Module 6: Designing the Optimal Trials for Understanding OA Panel and Future Directions

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David Hunter:

Discussion Topic 1. In the setting of an acute joint injury clinical trial we are considering conventional MRI for assessment of joint morphology and T1 Rho MRI for assessment of cartilage composition. Please let me know if you agree with this approach or suggest a better one.

John Hardin: The basic idea is to catalyze the development of large scale multi center interventional trial for people with acute ACL injury. The question we have been asked is: What type of imaging technology would you apply now, given current capabilities to distinguish architecture and compositional makeup of an injured joint that can detect differences between the injured and uninjured joint, and to follow those changes over time, with the idea that any intervention that's carried out should be reflected in whatever imaging technique is being employed.

We also propose to apply a series of biochemical measures that can access cartilage and bone turnover to correlate with the imaging studies.

Response for joint injury assessments:

Erika Schneider: Argued against T1rho, not standardized, the reproducibility of technique is very poor (10-15%), would suggest OCT because it can be done quantifiably across sites and longitudinally. T1rho is a custom pulse sequence that is coded individually by researchers and reproducibility might be poor in terms of sensitivity to different KL grades. She suggests that since a certain fraction of patients will be scoped and repaired, use OCT.

David Hunter: How readily available is OCT?

Erika Schneider: It's not frequently available but it is a package that can be purchased and thus can be standardized.

David Hunter: John [Hardin] has a vision that there will be long term follow up, maybe 1 and 2 years to ascertain the efficacy of different interventions. Would that require repeat arthroscopies to ascertain the influence of OCT in that setting?

Erika Schneider: Yes, but now you've just characterized the initial injury. I don't know that the same technology is necessary to monitor longitudinally.

David Hunter: The first question is, what tissue parameter will we measure longitudinally at multi-centers, and how will we measure?

Xiaojuan Li (UCSF): If you are only looking at morphology, you will have cartilage thickening and thinning. How will you understand what's going on? Matrix and collagen will provide information

regarding natural history and treatment efficacy. Argues for T1rho because there are good preliminary data that it can detect proteoglycan.

Kent Kwoh: Agrees with Erika, there are challenges implementing T1rho across sites and platforms.

Marie-Pierre Hellio Le Graverand: In the A9001140 study to validate imaging measures over time, dGEMRIC was not standard and not practical.

David Hunter: Settle on T2 as basis and then T1rho as background if you can get it standardized

What imaging information should be obtained on morphology parameters?

Other than cartilage composition, (Richard Frobell) cartilage thickness, shape measures (Mike Bowes); Felix Eckstein, morphology definitions. –

Important to collect biospecimens to allow biochemical measures to correlate with imaging studies. – At this point we would encourage collecting specimens - Standardizing will not be easy but it needs to be done - lack of consensus of use of techniques.

Richard Frobell: -Joint and morphometry perspective - cartilage thickness - - shape measures/changes would be very interesting.

Be clear about the difference in morphological imaging - cartilage lesions and cartilage thickness.

Make sure you use a scanner that won't be changed in the next 2-3 years for longitudinal versus baseline (so probably use new scanners).

Start with the biomechanics of the injury.

Gayle Lester:

Discussion Topic 2. Given that OA is a disease with a long and slow-progressing course, how can we work with the regulatory bodies to generate different guidance criteria for different stages of intervention? For example, a therapy intended to prevent the onset of OA or treat the early stages of OA (which may include cartilage hypertrophy) is likely not well-served with criteria demanding comparison to 50% reduction in joint space narrowing on plain film radiographs. Did we actually give them a conclusive direction with the OARSI FDA recommendations?

OARSI/FDA project - no update from FDA - never really saw an executive summary of the results and areas to be addressed from the OARSI/FDA process - we provided FDA with a package that was overwhelming.

Gayle Lester: We didn't give them a conclusive outcome to be considered.

