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Review Article

How to define responders in osteoarthritis

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Abstract

Background: Osteoarthritis is a clinical syndrome of failure of the joint accompanied by varying degrees of joint pain, functional limitation, and reduced quality of life due to deterioration of articular cartilage and involvement of other joint structures.

Scope: Regulatory agencies require relevant clinical benefit on symptoms and structure modification for registration of a new therapy as a disease-modifying osteoarthritis drug (DMOAD). An international Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and International Osteoporosis Foundation was convened to explore the current burden of osteoarthritis, review current regulatory guidelines for the conduct of clinical trials, and examine the concept of responder analyses for improving drug evaluation in osteoarthritis.

Findings: The ESCEO considers that the major challenges in DMOAD development are the absence of a precise definition of the disease, particularly in the early stages, and the lack of consensus on how to detect structural changes and link them to clinically meaningful endpoints. Responder criteria should help identify progression of disease and be clinically meaningful. The ideal criterion should be sensitive to change over time and should predict disease progression and outcomes such as joint replacement.

Conclusion: The ESCEO considers that, for knee osteoarthritis, clinical trial data indicate that radiographic joint space narrowing >0.5 mm over 2 or 3 years might be a reliable surrogate measure for total joint replacement. On-going research using techniques such as magnetic resonance imaging and biochemical markers may allow the identification of these patients earlier in the disease process.

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REVIEW ARTICLE

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1

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Key words: magnetic resonance imaging, osteoarthritis, X-ray, responder, structure-modifying drug, pain

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2

ABSTRACT

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Scope: Regulatory agencies require relevant clinical benefit on symptoms and structure modification for registration of a new therapy as a disease-modifying osteoarthritis drug (DMOAD). An international Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and International Osteoporosis Foundation was convened to explore the current burden of osteoarthritis, review current regulatory guidelines for the conduct of clinical trials, and examine the concept of responder analyses for improving drug evaluation in osteoarthritis.

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Conclusion: The ESCEO considers that, for knee osteoarthritis, clinical trial data indicate that radiographic joint space narrowing >0.5 mm over 2 or 3 years might be a reliable surrogate measure for total joint replacement. On-going research using techniques such as magnetic resonance imaging and biochemical markers may allow the identification of these patients earlier in the disease process.

3

1.0. Introduction

About one tenth of the world's population aged over 60 years is estimated to have symptomatic problems that could be attributed to osteoarthritis.[1] As one of the most common musculoskeletal disorders, osteoarthritis is a major cause of pain, disability, and reduced quality of life. The prevalence of the disease increases with age and is strongly related to that of obesity. Osteoarthritis is therefore expected to become a major health-care concern in the future with the aging of the population and adoption of Western lifestyles.[2] The prevalence of symptomatic osteoarthritis in those aged over 60 years is predicted to be 30% by the year 2030.[3]

On a global level, osteoarthritis is the fourth leading cause of years lost to disability,[1] and is associated with an extremely high economic burden. As an example, UK-based figures estimate the total direct and indirect costs associated with osteoarthritis to be £2 billion/year, including 3 million GP consultations and 115 000 hospital admissions. Analysis of temporal trends in hip and knee replacement in the UK since 1991 indicate that the rates of joint replacement have risen particularly steeply in the last decade.[4] Similar results have been reported from other countries, for example, in the Italian population.[5]

Despite this, its management remains mainly symptomatic (i.e. analgesics such as paracetamol, non-steroidal anti-inflammatory agents [NSAIDs/coxibs], and physical therapy),[2] and there is currently no effective pharmacological strategy to prevent the progression of the disorder. Disease-modifying osteoarthritis drugs (DMOADs) have therefore become a major focus of research, though there are

4

significant development challenges, such as selection of clinically meaningful endpoints and definition of responders to treatment. The regulatory requirements for osteoarthritis drugs have recently been reviewed and updated.[6,7]

Against this background, an international Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and International Osteoporosis Foundation was convened to highlight the current burden of osteoarthritis, review current regulatory guidelines for the conduct of osteoarthritis trials, and examine the concept of responder analyses for improving drug evaluation in osteoarthritis and the management of patients. This discussion paper addresses these issues.

