The Journal of Rheumatology Volume 38, no. 8

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J Rheumatol 2011;38;1765-1769
http://www.jrheum.org/content/38/8/1765

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ABSTRACT. ***Objective.*** To define pain and physical function cutpoints that would, coupled with structural severity, define a surrogate measure of "need for joint replacement surgery," for use as an outcome measure for potential structure-modifying interventions for osteoarthritis (OA).

Methods. New scores were developed for pain and physical function in knee and hip OA. A cross-sectional international study in 1909 patients was conducted to define data-driven cutpoints corresponding to the orthopedic surgeons' indication for joint replacement. A post hoc analysis of 8 randomized clinical trials (1379 patients) evaluated the prevalence and validity of cutpoints, among patients with symptomatic hip/knee OA.

Results. In the international cross-sectional study, there was substantial overlap in symptom levels between patients with and patients without indication for joint replacement; indeed, it was not possible to determine cutpoints for pain and function defining this indication. The post hoc analysis of trial data showed that the prevalence of cases that combined radiological progression, high level of pain, and high degree of function impairment was low (2%–12%). The most discriminatory cutpoint to define an indication for joint replacement was found to be [pain (0–100) + physical function (0–100) > 80].

Conclusion. These results do not support a specific level of pain or function that defines an indication for joint replacement. However, a tentative cutpoint for pain and physical function levels is proposed for further evaluation. Potentially, this symptom level, coupled with radiographic progression, could be used to define "nonresponders" to disease-modifying drugs in OA clinical trials. (J Rheumatol 2011;38:1765–9; doi:10.3899/jrheum.110403)

Key Indexing Terms:
OSTEOARTHRITIS SEVERITY PAIN FUNCTION STRUCTURE OUTCOME MEASURE

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Supported by unrestricted grants from OARSI and OMERACT and pharmaceutical companies Pfizer, Expansciences, Novartis, Negma Lerads, Rottapharm-Madaus, Fidia, and Pierre Fabre Santé Laboratories. Procter and Gamble Pharmaceuticals provided unrestricted access to placebo data from the KOSTAR study and an unrestricted grant to COB. LSL was supported by the Swedish Research Council; JAS was supported by the National Institutes of Health (NIH) Clinical Translational Science Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research). MSA holds a K24 award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and is partially supported by the Agency for Healthcare Research and Quality through funding of the Houston Center for Education and Research on Therapeutics (CERT). RLM is supported by NIH Training Grant T32 AR48522-06. P. Coste is an employee of Expanscience; A. Lanzarotti and E. Tajana-Messi are employees of IBSA; L.C. Rovati and G. Giacovelli are employees of Rottapharm-Madaus; COB served as a consultant and investigator for Procter and Gamble Pharmaceuticals, Novartis, and Merck and received an unrestricted grant from P&G Pharmaceuticals; LM has received a speaker honorarium and travel grant from Servier. JAS has received speaker honoraria from Abbott; research and travel grants from Allergan, Takeda, Savient, Wyeth and Amgen; and consultant fees from Savient and URL pharmaceuticals.

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For many years, there has been great interest in the scientific community, pharmaceutical companies, and regulatory agencies in the development of drugs that might influence the natural history of osteoarthritis (OA) by preventing, slowing, or reversing joint tissue breakdown. These so-called disease-modifying OA drugs should be evaluated using primary outcomes that reflect the disease's natural history. It would be useful to identify a valid dichotomous outcome measure that would reflect the natural history of OA. In particular, candidacy for total joint replacement (TJR) is discussed as a "hard" outcome measure[1]. Limitations exist, however, in the use of such an outcome, in particular in variability in the decision to perform surgery[1]. It would therefore be of interest to obtain a modified outcome measure, derived from "time to surgery" but avoiding some of its limitations. An alternative is "time to fulfill the criteria for surgery." This type of "surrogate hard endpoint" is widely used in other specialties. For example, treatments for heart failure are evaluated based on "time to fulfill criteria for heart transplant." However, the main limitation for OA trials is that no consensus exists, regarding when TJR should be proposed, that could be used for clinical research purposes.