Marc Hochberg: From the point of view of structural changes, to adopt magnetic resonance imaging as an outcome for structure modifications - from the point of view of clinical outcomes, the group favored a composite endpoint. The FDA representative said "No they were not ready to adopt that," 3 separate

co-endpoints) - recommendations were made in each individual document. There were bulleted points that reflected the major points brought up by the manuscripts.

David Hunter: Maybe cartilage thickness or MRI has most validity now but without a response from the FDA how to take this forward? MRI stands above and beyond what any radiograph can achieve.

Sahar Dawisha: For agency right now MRI is still a new endpoint so what links MRI to XRAY to give FDA large comfort level - validity of metrics. MRI not clear – it's a very comprehensive document, some areas they were very clear on recommendations, struggling with MRI information - consensus needed - which of these parameters are important and what methodology? Needed by regulatory agency.

David Hunter: Radiograph has merit (but some limitations), MRI can be used as an outcome in clinical trial -most valid and most data as it currently standsis Cartilage thickness on MRI - we don't know how to move forward from the recommendation with no response from the FDA.

Sahar Dawisha: Is MRI being proposed as a biomarker qualification? What potentially could be qualified as a biomarker? What is the comfort level that MRI is a good endpoint? We need understanding what you're looking for.

David Hunter: Validity of metrics (other endpoints), recommendation as using MRI has an endpoint with symptom endpoint, in comparison to xray it performs better - how will the use of MRI as an endpoint in clinical trials going to be received? There is linkage to radiographs and histology, David attached to end of the FDA document.

Sahar Dawisha: Yes, well received, and early on, but need information like, what methodology, how much change to be expected?

Christoph Ladel: How should it be used as a primary or a secondary endpoint?

Sahar Dawisha: Include MRI with all the other endpoints, and then determine if you can use it later as a primary endpoint based on the study.

OA and MRI versus MRI and Cartilage Repair - not acceptable for use in OA, but maybe something to learn from looking at both.

Companies can use any endpoint in their study - if we want to push the use of MRI, it's the responsibility of the group. The highest probability of success, circular argument, putting yourself in a risky position - going to be more flexibility in what is going to be accepted?

Sahar Dawisha: Want to see more use of MRI, current version of the guidance is very old. Committee is reviewing the OARSI/FDA document to create the new guidelines.

Elena Losina: Combining clinical endpoint and biomarker together - BML is the endpoint of the trial - what is the clinical endpoint related to OA? Different concepts should be defined differently

Ali Guermazi- guidelines very outdated – x-rays date back to 1957. No other disease is based on standards that old. Scientists need to come up with the consensus and then introduce it to the FDA.

Felix Eckstein: Correlations between radiographs and MRI done, but don't still have clinical correlations.

Elena Losina:

Discussion Topic 3. **What is the relation between changes in imaging/ biomarkers and changes in symptoms? (Precedents or extrapolations from existing studies, including animal studies)**

Has anyone in any OA clinical trial yet shown any association between change in an x-ray or MRI parameter and change in function? (e.g. whether a patient-reported functional outcome such as WOMAC function, or an objective measure of function like: walk test, "get up and go" test, or activity monitoring.)

How can we identify which structural changes are most specifically associated with clinical endpoints in (knee) OA, and hence worthwhile being treated, given that many of these (bone, cartilage, meniscus, BML, synovitis [changes]) seem to exist (and progress) in parallel?

Need to come to a consensus on standardized clinical endpoint to be able to compare studies (everyone using different endpoints, methods, etc).

Felix Eckstein: - OAI data is underused, we (imaging) don't have the statistical and clinical background to exploit the data - different specialties need to come together to exploit the data.

Christoph Ladel - agrees with Felix -placebo - put objective measures together, quality of life for patient and pill.

Marc Hochberg: Issue of virtual total joint replacement – pain and structural changes – pain and function. There is validity in this outcome.

Elena Losina: Tolerance for adverse events/limitations in each person varies drastically.

Felix Eckstein: Imaging parameters and functional/pain parameters.

