Concomitant Therapy: An Outcome Variable for Musculoskeletal Disorders? Part 2: Total Joint Replacement in Osteoarthritis Trials

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ABSTRACT. Interest has grown in using the requirement of total joint replacement (TJR) as a "hard" outcome measure. Limitations exist, however, in the use of such an outcome, in particular the variability in the decision to perform surgery, length of surgical waiting lists, and sensitivity to change. This special interest group is exploring ways of retaining the clinical relevance of TJR but overcoming the problems — 2 alternative outcomes are being considered: "time to physician's decision to recommend surgery" and "time to fulfilling criteria for total joint replacement." (J Rheumatol 2005; 32:2449–51)

Key Indexing Terms:
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TOTAL JOINT REPLACEMENT CONCOMITANT THERAPY

Definition of Concomitant Therapy

Concomitant therapy in randomized controlled trials can be defined as any therapy other than the study drugs. This comprises 3 main situations:

1. Rescue therapy: A drug initially planned in the protocol that is given as backup in case of necessity.
2. Concomitant therapy: A drug that was begun prior to the study and continues throughout; the quantity may be modulated according to necessity.
3. "Alternative" therapy: A therapy that, when instituted, results in the primary endpoint being considered a failure. Alternative therapy is given only in the case of inefficacy of the study drug, for example, total joint arthroplasty in osteoarthritis (OA) trials. From that point, the primary outcome measure is no longer measurable — for example, radiographic joint space width in OA following total hip replacement.

Total Joint Replacement (TJR) as an Outcome Measure in OA Trials

Most treatments used in OA aim to relieve joint pain and disability. However, interest has grown among the scientific community, drug companies, and regulatory agencies in the development of drugs that can influence the natural history of the disease by preventing, retarding, or even reversing cartilage breakdown. These so-called disease-modifying OA drugs (DMOAD) have to be evaluated using primary outcome measures that reflect the disease's natural history. At present, structural variables, particularly minimal joint space width on plain radiographs, are considered the most appropriate primary outcome measure: they are accurate and have high intrinsic validity. However, they provide only indirect evidence of the influence of a drug on the disease's history, and the clinical relevance of the results remains

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debatable, since there is a documented poor correlation between radiographs and disease symptoms and disability in OA[1]. Moreover, since joint space width is a continuous variable, the results are presented as the mean changes in the outcome. While this is a powerful parameter for statistical analysis, it does not allow the presentation of results, except using artificial dichotomization, as "percentage of patients with or without progression," "time to progression," or "number of patients needed to treat to prevent progression," an approach applied in studies of therapies for other disorders. Finally, the question of how to evaluate patients lost to followup or patients undergoing joint surgery during the trial remains unanswered.

Interest exists, therefore, in identifying a valid, dichotomous outcome variable that reflects the natural history of OA. In particular, interest has grown in using the requirement of TJR as a "hard" outcome measure. This variable is simple and easy to collect. TJR has been shown to be a highly cost-effective procedure that dramatically reduces joint pain and disability in most cases. It is generally recommended after failure of nonsurgical treatment and is usually performed in patients with severe disease. Thus requirement of TJR might be considered as a failure of the study drug. The intuitive validity was confirmed in a study using data obtained from a cohort of 506 patients with hip OA who were followed prospectively for 3 years[2]; a highly significant difference in clinical severity and structural progression was demonstrated between groups of patients who were referred or were not referred for TJR during the followup period.

Limitations exist, however, in the use of such an outcome, in particular the variability in the decision to perform surgery, the length of surgical waiting lists, and sensitivity to change. Recourse to surgery reflects the severity of OA, but also other factors that are related (patient age, willingness, concomitant diseases, etc.) or not related (doctor's and/or surgeon's opinion, healthcare system, etc.) to the patient's condition[3]. One study found that among a population-based cohort of individuals with advanced hip or knee OA and no contraindication to surgery, only one-third were either probably or definitely willing to consider joint replacement as a treatment option[4]. Moreover, area variations in patients' willingness to have surgery have been demonstrated[4]. Further, racial, socioeconomic, and gender disparities in the rates of TJR have been demonstrated[5-7]. In addition to the variability inherent in the indication for TJR, the second limitation to TJR as an outcome measure for DMOAD trials is variability between countries in the time from indication for TJR to performance of surgery, i.e., variability in length of waiting lists. In a 3-year study, several months of delay between indication for surgery and surgery itself would potentially interfere with results, since patients in whom surgery is indicated but not performed during the study period would be considered "non-progressors." A third limitation is the number of events. In a recently published 3-year trial, only 17% of the patients underwent total hip replacement during the trial period[8]. Based on the estimate of such a number of events, a trial using TJR as the main outcome might not be feasible, 200 patients per group would be needed for a 3-year trial to show a 50% treatment effect (alpha = 5%, 1 – beta = 80%), and 600 per group for a trial with a 30% treatment effect[9].