2.0. Methods

Relevant articles, reviews, and abstracts were identified through a PubMed/MEDLINE search of English-language articles published between 1990 and September 2011. The initial search strategy included the terms: regulatory affairs in osteoarthritis, osteoarthritis, lower limbs, response in osteoarthritis, prognosis, responder rate, definition of responders, joint space narrowing, and joint space width. Separate subsearches were also performed using a cross-search of the above terms combined, as well as the reference lists of the selected articles. Other items were identified from the presentations made during the meeting. Overall, 69 relevant items were selected by the authors according to their quality and pertinence for discussion by the ESCEO working group and for inclusion in this review.

5

3.0. Natural history and outcome of osteoarthritis

3.1. Definition and descriptive epidemiology

Osteoarthritis refers to a clinical syndrome of failure of the joint accompanied by varying degrees of joint pain, functional limitation and reduced quality of life. It is defined by focal loss of articular cartilage, a variable subchondral bone reaction, and involvement of other joint structures, including the ligaments, meniscus, capsule, synovial membrane, and periarticular muscle. It predominantly involves the knee, hip, spine, hands, and feet. The classical pathological hallmark is cartilage deterioration, with fibrillation, fissures, ulceration, and ultimate loss, associated with hypertrophy of subchondral bone. When severe, these structural changes (e.g., loss of joint space, presence of osteophytes, changes in subchondral bone, and cyst formation) can be used in epidemiological studies to define the disorder and estimate the prevalence of osteoarthritis. Radiographic changes are variably associated with joint symptoms (stiffness and loss of function); the relationships may change with time, as well as between joint sites, and are dependent on many variables. A conceptual model for the pathogenesis of osteoarthritis is that systemic factors (e.g., age, gender, ethnicity, metabolic syndrome, and genetic factors) increase general susceptibility to the disease, while local mechanical factors (e.g., obesity, joint injury or deformity, and muscle weakness) influence its site and severity.[8]

6

Population-based longitudinal studies, mostly based on radiographic measures, have provided information on the rate of transition from normality to joint failure. The majority of individuals with chronic knee pain aged 35 to 55 years are likely to develop knee osteoarthritis over the next decade.[9] In well-aligned joints, osteoarthritis is associated with a joint space narrowing (JSN) of 0.1 to 0.3 mm/year, though there is a wide range around these values.[10,11] In a population sample of 354 men and women in the Chingford study (mean age at follow-up 75.8 years), the incidence of radiographic osteoarthritis over 5 years was 2.5% (for Kellgren-Lawrence grade 2 or higher) with a progression rate of 3.6% (change to a higher grade from grade 1 or above).[12] A further analysis within the same cohort of 1048 women revealed that over a 15-year period, 57% of subjects remained stable (i.e. in the same Kellgren-Lawrence grade), 41% progressed, and 2% regressed.[13] The most rapid progression was experienced by subjects with Kellgren-Lawrence grade 1 at baseline, who were 3.2 (95% confidence interval [CI] 2.3 to 4.4) times more likely to progress to grade 2 or higher than those with baseline grade 0.[13] A recent study with 5 years of observation reported that while 19% of patients with knee osteoarthritis had radiological progression, as many as 54% of those with certain baseline radiographic characteristics progressed.[14] Future studies using continuous measures such as joint space width (JSW) may provide information on whether there is a smooth transition from one grade to another, or whether progression arises through discrete step-wise changes in structure.

The Chingford Study also confirmed the variable natural history of knee osteoarthritis with approximately 35% of subjects remaining asymptomatic, 10% remaining painful, 25% developing new pain that remained, and 30% having intermittent pain over a 15-year follow-up

7

period; overall, around 60% of subjects suffered knee pain at some point in the six evaluations over that period.[15]

Most currently recognized risk factors for prevalent knee osteoarthritis (obesity, knee injury, excessive occupational or leisure physical activity, and osteoarthritis of the hand) have a greater effect on the incidence of the condition than radiographic progression.[12] In this context, obesity is a risk factor for other comorbidities affecting this population, such as hypertension, venous thrombosis, and pulmonary embolism. A recent systematic review examined patient characteristics that could be used by health-care providers to predict the likelihood of progression of knee osteoarthritis.[16] Consistent, statistically significant associations were reported for age, varus knee alignment, presence of osteoarthritis in multiple joints, and radiographic changes. Body mass index was also found to be a strong predictor of progression beyond 3 years.

