OARSI/OMERACT Criteria of Being Considered a Candidate for Total Joint Replacement in Knee/Hip Osteoarthritis as an Endpoint in Clinical Trials Evaluating Potential Disease Modifying Osteoarthritic Drugs

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ABSTRACT. ***Objective.*** A disease-modifying osteoarthritic drug (DMOAD) should interfere with the cartilage breakdown observed and improve symptoms or prevent deterioration of the patient's clinical condition. We propose a composite index including structural and symptomatic variables of osteoarthritis (OA) as criteria for being considered a candidate for total joint replacement as an endpoint in clinical trials evaluating potential DMOAD.

Methods. An OARSI/OMERACT task force conducted this study in 3 steps: (1) The 3 main domains — pain, function, structure — were revisited; (2) For each of the domains a "non-acceptable state" and a "relevant" progression for their structure were defined; and (3) a set of criteria was proposed combining the information from these 3 domains.

Results. A questionnaire was elaborated for the domains "pain" and "function." Systematic research of the literature and evaluation of different databases concluded that the domain "structure" should be evaluated by radiological joint space width in millimeters. An unacceptable radiographic progression was defined as a change in the joint space width over the measurement error. An international, cross-sectional study is proposing a definition of a "nonacceptable symptom state."

Conclusion. The objective of the ongoing OARSI/OMERACT initiative is to propose criteria for being considered a candidate for total joint replacement to be used as an endpoint in clinical trials evaluating potential DMOAD. The preliminary steps of this initiative have been completed. (J Rheumatol 2009;36:2097–9; doi:10.3899/jrheum.090365)

Key Indexing Terms:
OSTEOARTHRITIS TOTAL JOINT REPLACEMENT ANTI-OSTEOARTHRITIC DRUGS

Osteoarthritis (OA) is one of the most common causes of disability, particularly in the elderly, and it has become a major health problem as a consequence of the growing proportion of elderly individuals in the population. Most current treatments for OA are aimed at relief of symptoms, but there is modest evidence that some treatments can also retard the breakdown of articular cartilage as evaluated by radiography or arthroscopy. A naïve and simple classification of drugs has been proposed. There are drugs that relieve symptoms without any effect on the structure, and there are

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drugs that interfere with cartilage breakdown with or without an effect on symptoms. This latter concept can be easily understood. However, when considering registration of drugs for use in clinical practice, everyone agrees on the necessity of a demonstration of clinical benefit of such drug intake.

The incidence of total joint replacement has been proposed as an outcome measure for DMOAD trials[1,2] because this surgical procedure is generally recommended after failure of non-surgical treatment and is usually performed in patients who have severe disease.

This criterion could be considered as fulfilling the OMERACT filter because of intuitive validity, simplicity, sensitivity to change, and discriminant capacity[1]. However, the decision to perform total joint replacement is influenced by factors unrelated to the severity of OA, such as age, comorbidity, a patient's willingness to undergo the procedure, and other factors such as the number of trained surgeons, availability of beds, and operating room time. A recent study showed a major variation in the rate of total joint replacement between developed countries[3]. This criticism has led to the suggestion that the appropriate endpoint might be the time to fulfill criteria for being considered a candidate for total joint replacement rather than time to surgery[4].

To our knowledge, 5 sets of criteria for total joint replacement have been proposed: (1) The US National Institutes of Health guidelines, which provide a general statement rather than a set of criteria and, thus they are not useful as an outcome measure[5]. (2) Hawker, *et al*[6] define potential candidates for total joint replacement as patients who have a summed Western Ontario and McMaster Universities osteoarthritis index score ≥ 39, clinical and radiographic evidence of OA, and no absolute contraindication to total joint replacement. (3) Lequesne's index is an algofunctional index that is used as an outcome measure in clinical trials[7]. However, it was designed as an index for OA patients who were under consideration for total joint replacement. The intuitive score greater than 12 (possible values 0–15) as an indicator for considering surgery was recently revisited in a cohort of hip OA patients and has been confirmed[8]. (4) The New Zealand criteria[9] are based on the sum of a set of scores for a variety of clinical factors including pain, functional impairment, range of motion, deformity, and other features such as impact of disease on a patient's lifestyle. (5) The Hôpital Cochin composite index[4] is based on symptomatic and structural severity and the response to prior pharmacologic therapies.

The above 5 proposed indices are very attractive; however, none of them completely fulfills the face validity criterion. In particular, most do not take into account structural OA severity[5,8,9] and some do not propose a cutoff to evaluate results as a dichotomous variable yes or no[5,9]. Finally, some (such as the Hôpital Cochin composite index[4]) do not indicate in which patients total joint replacement is required; they indicate in which patients total joint replacement has been performed.

Thus, an international working group was created under the auspices of recognized international organizations, OMERACT (Outcome Measures in Rheumatology Clinical Trials) and OARSI (Osteoarthritis Research Society International) to elaborate a set of criteria defining a non-acceptable symptom and structural state in knee/hip OA to be used as an endpoint in clinical trials evaluating potential DMOAD in osteoarthritis.

MATERIALS AND METHODS

Study design. During a meeting in Paris in December 2004, the members of the working group agreed on subsequent steps of this initiative: (1) Choice of domains to be included in the final set of criteria; (2) Choice/elaboration of the optimal tool for evaluating each selected domain; (3) Definition, in the tool evaluating a domain, of a threshold value above which the patient's condition can be considered as non-acceptable; and (4) Proposition and evaluation of the final set of criteria.

Choice of domains. Choice of domain was made using an expert opinion approach during the December 2004 Paris meeting. Three domains were selected: pain, functional impairment, and structure.