Thus, an international working group was created in 2004, under the auspices of the international organizations Outcome Measures in Rheumatology Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI), to evaluate the issues related to severity of hip and knee OA[1,2,3]. The objective of the working group was to create a composite index that could define states of OA severity. This surrogate marker could then be used to evaluate treatment response to disease-modifying drugs in OA clinical trials.

The aim of this article is to present the methodology used by the working group, and the results of the exploratory analyses conducted on pain and function as predictors of fulfilling criteria for TJR.

MATERIALS AND METHODS

This article will present an overview of the methods and results, partly detailed elsewhere[1,2,3,4,5,6,7,8,9,10,11].

Previous and Ongoing Work

Choice of domains and tools defining severity and essential in the decision to implement surgery. During a meeting in Paris in December 2004, the members of the working group discussed which domains are essential in defining OA severity and in deciding to refer a patient for TJR. Based on their expertise and on an extensive literature review[1], the following 3 domains were selected: pain, functional status, and structural damage. The consensus was to consider the level of pain and function at one point, and a definition of radiological progression between 2 timepoints[11]. However, it was also planned to analyze the effect of persistence of the pain/function levels. The final binary outcome could then be used as a definition for "responders/nonresponders" in OA clinical trials.

Elaboration of tools to assess each domain. For each domain, one or several tools were selected or created: for pain, the ICOAP score (intermittent and constant OA pain)[4,5]; and for physical function, the Hip Disability and Osteoarthritis Outcome Physical Function Short-form (HOOS-PS) for hip and knee injury, and the Osteoarthritis Outcome Score Physical Function Short-form (KOOS-PS) for the knee[6,7,8].

For structural damage, it was decided to use minimal joint space width (JSW) on plain radiographs[9,10], and to define structural progression as progression beyond measurement error[11].

Cross-sectional study to determine cutpoints for pain and functional disability. The objective of the study was to define cutpoints for both pain and functional disability of sufficient magnitude that TJR may be indicated. To this end, a data-driven approach, based on real patient data, was chosen. A large multicenter cross-sectional study was performed to define cutpoint levels for pain and functional disability among patients with hip or knee OA being evaluated by orthopedic surgeons for possible need of TJR. The full report is in preparation.

Study design: This international observational cross-sectional study was conducted in the orthopedics departments of tertiary-care and secondary-care centers in Europe, North America, and Australia (12 centers). Study population: Consecutive outpatients with a diagnosis of hip or knee OA consulting with an orthopedic surgeon in one of the participating centers. Gold standard: Indication for TJR according to the orthopedic surgeon's opinion. Pain and functional disability: These were collected using the ICOAP score for pain[4,5]; and for physical function, the HOOS-PS for hip and KOOS-PS for the knee[6,7,8]. Statistical analysis: The distributions of the 2 variables were analyzed for both hip and knee OA, according to the gold standard outcome (recommendation for TJR, yes/no) and compared using Student's t test or the Wilcoxon rank test. The ability of pain and functional disability to predict the gold standard was assessed in a univariate manner by a nonparametric receiver-operating characteristic curve and area under the curve was calculated. To take radiographic severity into account, the analyses were stratified on radiographic severity. The 75th percentile technique was also applied.

Current Study

Post hoc analysis of available trial data in knee and hip OA. A further step was to assess cutpoints for pain and function, in existing randomized clinical trial datasets of putative disease-modifying OA drugs. Thus, the prevalence of sustained high pain and functional disability levels, in populations of patients with symptomatic hip/knee OA participating in clinical trials, was assessed. Indeed, if such a criterion were to be used as a primary outcome, the sample size would be heavily influenced by the prevalence of the outcome. The full results from this study will be submitted as a separate publication.

