

Assessment of structure-modifying drugs in osteoarthritis: surrogate or hard clinical end points?

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Current regulatory requirements for the development of disease-modifying drugs in osteoarthritis (OA) still consider the measurement of joint space narrowing (a change in joint space width over many years) on plain x-rays as the appropriate primary end point for the demonstration of efficacy. However, other outcomes have recently been proposed. Among these, time to joint replacement appears to be an attractive option. Preliminary results are encouraging; however, more data are needed before recommending joint replacement as a primary outcome in disease-modifying OA drugs. It should be acknowledged that, owing to potential biases (e.g., absence of recommended guidelines, socio-economic and gender disparities in the rates of knee surgery, variability from country to country and willingness of patients to undergo the surgery), a recent expert consensus panel did not recommend this particular outcome as the primary end point for assessing the success or failure of a disease-modifying drug. Other tools, such as magnetic resonance imaging or biochemical markers, have potential as outcome measures but more studies are needed.

During the last few years, major advances have been made in the treatment of osteoarthritis (OA). Current management of OA includes nonpharmacological and nonsurgical measures, the use of pharmacological agents and surgery [1,2]. According to recommendations by expert panels and regulatory authorities, drugs for the treatment of OA could be classified as symptom-modifying or structure-modifying drugs, depending on their ability to control the symptoms of the disease or the progression of joint structure changes [3–5]. Joint structure modification has been emphasized as the most important determinant for disease progression. Thus, structure-modifying drugs have been synonymous with disease-modifying drugs. In OA, there is no theoretical framework on which to hang the concept of outcomes. However, various outcome variables have been recommended by experts in this field for the evaluation of disease-modifying drugs in OA [3,4,6]. For the symptom-modifying effect, these outcomes (i.e., Western Ontario and McMaster Osteoarthritis Index [WOMAC] and Lequesne index) are validated and accepted worldwide. Currently, the main outcome variable for the structure-modifying effect of an OA drug in a Phase III trial is the assessment of changes in joint space width (JSW) by plain radiograph. However, other clinical outcomes, such as magnetic resonance imaging (MRI) or biochemical markers, have recently been proposed. Among these, the

requirement for arthroplasty could be an attractive option as an outcome measure of clinical disease progression [6]. The aim of this review is to discuss the proposed outcomes for disease-modifying OA drugs.

Hard clinical end point

Existing regulatory guidelines for the approval of drugs to be used as structure-modifying drugs for the treatment of OA have been published in the USA and Europe. The recommended outcome variable for the structure-modifying effect of an OA drug is the assessment of changes in JSW, assessed on a plain radiograph [4]. However, the clinical relevance of this outcome has not yet been fully understood. In osteoporosis or heart disease, a clinically relevant outcome is fracture and myocardial infarction, respectively. In patients with OA, surgical procedure (i.e., total joint arthroplasty) has been suggested as a clinically relevant outcome.

The rationale for the use of total joint replacement as a relevant outcome in OA is based on the fact that this surgery is generally recommended after failure of nonsurgical treatment and is usually performed in patients who have severe disease [7–9]. However, despite the success of total hip and knee replacement over the last 30 or more years, the criteria for performing such surgery are not clear. Total joint replacement is an option for nearly all patients with diseases of the hip that cause chronic