Marie-Pierre Hellio Le Graverand:

Discussion Topic 4. What is the relation between structural changes to cartilage and subchondral bone and 'soft' tissues of the articular organ (synovium, bone marrow, synovial fluid) that can be seen on MRI?

As a potential future endpoint in OA clinical trials, what is the current validation status of "virtual joint replacement" [i.e. "virtual knee replacement", "virtual hip replacement"]. In addition, what

parameters are most likely to become component parts of that endpoint? For example - a measure of pain [WOMAC pain? VAS pain?], a functional assessment [WOMAC function? or objective measure of function like: a walk test, a "get up and go" test, or activity monitoring?), and a structural assessment [e.g. x-ray and/or MRI parameter]?

Match pathology you can treat with proper imaging methodology to support, eg, synovitis, BML, eliminate JSN or fail because a single drug will have no effect.

Kent Kwoh: Virtual joint replacement - allow for sensitivity analysis in definition when you are looking at a larger sample size - look at time for attainment of that - parameter of how quickly - sensitivity analysis within our definition – harder to recruit if need TKA as opposed to virtual TKA.

Elena Losina: trends of TKA, number of people with KL>2, why so hard to see TKA in studies?

Recruitment

Markus John: No "virtual" things – company prospective . What would have helped – get rid of joint space narrowing and change something that you have targeted .

Richard Frobell: 30-50% improvement? If structure, maybe less. Not going to see something with joint space narrowing.

Susanne Wang: reminder that FDA is open to suggestions and to move forward, need more validation for MRI - need a scientific consensus - academia, govt and industry need to discuss together

Linda Sandell:

Discussion Topic 5. What is the current thinking on type and frequency of imaging or biochemical markers to assess safety of highly effective analgesic drugs?

David Hunter: The question may be getting at the question of anti-NGF and how to monitor the safety of these agents.

Peter Steiger : Yes it is anti-NGF. So people are getting an agent for one joint and another joint ends up damaged and we don't know why.

NGF - high rate of going in to joint replacement - underlying pathology is unclear and why - how do we monitor.

David Hunter – analgesic arthropathy – probably not

Walking on pain-free but damaged joints? Maybe not

What is pathology? This is central to this question and at present as we don't understand it measuring for it is challenging.

These agents have strong symptomatic, but eventually long term deleterious effects

Virginia Kraus: Until recently did not have joint specific markers – COMP– report difference between hip and knee (for at risk patients) or baseline bone scan for at risk joints - would be interesting in patient population exposed to anti-NGF - baseline bone scan to determine the at risk joint – anti-NGF could be masking symptoms as a pain reliever.
Because some people so good at withstanding pain, can't follow symptoms.

Robin Poole: Joint specific markers.

Stefan Lohmander: Ask the patients in regular intervals for symptoms.

Colin Miller: Individual patient basis – stress at patient level, issue with this class of compounds – what is this? Multi center trials have their own issues - area of discussion and different companies are taking different approaches to it

Frank Roemer: Involves large resources, do we do MRI on all 6 joints? need to know the pathology.

Elena Losina: Agrees with Stefan about asking patients, interest in preserving quality of life over next 5 years.

Ali Guermazi: Issue is complex – If necrosis then joint is dead so need to pick up early.

Bottom line: measure pain, radiographic screening, biochemical markers until identifiable safety signal being seen.

Felix Eckstein

Discussion Topic 6. Is quantitative MRI, either morphological (area, size, volume, bone in growth, subchondral bone edema, etc) , or compositional (T1, T2, dGEMRIC, etc.), or semi quantitative (MOCART, WORMS, etc.), used as an endpoint, a suitable method to be used in cartilage repair trials and for long term follow up as well?

The quantitative MRI (either morphological, compositional or semi quantitative) use for the follow up cartilage repair: how feasible is it in the normal clinical setting? Or is it only a research tool?

The MRI study of the boundaries between native and repaired articular cartilage tissue has been somehow neglected, and MOCART, a semi quantitative tool (which is still evolving) is the only scoring method which addresses, very superficially, that issue. What type of analysis is being worked presently to assess that zone of a repaired lesion?

