Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group

P.G. Conaghan, D.J. Hunter, J.F. Maillefert, W.M. Reichmann, E. Losina

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- P.G. Conaghan[†, ‡, ⁎],
- D.J. Hunter[§, ‖],
- J.F. Maillefert[¶, #, ††],
- W.M. Reichmann[‡‡, §§],
- E. Losina[‡‡, §§]

- [†] Section of Musculoskeletal Disease, University of Leeds, Leeds, UK
- [‡] NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK
- [§] Rheumatology Department, Royal North Shore Hospital and Northern Clinical School, University of Sydney, Sydney, NSW, Australia
- [‖] Division of Research, New England Baptist Hospital, Boston, MA, USA
- [¶] Department of Rheumatology, Dijon University Hospital, Dijon F-21078, France
- [#] University of Burgondy, Dijon F-21079, France
- [††] INSERM U887, Dijon F-21079, France
- [‡‡] Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA
- [§§] Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

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Summary

Objective

The Osteoarthritis Research Society International initiated a number of working groups to address a call from the US Food and Drug Administration (FDA) on updating draft guidance on conduct of osteoarthritis (OA) clinical trials. The development of disease-modifying osteoarthritis drugs (DMOADs) remains challenging. The Assessment of Structural Change (ASC) Working Group aimed to provide a state-of-the-art critical update on imaging tools for OA clinical trials.

Methods

The Group focussed on the performance metrics of conventional radiographs (CR) and magnetic resonance imaging (MRI), performing systematic literature reviews for these modalities. After acquiring these reviews, summary and research recommendations were developed through a consensus process.

Results

For CR, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness of metric measurement of joint space width (JSW). Trials off at least 1 and probably 2 years duration will be required. Although there is much less evidence for hip JSW, it may provide greater responsiveness than knee JSW. For MRI cartilage morphometry in knee OA, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness. The responsiveness of semi-quantitative MRI assessment of cartilage morphology, bone marrow lesions and synovitis was also good in knee OA.

Conclusions

Radiographic JSW is still a recommended option for trials of structure modification, with the understanding that the construct represents a number of pathologies and trial duration may be long. MRI is now recommended for clinical trials in terms of cartilage morphology assessment. It is important to study all the joint tissues of the OA joint and the literature is growing on MRI quantification (and its responsiveness) of non-cartilage features. The research recommendations provided will focus researchers on important issues such as determining how structural change within the relatively short duration of a trial reflects long-term change in patient-centred outcomes.

Keywords

- Osteoarthritis;
- Conventional radiography;
- Magnetic resonance imaging;
- Validity;
- Responsiveness;
- Reliability

Introduction

Current status of guidance for assessing osteoarthritis (OA) disease modification

The development of disease-modifying osteoarthritis drugs (DMOADs) is faced with many challenges. There remains an inadequate understanding of the primary endpoint for demonstrating DMOAD efficacy. The actual result of clinical OA symptomatic progression, arthroplasty, is associated with multiple problems as an endpoint in clinical trials including the variability in rates of surgery, in part related to socioeconomic disparities, different healthcare environments and the relatively low incidence rate of arthroplasties compared with the total OA burden [1] and [2]. Alternative clinical endpoints for DMOAD clinical trials have therefore been considered and the Food and Drug Administration (FDA) previously provided regulatory draft guidelines for use in DMOAD development[3]. The FDA Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA draft guidelines defined the current acceptable structural endpoint for DMOAD clinical trials as a slowing in the loss of knee or hip joint space narrowing (JSN) using conventional radiographs (CR); depending on the structural change this would need to be accompanied by symptom improvement. Similar recommendations were adopted by the European Medicines Agency (EMEA) in Europe[4] (also adopted by the Therapeutic Goods Administration (TGA) in Australia) and remain in their recently revised Guideline[5].

The current hierarchy of claims for structural outcome as defined by the FDA Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA draft guidance is as follows:

1. Normalise the X-ray (reverse progression).
2. Improve the X-ray (halt progression).
3. Slow JSN by at least a pre-specified amount (slow the rate of progression).