Choice/elaboration of the optimal tool for evaluation of each domain. For domains pain and function, the task force concluded that no single available tool was optimal to evaluate these domains for this purpose. Therefore, it was decided to elaborate a tool *de novo*: the methodology used for the domain pain was mainly focused on focus groups and one-on-one interviews[10]. The methodology used for the domain function was to propose a short version of the available HOOS (hip dysfunction and OA outcome score)[11] and KOOS (knee injury and OA outcome score)[12].

For domain structure, a systematic literature review and evaluation of radiographs of available databases were performed[13].

Definition of a threshold for each tool defining a non-acceptable state/structural progression. For the domains pain and function, a cross-sectional study was designed in which the orthopedist's opinion (optimal condition for proposing a total joint replacement: yes/no) defines the gold standard and the new OARSI-OMERACT pain and function tools are the evaluated variables.

For domain structure, a systematic literature research together with expert opinion approaches defined the used methodology.

Proposition and evaluation of the final set of criteria. The methodology of such a step is still under consideration.

RESULTS

Although this initiative is still ongoing, some results are already available:

New tools evaluating pain and function. Tools (OARSI-OMERACT pain index and OARSI-OMERACT function index) are now available for use[10,14,15].

Definition of structural progression. This task force subgroup first conducted a study aimed at defining the optimal tool to evaluate the structural aspect of OA. It was concluded that such a domain should be evaluated using radiological joint space width in millimeters[16,17]. Concerning the definition of "relevant" progression, the task force concluded that this should be related to any radiological progression above the measurement error[13]. Such measurement error

should be evaluated for each study following standardized and strict procedures. These conclusions emerged from systematic literature research for both hip and knee OA radiological evaluation[13].

Definition of a non-acceptable symptom state and proposal of a set of criteria. These steps are the main purpose of an ongoing international study. Such study including 12 centers from 3 continents (Europe, North America, and Australasia) is recruiting patients visiting an orthopedist for hip or knee OA. The orthopedist's opinion regarding indication of surgery (e.g., joint replacement) will define the external gold standard. Independently, OARSI-OMERACT pain and function tools are collected. It is anticipated to propose cut-offs of such tools above which an indication to surgery is reasonable.

DISCUSSION

This large international initiative involving experts from different specialties has strongly improved our knowledge in the field of outcome measures in OA. The current available results (e.g., new tools for evaluating pain and function, clear definition of a clinically relevant radiological progression) are already proving useful in the conduct of new studies. One potential limitation of this initiative might be the technique of selection of domains, which has been based on an expert opinion approach; other techniques such as Delphi consensus exercise might result in different domains. The current available tools have been validated in terms of validity. Their reliability and sensitivity to change now need to be validated according to the OMERACT filter.

The planned set of criteria (composite index including both symptomatic and structural state) will greatly facilitate the design, conduct, and interpretation of clinical trials evaluating potential disease modifying antiosteoarthritic drugs.

REFERENCES

1. Dougados M, Gueguen A, Nguyen M, et al. Requirement for total hip arthroplasty: an outcome measure of hip osteoarthritis. J Rheumatol 1999;26:855-61.
2. Abadie E, Ethgen D, Avouac B, et al. Recommendations of the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12:263-8.
3. Merx H, Dreinhöfer K, Schäder P, et al. International variation in hip replacement rates. Ann Rheum Dis 2003;62:222-6.
4. Maillefert JF, Gueguen A, Nguyen M, et al. A composite index for total hip arthroplasty in patients with osteoarthritis. J Rheumatol 2002;29:347-52.
5. NIH consensus conference: Total hip replacement. NIH Consensus Development Panel on Total Hip Replacement. JAMA 1995;273:1950-6.
6. Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. N Engl J Med 2000;342:1016-22.
7. Lequesne M, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation-value in comparison with other assessment tests. Scand J Rheumatol 1987;65 Suppl:85-9.
8. Lequesne M, Taccoen A. Clinical and radiographic status of patients in the ECHODIAH study who underwent THA. Pertinence of the pain-function index for operative decision making. Presse Med 2002;31:4518-9.
9. Hadorn HC, Holmes AC. Education and debate: the New Zealand priority criteria project. Part 1: overview. BMJ 1997;314:131-4.
10. Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis. An OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415-22.
11. Nilsdotter AK, Lohmander LS, Klassbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS)-validity and responsiveness in total hip replacement. BMC Musculoskeletal Disorders 2003;4:10.
12. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) — validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes 2003;1:17.
13. Ornetti P, Brandt K, Hellio-Le-Graverand MP, et al. OARSI/OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. Osteoarthritis Cartilage 2009; Feb 9 [Epub].
14. Davis AM, Perrucio AV, Canizares M, et al. The development of a short measure of physical function for hip OA HOOS. Physical function shortform (HOOS-PS): an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:551-9.
15. Perruccio AV, Lohmander LS, Canizares M, et al. The development of a short measure of physical function for knee OA KOOS. Physical function shortform (KOOS-PS): an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:542-50.
16. Gossec L, Jordan JM, Lam M-A, et al. Comparative evaluation of 3 semi-quantitative radiographic grading techniques for hip osteoarthritis in terms of validity and reproducibility in 1404 X-rays: report of the OARSI-OMERACT Task Force. Osteoarthritis Cartilage 2009;17:182-7.
17. Gossec L, Jordan JM, Mazzuca SA, et al. Comparative evaluation of 3 semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the OARSI-OMERACT Task Force. Osteoarthritis Cartilage 2009;17:742-8.