, since those outcomes might not respond to the same set of biomarkers.

Ironically, no patients were in the room to articulate their priorities, and Pamela Tenaerts, executive director at the Clinical Trials Transformation Initiative, lamented that oversight.

“If you have another meeting like this, I challenge you to include patients in the room, as well,” she said.

In fact, she challenged stakeholders at the meeting to engage patients at the front end of OA trial design, noting that investigators and sponsors often end up with the “Christmas tree effect” by adding ornamental factors into trials that ultimately matter little to patients.

“Patients should be at the same table as your operations staff and academicians and on your steering committee,” Tenaerts said. “They should have a role at every stage.”

Patients, for instance, are in the best position to evaluate whether investigators are using the appropriate research questions, inclusion and exclusion criteria and endpoints.

“Whether to study structural changes or pain is for patients to decide,” she maintained. “If you come up with right arguments, regulators would have a hard time pushing back on the validity of your study.”

As for whether pain or structural changes must be an either/or decision, Timothy McAlindon, chief of the division of rheumatology and professor at Tufts University School of Medicine, suggested in an intriguing analysis that the problem in developing OA studies is less with the measurements than with the analysis.

“People say there's no relationship between structure and pain, but one is a measure of activity and the other of accumulated damage,” he pointed out. “There's actually a very strong relationship.”

Studies of OA interventions should include both, McAlindon maintained, despite the inherent challenges and regulatory uncertainties. And, he advised, researchers need to look more closely at the variability in their instruments, such as use of the Western Ontario and McMaster Universities Arthritis Index, or WOMAC, which includes two subdomains – weight-bearing and rest – that could be measuring separate OA processes. The tool was designed in an era of NSAIDs for short-term pain and may be inadequate to measure chronic, fluctuating pain, he added.

McAlindon also advised investigators to look at the manner in which they recruit patients. If measurement of OA begins with people at peak pain, a high placebo effect – perhaps even exceeding drug effect – is not surprising, he said. Rather than relying on “old-fashioned trial design, which measures average outcomes,” researchers need to develop tools that will capture a more personalized response, he suggested.

The OA workshop continues on Thursday. //

**OSTEOARTHRITIS WORKSHOP****OA trials numerous but endpoints tricky as stakeholders search for better way****By Marie Powers, News Editor**

ATLANTA – Speakers at the second day of the Accelerating Osteoarthritis (OA) Clinical Trials Workshop co-sponsored by the Arthritis Foundation and the FDA pointed to a wealth of trials examining drug, surgical and other interventions to treat the disease, citing more than 500 studies in the U.S. and five dozen in Europe under the sponsorship of dozens of biopharmas and academic institutions. Most are using conventional designs and outcome measures, including Western Ontario and McMaster Universities Arthritis Index, or WOMAC, to measure pain, even though OA presents across young and older adults, athletes and obese individuals, patients with previous joint injury and those with idiopathic disease.

The vastness of the indication, and the imprecision of regulatory guidance to sponsors seeking to advance therapies in the field, prompted calls for a single roadmap that can be used by drug- and device developers to prevent the OA community from, as one participant observed, “swimming around in circles.”

Francis Berenbaum, director of the department of rheumatology at AP-HP Saint-Antoine Hospital in Paris and former president of the Osteoarthritis Research Society International (OARSI), and Nancy Lane, professor of medicine, rheumatology and aging research at the University of California at Davis School of Medicine, reviewed an array of agents under investigation in OA, including nerve growth factor and tropomyosin receptor kinase A, or TrkA, receptor antagonists, hyaluronic acid agonists, a fibroblast growth factor-18 ligand, a cathepsin K inhibitor and others. Of interest, few studies under way in Europe included U.S. sites and vice versa, they said.

Steve Messier, professor and director of the J.B. Snow Biomechanics Laboratory at Wake Forest University, where he studies clinical trial research and exercise, diet, gait and patient-reported outcomes (PRO) for people with knee OA, provided an overview of efforts to pioneer prevention. Attempts to improve trial design in OA preventive measures either will need to go much larger – likely untenable, he admitted – or smaller – for example, by restricting trials to participants with traumatic knee injury, which in 50 percent of patients progresses in 10 to 20 years to knee OA.

Trials to assess drugs and other measures aimed at slowing or preventing structural damage also need longer intervention periods – “10 to 20 years is a pretty long time for a clinical trial,” Messier conceded – or a surrogate biomarker for early onset OA that is uniformly accepted by researchers, sponsors, clinicians and regulators. Other key questions around the design of such trials include whether the findings could be generalized to idiopathic OA and what primary outcome would determine the success or failure of a trial in an indication in which no gold standard exists.

“If you’re going to spend this kind of money on trial, clinicians and scientists must believe in it,” Messier said.

In short, he advised, the OA community needs to build consensus on the road forward.

But some participants suggested that consensus-building may need to coalesce around a series of targets rather than throwing resources at the broader disease.

Young athletes, for instance, need more sensitive markers of early stage disease and progression since traditional PROs are less effective. Because that group is focused on remaining competitive athletically, they’re less inclined to complain about pain and are motivated to enroll in trials to assess interventions that could help them to remain active.