CR have traditionally been the method of choice in clinical trials because of their relative feasibility. Until recently, it was widely accepted that alteration in progression of JSN implies preservation of hyaline cartilage and consequently clinical benefit; measurement of joint space width (JSW) by X-ray was determined as the most appropriate structural endpoint measure [6] and [7]. However it was recognized that the nature and magnitude of structural changes that are likely to be clinically relevant remain uncertain. Whether parallel clinical outcomes should be included in the claim depends on what JSW outcome is achieved, but collection of these data (including measurement of pain, a patient

global assessment, a self-administered questionnaire and the time to the need for total joint replacement surgery) was strongly recommended regardless of the anticipated outcome since their assessment is critical for analysis of the overall risks and benefit of a product[3]. Since the concept of structural improvement connotes an element of durability, trials to demonstrate structure improvement were recommended to last at least 1 year[3].

As well, owing to the rapid growth of magnetic resonance imaging (MRI) studies in the last decade, there has been an increased awareness that symptomatic OA represents a process involving all the tissues in the OA joint, not just cartilage [8] and [9]. MRI has evolved substantially over the last decade and its strengths include its ability to visualise individual tissue pathologies, as well as the interrelationship between tissue pathologies.

Limitations of JSN as an outcome

Although a product showing a slowing of JSN would be expected to also affect symptoms, it is possible that certain products may affect structural progression without associated symptomatic evidence[10]. It is also possible that slowing of structural progression may occur at an earlier time-point with later reduction in symptoms (acknowledged in the recent EMEA Guideline[5]). A claim of structural improvement (i.e., slowing of JSN) might conceivably be dissociated from other claims when the mechanism of action of the product, and/or the size of the effect on slowing of JSN, are suggestive of future clinical benefits. If products are not anticipated to have different effects on these parameters or show only small improvements in JSN without demonstrated effects in symptoms they will not generally be considered for approval or for separate claims. In other words, as long as an observed delay in JSN progression is correlated to an improvement of clinical outcomes it is considered as an appropriate primary endpoint and as a surrogate endpoint for total joint replacement, the critical event characteristic of medical treatment failure for OA. It is assumed that a delay in JSN will consequently delay the need for total joint surgery, and can hence be interpreted as a treatment success for DMOADs.

The use of JSN measured by CR as a structural endpoint is associated with some concerns. Since disease progression is generally slow, minimal and variable within and between subjects [10] and [11], the use of JSW as an endpoint measurement requires long-term treatment periods (>1 year) and inclusions of large patient numbers. Moreover, the inability of radiographs to visualise cartilage leads to lack of sensitivity to detect early and small changes in this tissue[12]. There is difficulty in obtaining high quality reproducible images of OA joints, despite state-of-the-art standardisation of radiographic protocols to reduce the variability related to joint repositioning[13]. MRI studies have demonstrated that JSN represents a complex of hyaline cartilage loss, meniscal extrusion and meniscal degeneration[14]. Although structure is a critical component of OA assessment, the relationships between structure and

pain and/or function and between structure and future outcomes (e.g., arthroplasty) are not well developed and the definition of a clinically relevant change in JSN has not been established.

The use of JSW alone may not be entirely relevant as an outcome measure for DMOAD efficacy since it fails to capture the multi-tissue nature of OA [9] and [15]. As such, potential early beneficial changes in other components of the joint are missed by the use of JSN alone as the structural endpoint. Moreover, the insensitivity of JSN to early changes in cartilage and meniscus means that even "moderate" OA knees (Kellgren–Lawrence ≥ 2) may already represent a stage of the disease too molecularly and biochemically advanced for alteration of disease course by pharmacological intervention. Previous attempts at OA disease modification using JSN as an endpoint have provided important lessons about the design and conduct of such trials, including issues on radiographic positioning, measurement methods, and study "enrichment" for progressors in order to ensure progression in the placebo group; this has been previously well reviewed [7] and [16]. Despite the limitations as a measure for DMOAD efficacy, delay in JSN has been reported for a small number of potential DMOADs to date [7] and [16]. However the lack of associated symptomatic benefit in these studies has prevented any of these agents from being successfully registered.