Finally, there is continuing recent evidence that patients with osteoarthritis have excess all-cause mortality compared with the general population (age- and sex-adjusted standardized mortality ratio of 1.55, 95% CI 1.41-1.70).[17,18] Risk factors associated with this excess mortality include history of cardiovascular disease, cancer, diabetes, and the presence of walking disability.

3.2. Osteoarthritis and arthroplasty

Early in the disease, knee osteoarthritis is marked by successive episodes of pain rather than uninterrupted pain.[2] If pain is present every day for several months—and particularly if it is

8

aggravated by walking—and conservative approaches have failed (intra-articular injections, rehabilitation, and other therapies), then the best management strategy would be surgery.[19] Although osteoarthritis is the most common reason for knee and hip replacement surgery, a recent UK study reported a fivefold difference in the age- and gender-adjusted rate of total joint replacement compared with the epidemiologically derived incidence of osteoarthritis.[20] There was evidence of inequality in access to surgery, which was in turn dependent on age, sex, social deprivation, rural versus urban place of residence, and ethnicity. These points have generated significant concerns that total joint replacement may represent an inaccurate or biased outcome. Moreover, recent studies from the Osteoarthritis Research Society International and Outcomes Measures in Osteoarthritis (OARSI/OMERACT) task force suggest that pain and functional impairment do not predict joint replacement.[21,22] Together with the relatively low rate of such procedures, this represents a considerable limitation to the use of total joint replacement—or indeed referral for the procedure—as an outcome measure in international multicenter randomized controlled trials of drugs in osteoarthritis. This conclusion accords with that of independent working groups addressing this issue.[23,24]

Success of surgical intervention is increasingly determined using patient-reported outcome measures. The impact of joint replacement on health-related quality of life is well established,[25] with the greatest benefits reported in the first 6 months. On the other hand, while total hip replacement appears to be effective in the short term, most studies only follow patients for 6 to 12 months after surgery. A prospective cohort study interviewed 799 patients at 12 and 24 months after total hip replacement and revealed that age, gender, functional status, and patient expectations at baseline were predictive of a good outcome at 2 years.[26] A smaller study that monitored 282 patients for 8 years after surgery showed that improvements in physical function following total hip replacement for osteoarthritis were

9

sustained and were more frequent in patients with more severe radiographic features of osteoarthritis

before surgery.[27] A related issue is response to rehabilitation, which appears to be predicted by a range

of factors, including female gender, absence of depression, and low rates of comorbidities.[28]

Attention is now focusing on methods to enhance these post-operative outcomes, and improve

prosthesis survival. A recent example of this approach evaluated the role of bisphosphonates in

prosthesis survival after total joint replacement in a population-based study. The UK General Practice

Research Database was used to identify patients undergoing total hip (n=23 269) or total knee

replacement (n=18 726) for osteoarthritis between 1986 and 2006,[29] and bisphosphonate use was

recorded (≥6 months' treatment duration at >80% adherence). In an observational study,

bisphosphonate use was associated with a significantly lower rate of revision surgery over 5 years (0.6%

in users versus 1.3% in non-users, p=0.04). There was an increase in prosthesis survival time compared

with non-users and a doubling of the time to revision surgery.[29] Similar findings have been reported for

zoledronic acid, which appears to improve implant fixation.[30]

4.0. Current regulatory requirements for osteoarthritis drugs

Advances in the field of osteoarthritis research have led to recent initiatives by the European Medicines

Agency (EMA) Committee for Medicinal Products for Human Use and the FDA to update their guidance

for osteoarthritis drug development.[6,7] The EMA guidance came into effect in January 2010 with

revisions in six main areas, aiming to strengthen and bring up to date the design of randomized clinical

trials in osteoarthritis.

