Clinical trials in osteoarthritis

Of all the musculoskeletal diseases, osteoarthritis probably presents us with the greatest challenge. With our aging population, it will become the most prevalent disease in our society and generate enormous costs.\textsuperscript{1} Population surveys in Britain, Canada, and Australia have shown a high prevalence of disability associated with osteoarthritis, particularly in elderly people.\textsuperscript{2,3} Risk factors such as obesity and trauma have now been identified at least for osteoarthritis of the knee\textsuperscript{5} and new agents are being developed which might modify the progression of osteoarthritis. These new treatments will require carefully conducted, long term trials using well validated and sensitive endpoints.

The issues relating to clinical trials in osteoarthritis require a knowledge of the types of drugs which are to be tested, the end points to be used, and trial design. Drugs currently used for osteoarthritis such as the analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) provide symptomatic relief only. The vast majority of trials of NSAIDs have been performed against placebos and it is only in the past few years that formal long term studies have shown that a significant number of patients with osteoarthritis of the knee previously controlled on NSAIDs can be managed just as effectively with paracetamol alone.\textsuperscript{4,5} The newer agents should provide not only symptomatic relief but significantly slow the disease process. It is therefore important that we develop more accurate end points to measure progression of osteoarthritis and show their responsiveness to change.

Drugs for osteoarthritis can be classified as symptom modifying or disease (structure) modifying osteoarthritis drugs (SMOADs or DMOADs). It has been proposed that two classes of slow acting drugs for the treatment of osteoarthritis (SMOADA) be considered – symptomatic slow acting drugs for the treatment of osteoarthritis (SYSMOADA) and disease modifying osteoarthritis drugs (DMOADs).\textsuperscript{5} These two classes of drugs could be given orally, parentally, or by the intra-articular route. Symptomatic rapidly acting or slow acting drugs would continue to be assessed by standard clinical methodologies which test pain, function, global status from both the patient and observer perspective, and inflammation. Adverse events may provide important comparisons between drugs such as analgesics or NSAIDs and need to be measured carefully over a significant period of time. Even for rapid acting symptom controlling drugs such as analgesics or NSAIDs studies of short duration (three months) are probably inappropriate in a disease which can last a lifetime.

The DMOADs present a different challenge – they may relieve symptoms as well but the important thing is that they are shown to slow progression of disease. To this end imaging techniques, biochemical markers of cartilage breakdown, and direct observation by arthroscopy may need to be employed as end points for initial trials of effectiveness. Plain radiography, macroradiography, ultrasound, magnetic resonance imaging,\textsuperscript{10} and radionuclide scintigraphy can all be used to assess severity of the disease but whether they are sensitive enough to pick up change after an intervention is not yet established. Magnetic resonance imaging offers great potential for the study of cartilage but poor resolution and tissue discrimination still restrict interpretation. Techniques to improve resolution should improve its discriminant value\textsuperscript{11} but it is likely to remain an expensive tool, restricted to tertiary referral centres. An increasing number of biochemical markers of cartilage breakdown are now being employed.\textsuperscript{12,13} These include increased concentrations of hyaluronic acid, collagen 2 propeptide, and keratan sulphate in blood and urinary excretion products of collagen such as pyridinoline crosslinks. Just how specific these markers are in reflecting damage to articular cartilage and how sensitive they are to change induced by treatment remains to be tested. Minitarthroscopy or chondroscopy is also being developed as a new measure of cartilage integrity by direct visualisation and scoring methods for this procedure are now available.\textsuperscript{14} Even miniaarthroscopy, however, is an invasive procedure requiring appreciable resources and will need to be proved to be a cost effective investigation before being adopted for routine practice. Of course these markers of joint destruction will also have to be combined with functional indices and pain measurement and the studies continued for a period sufficient to show differences between treatments. Knowledge of the underlying disease process and its progression is important in determining these variables. Radiological data on progression are available for the hip\textsuperscript{15} and the knee,\textsuperscript{16} suggesting joint space loss of 0.22 mm a year and 0.26 mm a year respectively in most cases. However, progression is variable with some joints showing rapid cartilage loss and others either no progression or even demonstration of healing.\textsuperscript{17,18}

The challenges of developing and using appropriate outcome measures for osteoarthritis trials have been considered recently in two reviews.\textsuperscript{19,20} Any outcome measure that is used must fulfil the criteria defined by Bellamy – namely, simplicity, reproducibility, validity, and sensitivity to change.\textsuperscript{21} The problem is that although many of these suggested end points have great potential few
currently fulfil these criteria. Outcome variables might be placed in the following broad categories – clinical variables, biological variables, imaging and direct vision, the issue being that of poor correlation between the variables. Clinical variables will continue to be used to measure symptoms and therefore must be used as primary end points in trials of SYSADOA and as secondary end points for DMOAD. Imaging techniques and possibly arthroscopy, particularly if relatively non-invasive methods can be developed to measure cartilage function, will be the primary end points in DMOAD studies. Biological variables may be extremely useful in the future, particularly early in the disease, and serum, urine, and synovial fluid should certainly be collected when possible for future analysis in DMOAD studies. In designing a matrix of end points for DMOAD studies we will in the foreseeable future have to continue to take measures from each of these groups and look carefully for correlations and predictors of outcome.