Selection of trials: A call was sent out for available databases, to pharmacological companies involved in OA trials. Criteria for study inclusion were: randomized controlled trial in symptomatic knee or hip OA; included a placebo group; and where pain and function and the radiological JSW of the index joint at baseline and after at least 1 year of treatment were assessed. Data collected: The baseline characteristics of the patients (completers), the radiological parameters (assessed quantitatively as millimeters on plain radiographs): JSW at baseline, JSW at the end of the treatment period (final visit), smallest detectable difference in radiographic assessment if available, and levels of pain and function were collected for the placebo groups from each randomized controlled trial. Levels of pain and function were collected at each visit, with normalization of the scales (whatever the questionnaire used) from 0 = best to 100 = worst condition.

Cutpoints tested for pain, function, and duration: Different sets of criteria potentially defining sustained high pain and disability levels were derived from the previous study and tested for feasibility (in terms of prevalence) and validity; these were:

A. Pain + Function ≥ 80 during at least 2 consecutive visits
B. Pain + Function ≥ 80 during at least 3 consecutive visits
C. Pain + Function ≥ 80 during at least 4 consecutive visits
D. Pain + Function ≥ 100 during at least 2 consecutive visits
E. Pain + Function ≥ 100 during at least 3 consecutive visits
F. Pain + Function ≥ 100 during at least 4 consecutive visits
G. [Pain ≥ 50 and Function ≥ 30] OR [Function ≥ 50 and Pain ≥ 30] during at least 2 consecutive visits
H. [Pain ≥ 50 and Function ≥ 30] OR [Function ≥ 50 and Pain ≥ 30] during at least 3 consecutive visits
I. [Pain ≥ 50 and Function ≥ 30] OR [Function ≥ 50 and Pain ≥ 30] during at least 4 consecutive visits.

Statistical analysis: The prevalence of subjects fulfilling each set of criteria was calculated in each study to estimate feasibility. A priori, the final outcome defining a disease-modifying drug nonresponder was thought to be represented by: "sustained high patient-reported levels AND structural degradation," therefore the clinical criteria were then combined with structural degradation, defined as significant loss of JSW over the study duration (either by loss of JSW ≥ 0.5 mm, or greater than or equal to the smallest detectable difference). Face validity was also assessed (data not shown).

RESULTS

The main points of the meeting at OMERACT 10 included presentation of results and discussions of future steps.

Previous and Ongoing Work

Elaboration of tools to assess pain and functional disability in lower limb OA. For pain, a new questionnaire was developed, the ICOAP[4,5]. For physical function, 2 new questionnaires, one for the hip and one for the knee, were developed: the HOOS-PS for the hip and KOOS-PS for the knee[6,7,8].

Cross-sectional study to determine cutpoints for pain and functional disability. In all, 1909 patients were analyzed: 1130 knee OA and 779 hip OA. Patients with a recommendation for TJR had higher pain and disability levels than those not recommended for TJR; pooling knee/hip patients, mean pain was 55.5 (95% CI 54.2, 56.8) for those with TJR recommendation versus 44.9 (95% CI 43.2, 46.6) for those without TJR recommendation ($p < 0.0001$). Mean functional impairment was 59.8 (95% CI 58.7, 60.9) for those with TJR recommendation versus 50.9 (95% CI 49.3, 52.4) for those without TJR recommendation ($p < 0.0001$). However, due to high overlap in pain/function levels between patients with and those without a recommendation for TJR, in the pooled hip/knee population, it was not possible to determine relevant cutpoints for pain or function, defining recommendation for TJR, even when taking into account the duration of the symptoms or after stratifying on radiographic severity.

The 75th percentile technique indicated that a cutoff of around 90 for the sum "pain + function" (where both pain and function are on a 0–100 scale) had 75% sensitivity with 55% specificity for the indication of TJR by the orthopedic surgeon.

Current Study. Post Hoc Analysis of Available Trial Data in Knee and Hip OA

Eight clinical trials representing 1379 patients were included in these analyses[12,13,14,15,16,17,18,19]. Studies evaluated patients with hip (n = 2) or knee (n = 6) OA. The followup duration varied between 104 and 156 weeks.