10

4.1. Main efficacy variables

4.1.1. Symptoms

Symptom-modifying osteoarthritis drugs (i.e. those acting only on pain and functional disability) are not expected to affect the structural changes associated with osteoarthritis.[6] According to the EMA,[6] the recommended primary endpoint for clinical development in this area therefore remains pain attributable to the target joint, preferably with functional disability as a co-primary endpoint. If functional disability is not a primary endpoint, at least the absence of functional deterioration should be shown. For development toward a general indication for symptoms in osteoarthritis at all sites, efficacy should be explored at the knee, hip, and hand. The safety evaluation is characteristic of agents developed for long-term treatment of a chronic disease whether it is intermittent or continuous; symptom-modifying drugs should also be demonstrated to have no deleterious effect on structure. The guidelines also set out recommendations for topically applied products,[6,7] including NSAIDs/coxibs, hyperemic agents, and herbal medicines. Placebo-controlled trials are generally required to demonstrate efficacy, and safety data should be provided on local tolerability (skin tests) and systemic exposure after application of therapeutic doses. For intra-articular products, efficacy should be demonstrated in placebo-controlled trials with an established active comparator, and the residence time in the joint and the systemic availability of the active substance should be investigated for safety.

Insofar as osteoarthritis is associated with remitting and relapsing symptoms, the guidelines recommend

assessing changes in pain intensity at appropriate time points. These have been set at 2 to 4 weeks for

systemic NSAIDs and 1.5 weeks for intra-articular steroid injections or topical NSAIDs.[31] Trials

investigating slow-acting symptom-modifying drugs should last between 6 and 12 months. For rapid-

acting symptom-modifying drugs, the guidelines recommend a study duration of ≥3 months, with

follow-up for at least 1 year.[6,7]

12

In general, confirmatory studies to evaluate symptomatic efficacy should have a randomized, controlled, parallel-group design with three arms including placebo, followed by a long-term, double-blind phase with active comparator, or a long-term extension phase.[6,7] Often a flare study design is used, i.e. trial entry is restricted to patients whose pain increased during a wash-out phase. This design is recommended for rapid-onset symptom-modifying drugs, as it allows a more homogeneous course of symptoms and reflects conditions in daily clinical practice. The influence of a flare study design on response to symptomatic treatments should be considered. This has been illustrated in meta-analyses.[31,32] In one of these meta-analyses, patients using an NSAID with a baseline pain intensity >40 mm on a visual analogue scale (VAS) were categorized according to whether they experienced a flare in the pre-trial wash-out period. The difference in pain difference versus placebo was significantly higher in patients who experienced a flare during the wash-out (12% versus 8% in the group without a flare, $P<0.001$),[31] illustrating the increased chances of detecting a treatment effect. For slow-acting symptom-modifying drugs, a withdrawal period randomized to continue or discontinue treatment in order to evaluate the number of flares is often recommended.

The last decade has seen the development of a number of osteoarthritis-specific multidimensional assessment tools for evaluation of symptoms, including total questionnaires or subscales (pain or function), and quality of life questionnaires. These include the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and the Lequesnes index.[7,33] According to the EMA guidance,[6] questionnaires for measuring composite indices should be clinically meaningful and validated, demonstrate high responsiveness in the specific population for which the indication is sought, produce precise and reproducible results, and be at best

13

supported by evidence from already published study data in the field, which should be assessed.

Several psychometric tests are being developed for measurement of pain, function and disability

associated with osteoarthritis. Specific questionnaires or subscales are available,[34,35] such as the

Knee Injury and Osteoarthritis Outcome Score (KOOS); the WOMAC pain subscale; the

symptom subscales of both the Hip Disability and Osteoarthritis Outcome Score and the KOOS;

and the limitation dimension of the Late Life Function and Disability Instrument.