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**future
medicine**

discomfort and significant functional impairment [10,11]. A NIH Consensus Statement workshop concluded that candidates for total hip arthroplasty (THA) should have moderate-to-severe persistent pain, disability, or both, not substantially relieved by an extended course of nonsurgical management in association with radiographic signs of OA [10]. The level of pain needed to initiate surgery is also unclear. In a Canadian pre-operative evaluation of patients with hip OA, the mean average WOMAC pain subscale score was 53 mm (standard deviation [SD]: ± 17) [12]. In a study performed in the Netherlands, 62 patients averaged 63 mm (SD: ± 25) in a visual analog pain scale (VAS) score while waiting for THA [13]. In another study, the day before THA surgery the mean WOMAC pain subscale score was 55 mm (SD: ± 17) [14]. Although these numbers appear reasonably consistent, many patients were on analgesics and/or anti-inflammatory drugs. Other studies record a change in function prior to surgery, but no amount of change was proposed to suggest the need for surgery. In fact, there is no level of loss-of-function validated to indicate surgery. In a study performed in Canada, the WOMAC physical function subscale averaged 60 mm (SD: ± 16) in 188 patients before total hip replacement [12]. One other study showed similar results with a WOMAC physical function of 61 mm (SD: ± 15) in patients the day before THA [14]. In the Evaluation of the CHondro-modulating effect Of Diacerein In OA of the Hip (ECHODIAH) study, the mean Lequesne algofunctional index in 126 patients just prior to THA, was 12.6 mm (SD: ± 4.3) [15].

For the hip, some indices have been proposed for the indication of THA. The US NIH suggest that THA should be considered in patients with radiographic evidence of joint damage, persistent pain and disability interfering with daily activities. This surgery should not be recommended for patients who are at risk of infections or patients with poor general health [10]. The Lequesne index, assessing symptoms and function, was initially designed to identify candidate patients for THA [16]. The New Zealand criteria are based on the sum of a set of scores including pain, functional impairment, range of motion, deformity and the impact of the disease on lifestyle [17]. In another study, candidates for THA should be patients with a summed WOMAC score (Likert scale) of 39 or more, clinical and radiological

evidence of OA and no absolute contraindication to THA [18]. The authors also take into account the willingness to undergo surgery. A recent index has been based on symptomatic severity, structural severity and response to prior pharmacological therapies [19]. However, these indices for THA require validation in future studies conducted in various cohorts of patients in different countries.

Joint-replacement surgery criteria as clinical outcomes have some limitations. First, as previously discussed, there are currently no recommended guidelines that provide clinical indications for knee surgery, so indications for surgery could vary from one surgeon to another. This could explain why there are data to suggest that a certain percentage of joint-replacement surgery is clinically inappropriate. Second, in patients with mild-to-moderate OA, the number of surgical procedures can only be assessed in a large cohort of patients followed over a long period. Indeed, total joint-replacement surgery is the treatment of choice for severe knee OA [20] but most patients with OA do not progress very rapidly to joint-replacement surgery, increasing the study population in order to demonstrate a difference between therapy and placebo. Investigator and industrial companies would probably prefer to include patients with severe OA. However, patients with OA of the knee could respond less well to the structural effect of an OA drug [21]. Third, patients entering such a trial may already be candidates for joint-replacement surgery, which could introduce bias. Fourth, socio-economic (i.e., insurance status and surgeon remuneration) and gender disparities in the rates of knee surgery have been reported [18]. Fifth, there is variability from country to country in the time from indication for knee surgery to performance of surgery [22]. Sixth, the willingness of the patients to undergo surgery or the risk of comorbidities could influence the decision to perform surgery.

A multidisciplinary expert panel is currently exploring ways of retaining the clinical relevance of total joint replacement while overcoming the problems [23]. Some of the limitations reported previously could be reduced by the use of a modified time to surgery end point. In fact, two alternative outcomes are being considered: the time to the physician's decision to recommend surgery and the time to fulfilling criteria for total joint replacement. For instance, the time to reach indication for joint

arthroplasty could reduce some of the nonmedical limitations (e.g., waiting list and willingness of the patient).

