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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 ‡‡§§

† 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initiated a number of working groups to address a call from the US Food and Drug Administration (FDA) on updating draft guidance on conduct of osteoarthritis (OA) clinical trials.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.

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

* Address correspondence and reprint requests to: P.G. Conaghan, Section of Musculoskeletal Disease, Chapel Allerton Hospital, Leeds LS7 4SA, UK. Tel: 44-113-392-4883; Fax: 44-113-392-4991.
E-mail address: p.conaghan@leeds.ac.uk (P.G. Conaghan).

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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[1,2]. 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[6,7]. 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[8,9]. 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[10,11], 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 multitissue nature of OA[9,15]. 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[7,16]. Despite the limitations as a measure for DMOAD efficacy, delay in JSN has been reported for a small number of potential DMOADs to date[7,16]. 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