What are the criteria, from an imaging standpoint, to label a cartilage repair procedure as a "successful one"?

Is it possible to validate MRI as an outcome measure for clinical trials using second-look biopsies after cartilage repair and if so, which MRI techniques and which histological parameters are key? How can we determine a "successful repair" both radiologically and histologically?

Discussion:

Need to measure collagen/GAG, quantitative MRI for morphology suitability – compositional methods have problems and what they are measuring, inference of GAG, where the ideal would be direct assessment of pathology.

Ali – success story is the whole joint, both ways, if joint collapses, doesn't matter about the repair area. - dont believe we will be able to remove morphological; compositional should be based on claim in clinical trial

Ali -Guermazi : Agrees with Erika, when doing cartilage repair, you do not need to focus on just the specific cartilage repair, but also look at the rest of the joint.

IS IT IMPORTANT IN A CLINICAL SETTING?

Stefan Lohmander: Serious doubts on MRI in clinical settings - input/recommendations from clinical radiologists from MRI is not reliable in routine setting.

BOUNDARY BETWEEN NATIVE AND REPAIRED –

Saara Totterman: Depends on the cartilage repair you are working on - Not likely to use imaging (MRI) for long term cartilage repair – boundary between native and repaired cartilage – MOCART? – how to improve T2?

WHAT ARE CRITERIA FROM IMAGING TO LABEL MATERIAL SUCCESSFUL?

Gloria - percent fill, integration of the repair tissue, native versus the new tissue, bone formation, edema signals , edema signal pretty common after surgery, if precedes predicts delamination - SINGLE ONE: Percent Fill.

WHAT IS SUCCESS?

Choosing the right patient, right intervention, right outcome. Need to be mindful of what one considers successful and depends on the patients idea and their expectations.

Virginia Kraus:

Discussion Topic 7. What is the value of synovial biomarkers versus systemic biomarkers if any?

What is the value of urinary biomarkers versus systemic biomarkers if any?

How many baseline samples are needed / are regarded as sufficient for a later normalization to baseline?

Are there preferred points in time after first dosing for putative efficacy biomarker based on serum samples?

How important is the recording of activity levels prior blood sampling?

What is more important to take into account - activity level prior blood sampling or daytime of blood sampling?

Virginia: VALUE of Synovial Fluid- sample directly from the "test tube of the joint", correlates with histology, patient doesn't like and doctors don't like to do it, changes much more rapidly than imaging changes. For example, hyaluronic acid changes in minutes. For some, biomarkers in urine may be good because it's not invasive, but it needs to be normalized because it's not near the joint.

Response to Virginia:

Synovial vs systemic – sample joint or total body and can change more rapidly. T1/2s are shorter – sometimes can compare

Urinary biomarkers vs systemic – UTIINE – clearance is rapid in serum

How many baseline samples are needed? Virginia feels more important to standardize collection. Not done yet in OA studies, collecting samples in a standardized instead of baseline is more helpful.

Preferred time points early phase - lots of time points.... after first dosing for putative efficacy?

Virginia Kraus: Test to see when effect occurs – 16 mon has been predictive of joint space changes. Two to six month intervals.

Activity Level vs Daytime - consistency is the most important.... time of day after time of activity doesn't seem to matter that much - Activity levels prior to blood sampling – COMP – seat person for 30 min

More important activity levels or time of day? Consistency most important. Time of day after morning activity POP – all two hours post-prandial. Or morning fasting.

Robin Poole: Standardize. HA – even what you eat – peristalsis (from RA studies). Now work on assays that pick up more pathological related events –

Urine particularly valuable for collagen markers. Often different fragments in blood – can find a predominant fragment.

David Eyre: Each assay can have their own quirks – CTX-I needs overnight fasting.

Don't need to specify blood or urine now.

Virginia Kraus: A little bit of something worthwhile is worth moving forward. It's OK to have an empirical test that works and that correlates with the disease.