Few studies have been performed with joint surgery as a clinical outcome. The ECHODIAH study evaluated the effect of diacerein on the progression of joint space narrowing (JSN) in patients with hip OA after 3 years of therapy [24]. In the intention-to-treat analysis, the mean JSN was 0.39 mm/year (SD: ± 0.81) in the placebo group and 0.39 mm/year (SD: ± 0.75) in the diacerein group, without any statistical differences between the two groups. However, in patients who completed 3 years of treatment (per protocol analysis), the rate of JSN was significantly lower with diacerein. Moreover, the proportion of patients with severe radiographic JSN (at least 0.5 mm) during the study period was lower in the diacerein group compared with placebo. Total hip replacement of the signal hip during the study and during the 3 months following discontinuation of the study treatment was performed in 87 patients: 14.5% of the diacerein group and 19.8% of the placebo group. Comparison between the two groups showed a trend in favor of diacerein treatment that did not reach statistical significance ($p = 0.29$), but it should be emphasized that the study was not powered for this outcome measure. A randomized, placebo-controlled, double-blind study demonstrated that 3-year administration of oral glucosamine sulfate prevented joint structure changes in patients with knee OA, assessed by radiographic JSN, with a significant improvement in symptoms [25]. These results have been confirmed in a second, independent trial [26]. A 5-year follow-up evaluation of patients from the first trial was performed to assess long-term outcomes of disease progression after the end of the study [6]. The primary end point of this follow-up study was the occurrence of OA-related joint surgery. Of the 177 patients participating in this follow-up evaluation, 26 (14.7%) underwent OA-related lower limb surgery during the follow-up period. There were twice as many patients from the former placebo group that underwent surgery, with a 48% decrease in risk with glucosamine sulfate that was borderline statistically significant ($p = 0.06$). The time-to-event analysis confirmed the results of the crude primary outcome, indicating a decreased ($p = 0.05$) cumulative incidence in OA-related lower limb surgeries for the patients formerly

on glucosamine sulfate. When only total hip and/or knee replacements were considered, the trend was similar with an over 40% reduction in risk after glucosamine sulfate, but the level of probability was lower and only showed a trend towards the significance threshold ($p < 0.2$).

In conclusion, more studies are needed before recommending joint replacement as a primary outcome in disease-modifying OA drugs. Indeed, none of these preliminary studies were specifically designed to assess the effect of a structure-modifying drug on the rate of joint surgery. However, both USA and European guidelines encourage the assessment of the delay in time to joint surgery in clinical trials of structure-modifying drugs.

Surrogate assessment

X-ray

The use of several outcome measures have been recommended in studies evaluating potential disease-modifying drugs [4,5]. Assessment of changes in JSW by plain radiography is currently the preferred target of regulatory authorities for joint structure changes in OA. Radiographic JSN is, therefore, the primary outcome measure for the efficacy of possible disease-modifying drugs, as recommended by scientific organizations and acknowledged by regulatory agencies, such as the European Medicine Evaluation Agency and the US FDA. Subsequently, there is a consensus within scientific organizations and regulatory authorities to use radiographic changes, for example, JSN over a period of 2–3 years as a surrogate to hard clinical end point. However, as JSN provides a continuous variable over time, it is difficult for the clinician to interpret it, as it does not present the results as a proportion of patients with or without a key event (e.g., the fracture end point in osteoporosis). Therefore, it could be interesting to dichotomize the variable JSW changes over time. At the level of the hip, a change of at least 0.5 mm in JSW has previously been suggested. It corresponds to the lowest difference in JSW exceeding the measurement error and represents an actual radiographic progression [27]. However, this threshold is statistically derived and does not necessarily reflect a clinically relevant progression of OA.

To be fully validated, a surrogate end point should demonstrate a natural course closely related to that of the relevant hard clinical end point (e.g., a decrease in JSW would be linked

with an increase in the incidence of joint surgery). The magnitude of change in the surrogate end point responsible for a subsequent increase or decrease in incidence should be clearly defined (e.g., a 0.5 mm decrease in JSW would be linked to a twofold increase in the risk of joint surgery). Eventually, this numerical relationship should also be validated following an external intervention (e.g., JSN reduced by 50% would result in a 25% decrease in the incidence of joint surgery).

