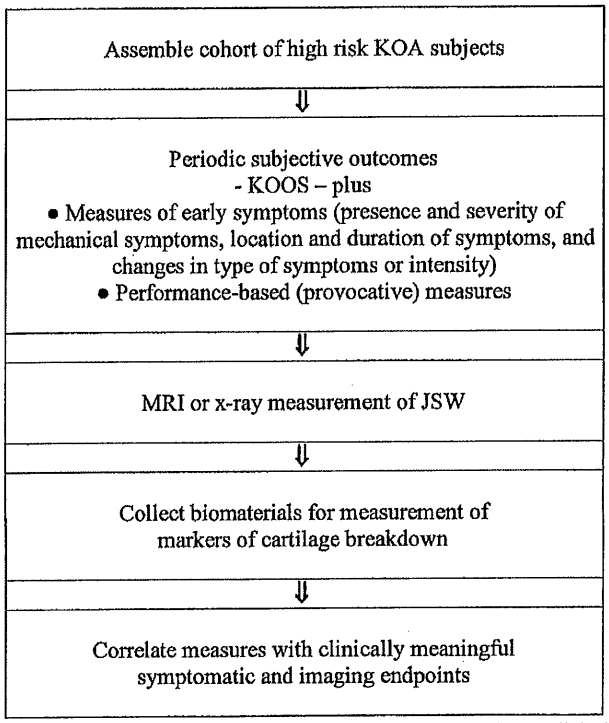


*Figure 8.* Study to identify patient-oriented biosurrogates in subclinical knee OA (KOA).

Although many risk factors for KOA have been suggested, young women with severe knee injuries represent a group who develop accelerated OA. With their numbers increasing, such subjects could be studied efficiently to identify clinical endpoints and biomarkers. The US National Institutes of Health OA Initiative has a goal of validating biomarkers, but it targets a much older population (45–79 yrs) in which disease has already been established and rate of OA progression is slower, thus prolonging the time to discovery.

However, whatever endpoint is to serve as an effective substitute for the clinical outcome, the effects of the intervention on the surrogate must reliably predict the overall effect on clinical outcome. Therefore, necessarily the endpoint should be related to meaningful, patient-oriented outcomes.

## ACKNOWLEDGMENT

Dr. Liang was supported by NIH grant AR47782. Dr. de Pablo was supported by a Kirkland Fellowship Award and by a Postdoctoral Fellowship from the Arthritis Foundation.

## REFERENCES

1. Liang MH. Pushing the limits of patient-oriented outcome measurements in the search for disease modifying treatments for osteoarthritis. J Rheumatol 2004;31 Suppl 70:61-5.
2. Pham T, van der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. J Rheumatol 2003;30:1648-54.
3. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605-13.
4. Lohmander LS, Ostenberg A, Englund M, Roos HP. High prevalence of knee osteoarthritis, pain and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 2004;50:3145-52.
5. Loughlin J. Genetic epidemiology of primary osteoarthritis. Curr Opin Rheumatol 2001;13:111-6.
6. Palotie A, Vaisanen P, Ott J, et al. Predisposition to familial osteoarthrosis linked to type II collagen gene. Lancet 1989;1:924-7.
7. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
8. Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS) — validation of a Swedish version. Scand J Med Sci Sports 1998;8:439-48.
9. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK, Bradshaw CR. Joint space width measures cartilage thickness in osteoarthritis of the knee: high resolution plain film and double contrast macroradiographic investigation. Ann Rheum Dis 1995;54:263-8.
10. Altman R, Brandt K, Hochberg M, et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage 1996;4:217-43.
11. Ravaud P, Ayral X, Dougados M. Radiologic progression of hip and knee osteoarthritis. Osteoarthritis Cartilage 1999;7:222-9.
12. Ravaud P, Giraudeau B, Auleley GR, Edouard-Noel R, Dougados M, Chastang C. Assessing smallest detectable change over time in continuous structural outcome measures: application to radiological change in knee osteoarthritis. J Clin Epidemiol 1999;52:1225-30.
13. Tiderius CJ, Olsson LE, Leander P, Ekberg O, Dahlberg L. Delayed gadolinium-enhanced MRI of cartilage (dGEMERIC) in early knee osteoarthritis. Magn Reson Med 2003;49:488-92.

## WHY CHOOSE HIP OSTEOARTHRITIS AS A HUMAN MODEL FOR EVALUATION OF DRUGS IN OSTEOARTHRITIS?

*Maxime Dougados*

Background

Most of the current treatments for OA are aimed at relief of symptoms, but there is modest evidence that at least some treatments can also retard breakdown of articular cartilage, as evaluated by radiography or arthroscopy. A naïve and simple classification of drugs has been proposed to distinguish drugs that relieve symptoms but have no effect on structure from those that interfere with cartilage breakdown without necessarily relieving symptoms.