Alternatives to TJR as an Outcome Measure in OA Trials

Therefore, it would be worthwhile to obtain a modified outcome, derived from "time to surgery" but avoiding some of its limitations. Clinical trials evaluating potential beneficial effect of drugs on the natural progression of OA would thus evaluate the capacity of such treatments to delay "time to the alternative outcome" rather than time to surgery.

Several alternative outcomes might be considered: "time to physician's decision to recommend surgery" or "time to fulfillment of criteria for surgery."

Time to physician's decision to recommend surgery would be a simple, easy to obtain outcome that would avoid the limitation of waiting lists, thus reducing variability and increasing sensitivity to change of the outcome. Moreover, it might be improved if modified to time to physician's decision to recommend surgery "irrespective of all the patient's sources of variability not directly connected with OA" (for example, a patient with severe OA, but with contraindication for surgery, would be considered as a non-progressor by the first modification and as a progressor by the second). However, variability due to a doctor's or surgeon's opinion on when surgery should be performed remains. Moreover, indications for surgery might be influenced by length of waiting lists, i.e., some physicians might anticipate and indicate surgery earlier in countries with long waiting lists.

Thus, a better alternative might be to change the criteria time to TJR to "time to fulfillment of criteria for TJR." The latter would avoid limitations due to a doctor's or surgeon's opinion on when TJR should be recommended, and would avoid the variability inherent in the length of waiting lists. Moreover, if the set of criteria includes only variables related to OA, variability due to comorbidity, age, or patients' willingness would be avoided. Finally, the change should increase the number of events. Thus, such an outcome might appear as ideal. However, the main limitation is that, although several sets of criteria have been proposed[6,10-14], no consensus exists regarding when or in whom TJR should be performed. Another limitation is that the existing sets of criteria have not been designed to be used as an outcome measure, so their metrological properties might not be adapted to therapeutic trials. Finally, some patients might undergo surgery without fulfilling the criteria.

Discussion in the Special Interest Group and Plenary Session

Special Interest Group

Several questions were discussed in the special interest group:

Question 1. Should "time to TJR" or "time to fulfil the criteria to TJR" be considered as an outcome measure in therapeutic trials evaluating potential DMOAD in OA? Most participants believed such outcomes should be considered.

Question 2. Which of these 2 potential outcomes, the real or the virtual, would be better? The virtual outcome, which might also be considered as a high disease activity set, was preferred by all.

Question 3. Should the existing sets of criteria for TJR indication be evaluated, or another study be undertaken to develop a new set of criteria, designed specifically to be used as an OA trial outcome measure?

Final Plenary Session

Two questions were voted on in the final plenary session:

Question 1. Requirement to surgery (actual surgery) should be considered as an outcome variable in longterm clinical trials (> 1 year).

Yes	79%
No	13%
Not enough data	4%
I don't know	5%

Question 2. A set of criteria for considering total joint arthroplasty in OA (virtual surgery) for use in clinical trials should be further developed.

Yes	73%
No	9%
Not enough data	8%
Don't know	9%

Based on these results, the next step will be to develop such a set of criteria. A group aiming at working on this development will be constituted.

REFERENCES

1. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam study. Ann Rheum Dis 1998;57:203-8.
2. 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.
3. Dieppe P, Basler HD, Chard J, et al. Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. Rheumatology Oxford 1999;38:73-83.
4. Hawker GA, Wright JG, Coyte PC, et al. Determining the need for hip and knee arthroplasty. The role of clinical severity and patients' preferences. Med Care 2001;39:206-16.
5. Charlson ME, Allegrante JP. Disparities in the use of total joint arthroplasty. N Engl J Med 2000;342:1044-5.
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. Hawker GA, Wright JG, Glazier RH, et al. The effect of education and income on need and willingness to undergo total joint arthroplasty. Arthritis Rheum 2002;46:3331-9.
8. Dougados M, Nguyen M, Berdah L, et al. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539-47.
9. Auleley GR, Giraudeau B, Baron G, Maillefert JF, Dougados M, Ravaud P. Hip osteoarthritis clinical trials: handling missing data may highly influence sample size requirements. J Clin Epidemiol 2004;57:447-53.
10. Hadorn HC, Holmes AC. Education and debate: the New Zealand priority criteria project, part I: overview. BMJ 1997;314:131-4.
11. Maillefert JF, Gueguen A, Nguyen M, et al. A composite index for total hip arthroplasty in patients with hip osteoarthritis. J Rheumatol 2002;29:347-52.
12. NIH consensus conference: Total hip replacement. NIH Consensus Development Panel on Total Hip Replacement. JAMA 1995;273:1950-6.
13. Lequesne M. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 1997;24:779-81.
14. 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.