4.1.2 Symptoms and structure

For DMOADs, the regulatory guidelines demand an effect on joint structure, as well as an effect on

symptoms, a long-term clinical benefit, and good long-term safety, as described above. The key

regulatory requirements for DMOAD trials are presented in **Table 1**. Phase 3 placebo-controlled trials for

DMOADs that are expected to slow structural damage should last at least 2 years. The main efficacy

endpoint for structure in clinical development programs is radiographic JSW (and JSN), which therefore

remains the gold standard for trials in osteoarthritis (**Table 1**).[6,7,36] The standardization of radiographic

techniques is important, and should include radioanatomic positioning, beam alignment, defined

anatomic boundaries, and patient positioning (anterior-posterior view).

JSW represents the thickness of articular cartilage, though in some joints, such as the knee, it also

reflects the presence of other structures (e.g., meniscus) and is a composite measure of the combined

thickness of those structures. In some cases, JSN in the osteoarthritic knee may reflect meniscal tissue

damage or extrusion.[37] While JSN has been shown to be sensitive to change,[38] the rate of narrowing

among cohorts with knee osteoarthritis is highly variable. Over intervals of 2 to 3 years (the typical

14

duration of DMOAD trials), JSW measurement may be affected by changing patient characteristics over time, inconsistent radiographic positioning of the knee during serial X-ray visits, and other technical factors.[39] The reliability and responsiveness of radiographic JSN have been found to be independent of the technique used: extension versus flexion views, fluoroscopy versus no fluoroscopy, computerized analysis versus manual.[40] The greatest responsiveness was observed in studies with longer follow-up times (>2 years) and in those with the knee in a flexed position.[40] For hip osteoarthritis, reliability and responsiveness of JSW measurements were both excellent.[41]

4.2. Secondary outcomes

4.2.1. Symptoms

Secondary outcomes for the evaluation of symptoms include landmark analyses (measured at clinically important time points over the course of the study); patient's global assessment of disease activity; treatment response (percentage of patients achieving a predefined level of symptom relief); onset of action (to obtain information about patients with exacerbations); health-related quality of life questionnaires; and consumption of rescue medication, including side effects and compliance.

4.2.2. Structure

Magnetic resonance imaging (MRI) is increasingly being used for structural joint assessment in osteoarthritis trials. There are a variety of quantitative and semi-quantitative MRI techniques available, such as parametric mapping techniques (dGEMRIC [delayed gadolinium-enhanced MRI of cartilage],

15

T1rho, T2 mapping, and sodium MRI]),[42] as well as scoring of joint tissue via WORMS (Whole Organ MRI

Score), BLOKS (Boston Leeds Osteoarthritis Knee Score), and MOAKS (MRI Osteoarthritis Knee Score).[43-45] The main parameter is cartilage volume loss as a measure of cartilage thickness, though a host of

other evaluations are possible (cartilage thickness, JSW, the presence of cartilage defects, and bone

marrow lesions). MRI parameters are considered to have potential as surrogate endpoints for evaluation

of structural changes.[42] However, a recent report concluded that it has a high specificity but only

moderate sensitivity for the detection of osteoarthritis,[46] and larger longitudinal studies are necessary to

establish clinical relevance and support its use for registration purposes.[6] The use of MRI as a potential

endpoint technique was reemphasized by a recent study by Cicuttini et al[47] in 123 subjects with mild to

moderate symptomatic knee osteoarthritis. The rate of tibial cartilage loss over 2 years, assessed by

MRI, was a predictor of future knee replacement surgery and, for every 1% increase in the rate of tibial

cartilage loss, there was a 20% increase in the risk of undergoing knee replacement surgery over 4 years.

A similar finding was reported by Raynauld et al in a knee osteoarthritis DMOAD trial.[48] It should be

pointed out, as discussed before, that surgical selection bias may have occurred and consequently,

interpretation should be done carefully. A series of reports from the OARSI FDA initiative have

addressed the issue of the comparison of radiographic and MRI measures.[36,40,41,49,50] Research into

alternative imaging techniques, such as ultrasonography, chondroscopy and scintigraphy, may also lead

to new efficacy parameters.