Among the 6 knee and 2 hip studies, 248 (22% of 1124) and 132 (51% of 255) patients, respectively, had radiographic progression (defined by loss of JSW ≥ 0.5 mm over the study period). Among the 9 clinical cutpoints tested, the one with the most patients fulfilling the criteria (n = 486, 36%) was the least stringent (pain + function ≥ 80 at ≥ 2 visits) and the one with the fewest patients fulfilling the criteria (n = 101, 7%) was among the most stringent (pain + function ≥ 80 at ≥ 4 visits).

The prevalence of the combination of "sustained high pain/function levels" with radiographic progression was assessed. When radiographic progression was added to the clinical criteria, the prevalence of patients fulfilling the tentative definitions of nonresponders ranged from 2% (n = 29) to 17% (n = 160) across different studies. An exploratory analysis of sample size calculations of patients that would be needed assuming the results from the different scenarios was also presented.

Discussions of the Special Interest Group (SIG) at OMERACT 10

At the SIG at OMERACT 10 at which the data were presented, the results of both the cross-sectional and clinical trial data were extensively discussed by attendees. There was discussion of a need for additional analysis of hip versus knee studies, and heterogeneity of studies in terms of visit timing that would require additional analysis as part of a research agenda.

DISCUSSION

This working group, under the aegis of OMERACT and OARSI, represents a large group of international experts to propose a definition of severity in lower limb OA that would correspond to a theoretical indication for TJR. Using existing study designs, few patients demonstrate significant radiographic progression. The numbers of patients needed and time to conduct a clinical trial with the "hard" outcome TJR is not feasible. Moreover, individual variations among surgeons, patients, and other issues of access confound such a hard outcome. Thus, a definition of "theoretical indication for TJR" could be used as an outcome measure in potential disease-modifying trials in OA.

Consensus was reached regarding the most important domains to be entered in such a set of criteria, namely pain, functional disability, and structural degradation. New questionnaires were developed to assess pain and functional disability in lower limb OA. A large international study was conducted to assess pain and function levels of patients against a gold standard of patients truly recommended for TJR, in orthopedic surgeons' clinics from representative international centers. Finally, post hoc analyses were conducted in existing randomized clinical trial databases from lower limb OA to assess the prevalence of patients fulfilling different clinical scenarios.

The first conclusion of this work is that, indeed, among patients with hip and knee OA referred to an orthopedic surgeon, the level of symptoms was higher among patients for whom TJR was indicated by the orthopedic surgeon. The second conclusion is that we could not find a cutpoint for pain and for physical disability (even when these levels were maintained over time) that accurately discriminated, across different countries, patients who did versus those who did not receive a TJR recommendation. The third conclusion is that the prevalence of patients achieving different scenario cutpoints encompassing sustained measures of pain and functional disability, with radiological progression, was low in available databases.

Several studies have indicated discordance between radiographs and symptoms in lower-limb OA[20,21,22,23,24]. In the cross-sectional study presented here, stratifying the analyses on radiographic severity did not modify the conclusions. Interestingly, the results indicated a stronger relationship between symptoms and surgical indication in hip OA than in knee OA.

The prevalence of subjects with sustained symptomatic OA of at least a moderate degree with concomitant radiographic progression was low in the placebo arms of available randomized clinical trial databases. Even using the most lenient criteria to define significant persistent clinical symptoms, coupled with radiographic progression above measurement error to represent a "virtual joint replacement indication," large numbers of patients would be required to detect differences between groups in potential disease-modifying trials.

The final proposal of the working group was that the cutoff corresponding to the less stringent cutpoint (high sustained symptom level) of "pain + function > 80 during at least 2 consecutive visits AND radiological progression" should be further evaluated in clinical trials. It will also be useful to obtain qualitative feedback from patients about this scenario.

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