Although OA can affect any joint in the body, it mainly affects 4 sites: the spine, hand, hip, and knee. Because of the complexity of structural evaluation of both spine and hand OA, trials of disease-modifying OA drugs are usually conducted in patients with either hip OA or knee OA. Despite tremendous improvement in the conduct of clinical trials in hand OA, the pilot and pivotal studies evaluating so-called symptomatic drugs similarly remain focused on either hip or knee OA.

The question that eventually confronts those designing an OA clinical trial relates to the choice between hip and knee. This choice can be based on several considerations:

- Burden of disease on patients and society
- Capacity to demonstrate a symptomatic effect of the drug
- Capacity to demonstrate a structural effect of the drug
- Capacity to use "requirement for total joint replacement" as an outcome measure.

Burden of Disease

The argument in favor of selecting subjects with knee OA over subjects with hip OA for clinical trials is probably related to the greater prevalence of knee OA in population studies. However, it must be emphasized that "epidemiological prevalence" takes into account not only the medial tibiofemoral localization (usually the site of the most severe damage in knee OA and the one that is logically evaluated in clinical trials) but also lateral tibiofemoral and patellofemoral localization, in which the disease is less severe and the evaluation more complex.

The number of total joint replacements per year is also a relevant marker of the burden of OA at different joint sites. Based on the data provided for the United States, in 1996 this number was 138,000 for hip OA and 245,000 for knee OA.

Demonstration of a Symptomatic Effect

The symptomatic effect of a drug can be evaluated by referring to the most relevant domains, e.g., pain, functional impairment, patient global assessment, or by referring to a composite index. Recently, OMERACT (Outcome Measures in Rheumatology) and OARSI (Osteoarthritis Research Society International) committees, through a combined initiative, proposed such a composite index, i.e., the OARSI-OMERACT set of responder criteria[1]. By applying this index in various databases containing evaluations of nonsteroidal antiinflammatory drugs in randomized placebo controlled trials, it is possible to evaluate the percentage of responders in the active treatment group and in the placebo group, and then to calculate the sample size required to obtain a comparable placebo effect and active treatment effect in future trials.

In the clinical trials in subjects with hip OA, the observed placebo effect was lower than in trials in those with knee OA (34.8%, 45.9%, respectively). On the other hand, the effect observed with active NSAID was slightly higher in trials in knee OA than in hip OA (OARSI responder rate = 65.4% vs 60.5%). The observed treatment effect (i.e., the difference between the effect of active drug and placebo) was greater in hip than in knee OA (25.7%, 19.5%, respectively).

Based on these observations, the sample size needed to obtain effects of comparable magnitude in the placebo group and the active treatment group are much lower in a study of hip OA than in a study of knee OA (n = 59, 101, respectively)[1]. Because it is always preferable to employ methodology that exposes the smallest number of subjects to risk in studying a potentially toxic new drug, the results suggest that the human hip OA model should be chosen over human knee OA.

Demonstration of a Structural Effect

Structural variables that define OA include changes in subchondral bone, synovium, and cartilage. Most experts agree that cartilage breakdown is the most important feature of the disease. It can be evaluated by a variety of techniques. Although assessment of cartilage breakdown by MRI (with quantification of cartilage volume or examination of cartilage surface defects) has recently been proposed, the "conventional" technique for evaluating cartilage damage in OA is the assessment of radiographic joint space width.

Procurement of the radiographic images, analysis, and interpretation are much easier for the hip than for the knee[2]. Moreover, and probably more important, results obtained in imaging the hip are more reliable. When comparing OA trials conducted in different countries and evaluating different drugs, it is interesting to note that among completer groups the mean annual change in joint space width of the hip is approximately 0.2 mm, with a standard deviation of 0.2 mm. In contrast, results of studies of knee OA may differ dramatically from one study to another. Again, data relevant to changes in structural variables over time strongly support hip OA as the preferred human OA model for evaluation of potential disease-modifying agents.

Total Joint Replacement as an Outcome Measure

In the development of potential structure-modifying drugs for OA, a persistent question is this: Which data will convince patients, doctors, and health authorities that a drug can be considered to be disease modifying in OA? Because of a long list of criticisms of the use of both symptomatic and structural variables, a composite index that takes into account both clinical status of the patient and structural damage in the OA joint seemed the logical choice as the gold standard. In this respect, fulfilling criteria for total joint arthroplasty appeared attractive as a composite index.

The incidence of total joint replacement has been proposed as an outcome measure for disease-modifying OA trials because this surgical procedure is generally recommended after failure of nonsurgical treatment and is usually performed in patients who have severe disease[3]. Data on this outcome measure are obviously easy to collect. The sensitivity to change is clearly different for hip OA and knee OA. The percentage of patients with hip OA who underwent total joint replacement in a recent 3-year trial (ECHODIAH) was 8% per year[4]. Among cohorts of patients with painful hip OA, the number requiring total joint replacement is high enough to consider conducting a study in which that variable is a primary outcome measure[5]. In a 2-year longitudinal followup study of patients with painful OA who had previously participated in a clinical trial, 37% of those with hip OA, but only 9% of those with knee OA, underwent total joint replacement[6,7].