Biochemical measurements in serum, urine, and synovial fluid that reflect degradation of

cartilage, bone, or synovium (e.g., enzymes, matrix fragments, and growth factors) may also be

considered as additional tools to assess efficacy. A biomarker detectable early in disease may

enable detection of osteoarthritis before joint destruction occurs, allow more accurate prognoses,

and permit monitoring of disease progression after treatment. There has been some success in the

classification of biomarkers and the correlation of radiographic or MRI disease progression with

an increase in a particular biomarker.[51] Elevated levels of CTX-II (C-terminal telopeptide of type

II collagen degradation) have also been shown to be associated with radiographic progression of

osteoarthritis.[52-54] Similarly, higher baseline values of interleukin-6, C-reactive protein (CRP),

and cartilage oligomeric matrix protein (COMP) have been found to be predictive of greater risk

of cartilage loss in osteoarthritis.[55] Baseline CRP was also found to be a good predictor of the

symptomatic response to treatment.[55] A further finding was that increases in matrix

metalloproteinase (MMP) levels correlated with disease progression measured by X-rays and

MRI.[55] MMPs are known to play a role in the pathologic breakdown of the joint extracellular

matrix in osteoarthritis. While there has been much progress in the field of biomarkers, further

work is required to elucidate the relationship with disease progression[6] and determine whether

measurement of biomarkers can be useful outside the research setting.

5.0. Responders in osteoarthritis

Objective assessment of hard endpoints in randomized clinical trials constitutes the backbone of

evidence-based medicine. However, the difficulties identifying a reliable hard endpoint may be

hindering the development of osteoarthritis drugs. This may be partly because of the lack of a

universal definition of osteoarthritis, notably due to the multitude of processes underlying its

pathogenesis. The absence of a hard endpoint considerably complicates the comparison of

clinical outcomes and may also underlie the poor correlation between the severity of cartilage

17

degradation, as reflected by radiographic JSN, and the severity of symptoms. Another factor may be the absence of consensus on the definition of a responder patient, though there are now a few studies that provide appropriate background information to explore this specific question. The ideal responder criterion—i.e. the most clinically relevant—is one that is clinically meaningful and produces clinically relevant symptom reduction (e.g., for rapid symptom-modifying drugs, 50% improvement and at least 20 mm pain relief) or that could be linked to a relevant endpoint of disease progression, notably to joint replacement (e.g., for DMOADs).[48,56] The EMA guidelines recommend presenting results using a predefined responder definition as a complementary endpoint to demonstrate individual relevance and robustness.[6]

5.1. Symptoms

Incorporating response levels into analyses of effects on symptoms has been shown to affect the capacity of randomized trials to detect a treatment effect.[57] The guidelines state that the minimal perceptible clinical improvement (MPCI) or the minimal clinically important improvement (MCII) of a drug may be used to evaluate clinically relevant changes. MCII has been defined as the smallest change in a measurement that signifies an important improvement in a patient's symptom score; this has been reported to be affected by the severity of symptoms at baseline, but not by age, disease duration, or gender.[58] Therefore, the extent of baseline symptoms should be sufficient (usually at least 40 mm on a 100-mm VAS) to detect changes. Furthermore, the difference in pain relief in the test group versus placebo should also be perceptible by the patient. The extent of minimal perceptible clinical improvement (MPCI) was determined to be approximately 10 mm.[59] This value is supported by the

18

results of a meta-analysis (best mean difference in pain relief versus placebo) including the results of

clinical studies of knee osteoarthritis patients treated with established NSAIDs.[31]

With regard to an adequate cut off for responders, 255 patients participated in a post hoc analysis in an

open-label randomized trial comparing appropriate care of knee osteoarthritis with and without Hylan

G-F 20.[60] Setting the MCII responder criterion as a decrease in WOMAC score of 20% or 50% detected

significant differences between treatment groups, but no difference was noted with a response level of

70% reduction in WOMAC score.[60]

In addition to change of pain intensity from baseline, the status of remaining pain intensity under

therapy can be assessed. For this purpose, the patient acceptable symptom state (PASS) can be used. It

determines the symptom level above which patients consider themselves well, i.e. they are satisfied

with their condition. It has been suggested that PASS may be more robust than MCII, since it is not

affected by initial level of symptoms[61]; it also has the advantage of encompassing a notion of quality of

life.[62] Further research is necessary, though the two techniques, MCII and PASS, do appear to be

complementary.