At the level of the hip, one study suggests that cut offs of absolute decreases in JSW of 0.2 and 0.4 mm could be considered clinically relevant on the basis of the subsequent need for THA [28]. Using an expert opinion approach, the same group of authors also suggests that a change of at least 0.4 mm in the radiological JSW could be considered clinically relevant [29]. Selection of these cut offs was based on the finding that it provided maximal sensitivity and specificity for the occurrence of THA over the subsequent 3 years. At the level of the knee, the clinical relevance of these cut offs remains unknown. The clinical relevance of a cut off could be assessed if an association was found between femoro–tibial JSN over several years and a relevant outcome in OA. Indeed, every treatment that prevents the natural structural evolution of knee OA could then influence the occurrence of the relevant outcome. A study was recently performed with the objective to assess the clinical relevance of femoro–tibial JSN to predict future OA-related surgery in patients with knee OA [30]. A total of 126 subjects with primary knee OA were followed prospectively for a mean period of 8 years. JSW was assessed from standard x-rays at baseline and after a follow-up of 3 years. The rate of knee OA-related surgeries was recorded for the following 5 years. The cut off for JSN, maximizing sensitivity and specificity to predict future surgeries, was a change of 0.7 mm or more in minimal JSW over a period of 3 years. However, no meaningful differences were observed for cut-off values between 0.5 and 0.8 mm (overall efficiency between 73 and 75% to predict the occurrence of knee surgery 5 years later).

It should also be noted that a recent expert consensus recommended including, as a secondary outcome, the percentage of patients who have a ‘failure’ [4]. The definition of a failure patient would be someone with a progression of JSN greater than 0.5 mm over a period

of 2–3 years, or who has significant worsening in pain and/or function based on validated cut off values.

It should be acknowledged that the use of JSN as a surrogate outcome is potentially limited by issues of reproducibility related to positioning [31]. Moreover, an evidence of the short-term reproducibility of a radiographic protocol is an insufficient basis on which to predict the quality of its longitudinal performance [32].

However, such statements require validation in other studies conducted in various cohorts of patients.

Magnetic resonance imaging

Although regulatory requirements for the development of disease-modifying drugs in OA still consider the measurement of JSN (a change in JSW over several years) on plain x-rays as the appropriate primary end point for demonstration of efficacy, radiography neither allows the detection of early structural damage nor constitutes an efficient way of monitoring the progression of OA in daily practice. Moreover, radiography assesses other features of OA poorly. In fact, OA is an episodic inflammatory disorder of synovial joints, characterized by the focal deterioration and abrasion of articular cartilage, with sclerosis and cyst formation in the underlying bone, as well as formation of osteophytes at the joint surface. Thickening of the joint capsule and chronic synovitis are also common features. MRI, with its superior soft tissue contrast, is the best technique available for the assessment of normal articular cartilage and cartilage lesions. Joint imaging has the potential to provide morphological information, such as the presence of fissuring, partial or full thickness cartilage defects and signal changes within residual cartilage [4,33,34]. Moreover, MRI, with its ability to discriminate articular tissues, holds the greatest potential as a tool for whole-organ imaging of the joint. A MRI global knee joint score has recently been validated [35]. Some studies have found a statistical association between changes in MRI findings and the currently accepted surrogate JSW changes. However, all studies dealing with the association between MRI and x-ray for the assessment of OA progression have provided heterogeneous results [33,36–38]. Thus, it re-emphasizes that more data on MRI should be provided before accepting it as primary end point in a clinical Phase III trial on disease-modifying OA drugs. However, it should be

noted that the use of MRI as a potential end point technique could be re-emphasized by a recent study by Cicuttini and colleagues [39]. In 123 subjects with mild-to-moderate symptomatic knee OA, the rate of tibial cartilage loss over 2 years, assessed by MRI, was a predictor of future (4 year) knee replacement surgery. For every 1% increase in the rate of tibial cartilage loss, there was a 20% increased risk of undergoing a knee replacement surgery after 4 years [39]. It should be noted that, in recent expert consensus publications, the use of MRI has been accepted as an outcome in Phase II studies, but that further data (e.g., associations between MRI and clinical assessment and/or x-ray, short- and long-term reproducibility, etc.) are needed before accepting MRI as a primary end point in a Phase III clinical trial [4].