Conclusion

As noted, arguments exist in favor of hip OA over knee OA as a human model for development of an OA drug, in particular the greater capacity of hip OA to demonstrate symptomatic and structural effects and the possibility of using requirement of joint replacement as an outcome measure. Indeed, the only argument favoring the knee over the hip is the lack of standardization in obtaining MRI views and the paucity of MRI analyses in subjects with hip OA. Because of the other advantages of the hip relative to the knee, it is our opinion that requirement for hip arthroplasty should be further evaluated as a primary outcome measure for OA clinical trials.

## REFERENCES


1. Pham T, van der Heijde D, Altman R, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria of osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12:389-99.
2. Altman RD, Bloch DA, Dougados M, et al. Measurement of structural progression of the hip: the Barcelona consensus group. Osteoarthritis Cartilage 2004;12:515-24.
3. Abadie E, Ethgen D, Avouac B, et al. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12:263-8.
4. 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.
5. Lane NE, Nevitt MC, Hochberg MC, et al. Progression of radiographic hip osteoarthritis over eight years in a community sample of elderly white women. Arthritis Rheum 2004;50:1477-86.
6. Tubach F, Baron G, Dougados M, et al. Predictive factors of total knee replacement due to primary osteoarthritis [abstract]. Arthritis Rheum 2003;48 Suppl:S77.
7. Gossec L, Tubach F, Baron G, et al. Predictive factors of total hip replacement due to primary osteoarthritis: a prospective 2-year study of 505 patients. Ann Rheum Dis 2005; Jan 7;[Epub ahead of print].


## INCREASED BIOLOGICAL ACTIVITY OF SUBCHONDRAL MINERALIZED TISSUES UNDERLIES THE PROGRESSIVE DETERIORATION OF ARTICULAR CARTILAGE IN OSTEOARTHROSIS

*David B. Burr*

The view that stiffer subchondral bone predisposes the joint to progressive osteoarthrosis (OA) by increasing stresses in the overlying cartilage is now giving way to the view that a dynamic process of progressive subchondral thickening, as the result both of increased bone turnover and reactivation of the secondary center of growth, is of pathogenetic importance in OA. This suggests a fundamental change in orientation in our understanding of the role of subchondral bone in OA: rather than being a mechanical consequence of a stiffer subchondral plate, the bone changes in OA represent the biological response of the subchondral bone and calcified cartilage to the altered joint mechanics that drive the process.

One reason for this change in viewpoint is that the stiffness of the tissue (i.e., the elastic modulus) has been shown to be reduced locally[1], under the influence of increased vascularization and a more rapid remodeling rate. The cause of the increased local bone turnover is not known, but it may be induced, in part, by the formation of microcracks that can initiate targeted repair[2]. These changes in the bone are intimately associated with reactivation of the secondary center of ossification, causing movement of the tidemark and thinning of the articular cartilage. A recent review[2] states: "The existing data are consistent with the view that reactivation of the secondary center of ossification and not the stiffening of the metaphyseal trabecular bone is a mechanism of cartilage loss in idiopathic OA. The stiffening of the subchondral calcified structures would appear to be etiologically incidental and... locally transient" (p. 681).

A thickened subchondral plate does not predispose to progressive joint deterioration[3,4], although the plate may thicken as the arthrotic process progresses[5,6] and may even predict joint space narrowing[7]. Indeed, subchondral thickening — which includes thickening of the calcified cartilage layer as a result of reactivation of the secondary center of ossification — may be required for the progression of OA.

Increased bone turnover may be a necessary precondition for subchondral bone to become thicker. In a study that compared 2 strains of guinea pig that develop spontaneous OA, Huebner, *et al*[6] showed that the strain with the higher rate of bone turnover at a young age had the greatest increase in subchondral bone thickness and developed more severe OA. The strain with the less severe form of OA exhibited a thicker subchondral plate initially, but a lower rate of bone turnover and no progressive thickening of the plate. In both these models, the progression of OA is associated with a high bone turnover rate and increasing thickness of subchondral bone, rather than initial thickening of the subchondral plate.

A current view of the interaction of mechanics and biology that integrates these various observations is that abnormalities in joint mechanics that prevent attenuation of impact initiate new bone remodeling and reactivate the secondary center of ossification. The accelerated bone turnover reduces the elastic modulus of the tissue, but results in thickening of the subchondral plate. Reactivation of the secondary center allows advancement of the tidemark into the hyaline articular cartilage, further increasing the thickness of the mineralized subchondral plate and reducing the thickness of the cartilage (Figure 9). Thus, the mechanical derangement of the tissues induces biological responses in both bone and calcified cartilage that fuel the progression of articular cartilage thinning, resulting in increased shear stress and progression to complete loss of cartilage.

There now seems to be general agreement that the cancellous bone distant from the subchondral cortical plate is