Methods

In the last decade since the FDA produced its draft guidance for industry, much evidence has been accumulated on the assessment of structural change in OA. The Osteoarthritis Research Society International (OARSI) FDA OA Assessment of Structural Change (ASC) Working Group comprised a wide range of expertise including clinical trialists, methodologists, academics, imaging experts and pharmaceutical company representatives with relevant trials experience; the Group was tasked with:

1.

Examining a number of key issues about the performance metrics (including predictive validity for relevant clinical outcomes and responsiveness) of the commonest imaging tools used to assess structural change in OA, focussing predominantly on CR and MRI, while briefly examining the information on other modalities especially the growing field of ultrasound. This was performed by conducting systematic literature reviews for CR and MRI. The draft strategy for the literature review was written in December 2008, sent to all members of the ASC Working Group, underwent iterative revision, and a final version of the protocol was approved in February 2009. Details of the protocol and the search terms are published separately [17], [18], [19] and [20]. The literature search was conducted using articles published up to the time of the search in April 2009. For examining the role of ultrasound, where it was acknowledged there was a much smaller literature base, we used a recently published systematic literature review on ultrasound in OA[21].

2. Producing state-of-the-art recommendations in assessing OA structural change for the purposes of optimising utilisation in OA clinical trials, based on the findings of the systematic literature reviews and *via* a consensus approach.
3. To also develop research recommendations again based on the literature reviews and through a consensus process of the ASC Working Group.

The following summary and derived recommendations attempts to overview the large amount of literature reviewed during this process. Much of the work summarised below is detailed in the more detailed accompanying systematic reviews of both radiography and MRI [17], [18], [19] and [20]; for this reason, individual references supporting each statement are not provided in this summary.

Summary and recommendations

The underlying assumption of these recommendations is that the manifestations of joint pain and disability currently associated with OA are strongly related to the pathophysiology of OA seen in joint structures. This postulate is to some extent supported by epidemiological evidence of the association between radiographic OA, joint pain and disability in the general population.

Much of the published evidence on imaging ASC relates to OA of the knee, with much less evidence (especially for modern imaging modalities) relating to OA of the hip and very limited information available for hand OA. This summary must therefore be seen as largely related to trials for OA of the knee and to a lesser extent, the hip.

Importantly most of the therapeutic studies on OA have included symptomatic and radiographically moderate to severe OA, so there is an absence of literature and definitions for “early” OA, especially studies entering people before the currently recognized clinical syndrome is apparent and when structural pathology is presumably minimal. So the literature on the performance of existing imaging modalities at this important stage of the OA process is sparse.

When mentioned, the term ‘*therapies’* refers to drugs, devices and biological products entered into the treatment of OA and regulated by the FDA; this could also include interventions such as weight loss.

Conventional radiography

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CR presents an image of the joint space of a diarthrodial joint, the width of which represents the thickness of articular cartilage. In some joints, notably the knee, JSW also reflects the presence, location and condition of other structures (e.g., meniscus), and JSW is a composite measure of the combined thickness of those structures. This should be considered when defining a relevant knee trial outcome.

- Much is now known of the performance metrics of CR JSW in the knee and to a lesser extent in the hip. There is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness of metric measurement of JSW. In terms of correlations with concurrent symptoms, there is a weak association between progression in JSN and progression of symptoms. There is little information on how progression in JSN during the course of a study reflects post-study (long-term) change in symptoms. JSN progression is associated with increased rate of subsequent total joint replacement, but these may not be truly independent events as radiographic JSN is one of the features used to select people for joint replacement surgery.
- In the knee, the use of fluoroscopic positioning and semi-flexed views improve responsiveness, although it is acknowledged that access to fluoroscopic facilities is restricted. Studies will generally need to be at least 12 and more likely 24 months duration.
- It is possible and therefore advisable to ‘enrich’ a knee OA study population to increase the rate of joint space loss, for example, by including higher Kellgren Lawrence (KL) grade.
- Automated methods for assessing parameters of JSW offer promise of improved precision and therefore improved responsiveness.
- The natural history of hip OA appears different to that of knee OA and although the literature concerning the hip is much less extensive, there is some evidence for better responsiveness for JSW measurement at the hip. Hip JSW as a construct does not include a meniscus. There is little evidence on enriching cohorts for purposes of increasing rate of JSN progression.
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We support the continued use of CR JSW as one option for assessing structural OA change, taking all the previous points into account when deciding on study endpoint.