Responder rates give an indication of the symptomatic efficacy for the individual patient in

osteoarthritis trials in addition to mean pain scores.[63] A meta-analysis of trials of etoricoxib for

osteoarthritis showed that responder rates were reproducible over different levels of response and

provided additional meaningful information.[64] A 10-mm difference on the VAS between the new

chemical entity and the placebo is currently considered as clinically relevant for drugs specifically aiming

19

at a fast pain relief.[31,59] However, at this stage, no clinically relevant threshold is defined or validated for slow acting drugs in osteoarthritis.

Studies from the OARSI have indicated that symptomatic status alone is insufficient to predict the progression of osteoarthritis to joint replacement.[21,22] On the other hand, it has been suggested that combining symptoms with radiographic criteria could potentially be used to define nonresponse to DMOAD treatment.[24]

5.2. Structure

Paradoxically, the current definition of response in the DMOAD trials involves identification of progressor patients, i.e. patients who are not responders to treatment. Thus, a radiographic JSN of >0.5 mm over a 2 to 3 year period has been suggested as the threshold to define patients who are treatment failures in DMOAD trials.[65,66] The value of 0.5 mm corresponds to the lowest difference in JSW exceeding the measurement error and represents an actual radiographic progression.

The threshold of JSN >0.5 mm has also been reported to be clinically relevant. In an 8-year prospective study, it was shown that subjects with JSN >0.5 mm after 3 years of follow-up were more likely to experience joint replacement surgery over the next 5 years than patients without such radiographic progression.[56]

The responsiveness and reliability of MRI generally appear to be very good,[50] making it a promising technique, though more research is necessary. The data from MRI studies have been useful in establishing the relationship between symptoms and osteoarthritic structural changes.[46,48-50,67] There are indications that bone marrow lesions and inflammation may predict pain, and that cartilage volume loss may predict disease outcome. Cartilage volume loss and defects as well as bone marrow lesions appear to predict total knee replacement.[47,48]

Factors predictive of total knee replacement have recently been investigated in a 2-year clinical trial evaluating licofelone versus naproxen.[48] The radiographic data revealed a 33% reduction in JSN at 2 years (–0.35 and –0.39 mm in the two treatment groups, respectively) (P=0.29). With MRI, there were 15% and 24% reductions in the loss of cartilage volume in the medial and lateral compartments, respectively. Radiographic JSN was predictive of target knee replacement. There appeared to be a cut-off at a JSN of 7%, with 94% of patients with JSN >7% undergoing knee replacement; and 52% of patients with JSN <7% not undergoing surgery. Patients losing more than 0.12 mm/year had a 15-fold greater chance of having to undergo total joint replacement.[48] MRI analysis of the same population indicated that an 8% reduction in cartilage volume in the medial compartment over 2 years was associated with an 18% increase in the risk of total joint replacement (P=0.005).[48] Support for this cut-off was provided by an observational study in which the rate of tibial cartilage loss measured by MRI over 2 years was an independent predictor of knee replacement at 4 years.[47] Patients with the highest rate of tibial cartilage loss (>8%) were at substantially higher risk (OR=7.1, 95% CI 1.4–36.5) of undergoing knee replacement than those with the lowest rate (<3%).[48]

There are a few limitations to these methods of evaluating cartilage loss. One drawback is the time between measurements, which means that the consistency between the various assessments cannot be accounted for. The linearity of the progression of disease is another important consideration in responder analyses. There have been mixed results regarding the linearity of the effect of osteoarthritis on radiographic JSN, with some studies reporting a linear effect,[48,55,68,69] some a non-linear effect,[70-72] and some remaining inconclusive.[11,73,74] Results from the MRI studies (cartilage volume loss) are also mixed[47,67,69] and suffer from similar drawbacks to the X-ray trials. This discrepancy may be due to the varying duration of the trials (2 to 3 years) and differences in patient characteristics or technologies to measure JSN, all of which are factors that can influence the linearity of disease progression over time. Other drawbacks are a substantial heterogeneity between patients in terms of progression and rate of progression, which may vary over time. This is an important point, since structure modification may be more easily demonstrated in subjects with rapid progression. This notion has important implications for study design in terms of sample size and study duration.