Identifying such patients also requires communication across subspecialties to ensure that physicians who manage those pre-symptomatic patients collect synovial fluid, serum and urine to capture data that could populate a repository where researchers might begin to tease out biological and molecular predictors of disease.

For example, Christian Lattermann, an orthopedic surgeon at the University of Kentucky, said the average age of his patients is about 17 years old.

“Not everyone who has a knee injury will rapidly progress to OA,” Lattermann pointed out. “Some will progress very slowly. To identify the true population at risk, which would allow us to focus our studies, we need better data.”

Benjamin Ellis, a rheumatologist and senior clinical policy adviser to Arthritis Research UK, noted that researchers have wrestled with whether findings from trials targeting young patients with rapidly progressing post-injury OA could be generalized to the larger OA population. But, he asked, “Is that an important question or not?” Young, athletic patients might represent a well-defined cohort that could be targeted as an OA subpopulation, he suggested. “If we worry about generalizing, we might miss an important opportunity,” Ellis said.

In terms of trial design, Lawrence Bonassar, a professor at Cornell University, also suggested that OA represents an ideal indication to incorporate the use of mobile devices and wearables that could provide quantitative data about movement and mobility and show differences in OA populations as the disease progresses.

“When you talk with patients, not only do they not want to have pain but they also want to be able to do the things they’ve always done,” Bonassar pointed out. Capturing such data could help sponsors to align PROs with real-world metrics about physical function when reporting findings to regulators, he suggested.

**'TO STIMULATE THE DEVELOPMENT OF NEW THERAPIES'**

The OA community already has a wide range of partnerships to help realize some of those goals. Stakeholders involved in the workshop included the public-private Clinical Trials Transformation Initiative, which conducts projects to assess current practice and alternative approaches and proposes recommendations for improvement; the multidisciplinary Innovation Task Force, established to improve coordination across the EMA and provide a forum for early dialogue with applicants; SPARK, the university/industry partnership facilitated by Stanford University School of Medicine seeking to advance research discoveries from the bench to the bedside; and OARSI, the global clearinghouse of research and education about OA for scientists and clinicians focused on prevention and treatment of the disease.

Another important partner is the Foundation for the National Institutes of Health, or FNIH, which last year completed a three-year study – in partnership with OARSI, the FDA, biopharmas and advocacy organizations – to prioritize imaging and biochemical biomarkers that measure and predict structural changes and treatment responses in OA.

The study, conducted by the FNIH Biomarkers Consortium, used longitudinal MRI, serum and urine data from nearly 5,000 patients with knee OA and controls. Virginia Kraus, professor of medicine at Duke University, and David Hunter, professor at the University of Sydney (Australia), who led the research team, presented some of their findings in Wednesday's session of the OA workshop. (See *BioWorld Today*, Feb. 25, 2016.)

David Wholley, who manages the FNIH research partnerships division and directs the Biomarkers Consortium, explained that "we take biomarkers from midfield and get them down into the net where they can support appropriate drug approvals by the FDA."

To do that, he said, the data must be robust and replicable, correlate with a clear clinical endpoint and involve validated measurement platforms that are sufficiently sensitive, with the goal of moving them into studies that confirm their effectiveness to measure or predict treatment response.

The OA project "tackled the first part of that process," Wholley told *BioWorld Today*.

The next step is to repeat the analysis using performance characteristics from existing trials to validate the markers.

"That will set the stage for qualification of the biomarkers that are selected" for OA studies, said Steve Hoffmann, scientific

program manager for the Biomarker Consortium. The biochemical and imaging markers could be used alone or, potentially, in combination to create even better predictive data, he added.

Qualifying biomarkers is an effort that's often too large for a single organization to tackle alone, Wholley said. "The ability to pull together data, resources and expertise that don't exist in any one company is critical to this partnership," he said.

Consensus also is essential.

"If one company goes to the FDA with results in this area, it's a lot more difficult for FDA to move forward than if the entire scientific community is at the table," Wholley pointed out.

The most promising biomarkers revealed by the study findings – appropriate use of X-ray and MRI as well as a dozen serum and/or urine markers matched to precise OA processes – have or will be published.

Although the biomarkers still must be qualified with regulators, Wholley is hopeful that the OA community won't wait for a formal decision from the FDA before incorporating them into trials, especially for enrichment.

"The qualification process is used for formal approval, but sponsors don't have to wait for that," he said. "We hope companies will take a look at the early results from these projects and start to incorporate those findings into their development programs. They can use a lot of these markers to make early go/no-go decisions on how to bring their therapies forward."

Ann Palmer, president and CEO of the Arthritis Foundation, was energized by the mood of the workshop and by the FDA's willingness to partner on the discussion about advancing OA trial development. She credited Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, with "cracking open the door" to look at a range of new measures to evaluate OA treatments.

"Our hope, in coming out of this, is that we will be able to stimulate the development of new therapies by creating an easier pathway to market," Palmer told *BioWorld Today*. Subsequent to discussions at the workshop, if the OA community can reach consensus with regulators around particular biomarkers and outcome measures as the elusive gold standard in OA, "that would be a breakthrough," she added. //