Research recommendations

To further understand the relationship between JSN and symptoms, future studies should focus on the following areas:

- Cross-sectional studies in which the patients are their own controls (such as one recently published[22]) to better evaluate the potential correlation.
- Longitudinal studies evaluating the relationship between changes in symptoms and changes in joint space.
- Predictive validity studies, i.e., does joint space predict subsequent pain and disability and subsequent joint replacement? For example, does JSN between month 0 and month 12 correlates with joint replacement by month 60?
- Construct validity studies, i.e., correlation between JSN and mean pain or function. For example, is JSW between month 0 and month 12 correlated with mean pain and function evaluated every 6 months between month 0 and month 12, or between month 12 and month 24?

For Knee OA:

- Studies of the relationship between symptoms and radiographic joint space evaluated on semi-flexed X-rays with fluoroscopy.
- Studies on predictors of joint loss evaluated on semi-flexed X-rays with fluoroscopy and optimal serial tibial plateau alignment.
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Studies on the effect of rate of joint space loss on treatment effect.

For Hand OA:

• Studies comparing the metrological properties of hand OA scoring systems.

MRI

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For assessing MRI cartilage morphometry in knee OA, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness. Using MRI it is possible to accurately and feasibly measure change in cartilage morphology over 12 months for knee OA and we recommend the use of MRI for assessing cartilage morphology in trials of OA structure modification.

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It is possible to 'enrich' a knee OA study population with MRI outcomes in order to increase the rate of cartilage loss, for example, by including higher KL grade.

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In terms of correlations with concurrent symptoms, there is a weak association between progression of cartilage loss and increasing symptoms. There is little information on how change in cartilage parameters during the course of a study reflects post-study change in symptoms. There is some predictive validity with progression of cartilage loss predicting subsequent total joint replacement.

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More information is required on the performance metrics of MRI semi-quantitative and compositional measures of cartilage morphology. There may be a role for semi-quantitative assessments for assessing focal cartilage defects.

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Structure modification should be considered in a broader context than that of cartilage alone. Since MRI has the capacity to image the other tissues, further work is needed on the quantification and predictive validity of non-cartilage MRI pathologies. The performance metrics of non-cartilage MRI features have not been extensively studied but there is a rapidly emerging literature in this field.

Research recommendations

As well as the areas recommended above, including research into ‘whole organ’ or multi-tissue assessment (currently *via* semi-quantitative scores) and improving the quantification of non-cartilage pathologies, the MRI OA field needs:

- Studies to define more responsive measures of structural change.
- Studies that measure change at an earlier stage of disease when it may be more suitable for DMOAD intervention.
- Studies to improve predictive validity of current structural measures for important clinical outcomes (e.g., total joint replacement (TJR), virtual TJR).
- Studies to improve assessment precision of structural measures more closely related to symptom change (e.g., bone marrow lesions, synovitis).

Other imaging modalities

The potential for non-CR or MRI modalities to assess relevant non-cartilage tissues should be considered. Ultrasound is currently the other recent imaging modality with most information available, and at this stage it appears it is most promising as a tool for evaluating OA synovitis. Ultrasound-detected pathologies have been associated with current OA symptoms. Further work is required to better understand the performance metrics of ultrasonographic quantification of pathology, with such work requiring improved pathology definitions.

Conclusions

The amount of publications assessing OA structural change has dramatically increased over recent years, related to the availability of large cohort studies. Though we now understand CR JSW represents a complex of pathologies, gaps still remain in our understanding of both construct and predictive validity. The growth of MRI as an OA imaging biomarker has evolved to a point where it can be recommended for clinical trials in terms of cartilage morphology assessment. Much still needs to be understood about compositional cartilage measures and just as importantly, quantification of non-

cartilage features. The literature reviews performed by the ASC Working Group, together with attention to the research recommendations listed here, should ensure that the current gaps in our knowledge regarding the performance metrics and clinical importance of existing tools will be filled.