Biochemical markers

The metabolic alterations in joint tissues associated with OA involve changes in both the synthesis and degradation of matrix molecules, which are then often released as fragments into joint fluid, blood and urine, where they may be detected [40–42]. Markers that reflect the ongoing repair and degenerative processes occurring within a joint might be regarded as predictive tools of the rate of OA progression. Biochemical markers have been shown to complement imaging techniques as surrogate markers of OA disease progression [42–45]. Indeed, some studies found a predictive value of hyaluronic acid [46], C-reactive protein [47], cartilage oligomeric matrix protein [48], bone sialoprotein [48], osteochondrosis [43], procollagen of Type II collagen (PIINP) [49], type II collagen C-telo-peptide (CTX II) [44,50,51], type II collagen (Coll 2)-1 [45] and Coll 2-1 nitrogen oxide [45] for radiographic OA progression. In particular, changes in biochemical marker levels have been associated with changes in the surrogate JSW changes [43,50]. However, biochemical marker levels have not yet been associated with the occurrence of total joint replacement.

Others (ultrasound & arthroscopy)

Other outcome tools have been proposed, such as arthroscopy [52–54] or ultrasound [55]. However, none of these studies have been shown to be related to structural progression assessed with validated tools. Moreover, additional studies are needed to determine the sensitivity and specificity of these finding in predicting joint-replacement surgery.

Conclusion

The time to joint replacement appears to be an attractive way to assess the clinical effect of a disease-modifying OA drug. However, potential biases (e.g., the absence of recommended guidelines, socio-economic and gender disparities in the rates of knee surgery, variability from country to country and willingness of the patients to undergo the surgery) make this outcome less useful and a recent expert consensus panel did not recommend this particular outcome as a primary end point for assessing the success or failure of a disease-modifying drug. More data are needed before recommending time to joint replacement as a primary outcome in disease-modifying OA drugs. MRI has great potential as a primary outcome but more studies are needed. In fact, current regulatory requirements for the development of disease-modifying drugs in OA still consider the measurement of JSN (a change in JSW over several years) on plain x-rays as the appropriate primary end point for demonstration of efficacy.

Future perspective

As discussed, MRI has great potential as a primary outcome. However, one of the most promising MRI capabilities could be a method developed to directly evaluate the changes in cartilage matrix components (e.g., collagen and glycosaminoglycan). These approaches could be of great interest for detecting early changes in cartilage components in response to pharmacological intervention. Several studies have shown that MRI T₂ relaxation can be used as a qualitative assessment of collagen in the cartilage matrix [56,57]. A technique known as delayed gadolinium enhanced MRI of cartilage, is being developed to directly image the glycosaminoglycan component in cartilage [58–60]. Other MRI markers of structural changes, such as cartilage defects, also have great potential. However, further work is still needed in order to assess the clinical relevance of these new MRI techniques. One other interesting potential outcome is the use of biochemical markers. There has been progress in the use of some of these markers for the prediction of progression of OA, as well as for the evaluation of response to therapy with compounds with disease-modifying activity. However, further work is still needed to investigate how the changes measured in some of these biochemical markers correlate with OA disease progression.

Executive summary**Definition**

- According to recommendations of expert panels and regulatory authorities, drugs for the treatment of osteoarthritis (OA) could be classified as symptom-modifying or structure-modifying drugs, depending on their ability to control the symptoms of the disease or the progression of joint structure changes.
- Joint structure modification has been emphasized as the most important determinant of disease progression. Structure-modifying drugs have therefore been synonymous with disease-modifying drugs.

Current recommendation

- Current regulatory requirements for the development of disease-modifying drugs in OA still consider the measurement of joint space narrowing (a change in joint space width over several years) on plain x-rays as the appropriate primary end point for the demonstration of efficacy.

Total joint replacement as an outcome

- The time to joint replacement appears to be an attractive way of assessing the clinical effect of a disease-modifying OA drug.
- However, potential biases make this outcome less useful and a recent expert consensus panel did not recommend this particular outcome as primary end point for assessing the success or failure of a disease-modifying drug.

Surrogate end point

- Magnetic resonance imaging or biochemical markers have great potential as outcome measures; however, more studies are needed before acceptance as a primary outcome in Phase III trials.

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