6.0. Discussion

This review paper is the product of discussions of an international Working Group of the ESCEO/International Osteoporosis Foundation. Similar conclusions have been drawn by other groups in the field, most notably the OMERACT-OARSI task force, which have produced recommendations for

22

responder criteria for symptoms[57] and structure,[66] or both,[24] as well as potential cutoffs for the point at which pain or physical function, coupled with radiological progression, should indicate a need for joint replacement.[21] These joint ventures underline the major challenge in the development of DMOADs: agreement on a primary outcome measure. Rate of progression to joint replacement may appear as an ideal hard endpoint but it is affected by a range of confounders, such as age, sex, socioeconomic status, surgical selection bias, rural versus urban place of residence, and ethnicity, compromising its use in international randomized clinical trials.[23] The proposed alternative endpoint of "being considered as a candidate for joint replacement"[75] is affected by similar confounders.

Therefore, alternative endpoints need to be identified and validated. In our view, the best candidate for a valid surrogate endpoint for predicting joint deterioration and thus the need for surgery is radiographic JSN. For example, patients with radiographic JSN >0.5 mm over 3 years have a statistically significant, three- to fourfold increased risk of joint replacement over 8 years.[23,56] As regards MRI, there is evidence that patients with a reduction in cartilage volume of >8% over 2 years are at greater risk for joint replacement.[47,48] MRI may also allow detection at an earlier stage of the disease. On the other hand, the sensitivity of MRI parameters is moderate[46] and we consider that further research is necessary in this domain.

Radiographically detected JSN remains the only structural endpoint currently accepted by regulatory bodies to demonstrate structural efficacy of DMOADs in phase 3 clinical trials. The evidence indicates that a trial JSN cutoff of 0.5 mm over 3 years defines severe joint structural damage. However, this does not take into account all assessments of JSW during a trial because the JSN of 0.5 mm only represents the end-of-trial value. Ongoing studies are evaluating whether a definition of progressors that takes into

23

account all JSN/JSW assessments during a trial, as well as the consistency between the various assessments, will increase the ability to predict joint surgery.

There remain a number of issues to be settled and areas for research. Three issues should be targeted for consensus. First, an agreement is required on an accepted definition of osteoarthritis, or even early osteoarthritis, as a disease entity. Second, surrogate endpoints for joint replacement should be identified and validated, and a consensus should also be attained on the definition of responders and progressors. Third, further consensus on the most valid and responsive set of MRI endpoints is required, as well as an established relationship with clinical endpoints such as pain, function and need for joint replacement.

The research agenda should focus on factors other than JSN that may contribute to the risk of structural progression. Indeed, the molecular events involved in the development of osteoarthritis are likely to occur long before the onset of symptoms. Characterization of these events will provide diagnostic tools and biomarkers to identify patients at risk of developing disease. In this way it may eventually be possible to act early with drugs that can modify the natural course of the disease before structural changes occur. Other research avenues include better characterization of the different types of pain in osteoarthritis (nociceptive, neuropathic, or mixed), together with their relation to structural changes, as well as better understanding of the drug target (cartilage or subchondral bone). The influence of flares on response to treatment and progression of disease also merits further exploration. Finally, further research should be performed into new imaging modalities, notably at all sites associated with osteoarthritis since much of the published evidence currently relates to knee osteoarthritis. Advances in these areas

24

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of research will improve our understanding of the disease process, prediction of progression and

drug response, and, ultimately, the management of osteoarthritis.

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Declaration of financial/other interests

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26

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27

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36

Table 1. Key regulatory requirements for trials of disease-modifying osteoarthritis drugs (DMOADs).

- Confirmatory phase 3 study duration ≥2 years
- Symptomatic and structural evidence of osteoarthritis of target joint at baseline
- Comparison of active treatment with placebo against a background of standard care
- Primary endpoint: radiographic JSN
- DMOADs should have efficacy on both structure and symptoms (radiographic improvement and improvement in pain). Separate shorter trials may be used to demonstrate symptom modification