It may be that osteoarthritis is a heterogenous disease in terms of clinical involvement. Primary generalised osteoarthritis and single joint disease may have differing natural histories and biologies. These differences need to be explored because they have important implications relating to entry criteria for trials for osteoarthritis. Although there may be significant clinical differences between these conditions, the basic disease process may be the same and hence different forms of osteoarthritis could be considered as one for the purpose of assessing a new treatment. At the present time, care should be taken with entry criteria and they should be clearly specified and adhered to and even within a trial involving a particular joint – namely, hip or knee – there should be the ability to treat lateral, medial or bicompartamental disease differently at entry or in analysis. One of the major problems with developing very homogenous entry criteria is that few patients with disease of the joint will fulfil entry criteria for randomisation.

Paulus and Bulpitt recently proposed some guidelines for the conduct and analysis of DMOAD studies considering specifically the issues of statistical analysis and additional treatment. For example, ethical issues may well arise in using DMOADs (which will hopefully provide symptomatic relief as a product of their disease modifying activity) which may require use of a pain relieving medication at the same time. Placebo comparisons could be used ethically if supplemental paracetamol or an NSAID were allowed for symptom relief. This statement, however, needs to be taken in the context of the recent suggestion that some NSAIDs (for example, indomethacin) may actually worsen radiological deterioration.5 24 25

The other issue that needs to be considered is that of the very powerful placebo effect of joint injections when considering SYSDOA or DMOADs given by this route. This will significantly impact on the number of patients required to show a difference. Paulus and Bulpitt also point out the significant dropout rate in long term trials of treatment in osteoarthritis.6 7 As most were due to lack of efficacy in the placebo group more attention to symptomatic relief may increase the percentage of completers. The second point was that radiographic deterioration was noted in less than 30% of patients at two years in those who completed the study but data were not available in the withdrawals. Power might be increased in future studies if the radiographic outcome could be performed on all patients with an intent to treat analysis.

Symptom relieving drugs for osteoarthritis can be adequately tested using n of 1 trial methodology.8 This method of randomising treatment (in this case NSAIDs or paracetamol) can be clinically useful in deciding on individual treatment in a variable condition such as osteoarthritis. Such methodology has the advantage over standard parallel or crossover randomised trials in that it takes into account individual variation in disease and response and does not require large numbers of patients. Trials of disease modifying drugs need to be carefully planned with a series of clear objective end points. The trials need to be controlled and to run for a sufficient duration (years) to be sure of demonstrating a difference in the objective treatment of cartilage loss. Repeated imaging techniques (the current gold standard) are expensive but only need to be performed infrequently (yearly probably).

Rheumatologists interested in treating osteoarthritis need to look at the way cardiologists have developed their large intervention studies in coronary artery disease. Studies on the lipid lowering agents or treatment for thrombolysis have thousands of patients followed up for long periods.26 27 We need to ask ourselves why this is not done in rheumatology. The advent of disease modifying treatments for osteoarthritis demands that we take this approach. Our trials may be subject to an interim analysis initially looking at the clinical end points perhaps at one and two years and then reporting differences in radiological progression at four and five years. The challenge will be to identify early markers that predict a good outcome. The initial studies need to be large to do this.

The outcome of osteoarthritis of the knee and hip may not be as dramatic as that of a myocardial infarct but it is certainly expensive in personal terms to an individual patient and in societal terms for the cost of services to cope with that individual disability and with the cost of the eventual joint replacement. The ultimate end point – the time to joint replacement – which has been used in at least one trial comparing non-steroidal anti-inflammatory drugs,28 is not viable practically because of the long natural history of the disease. It should, however, be factored into the equation, particularly in economic terms as joint replacement is becoming such a frequently performed operation.

The development of consensus guidelines for assessment of osteoarthritis and conduct of clinical trials will go a long way in helping us to meet the challenge of osteoarthritis.

Department of Rheumatology and Public Health Unit, L M MARCH
Royal North Shore Hospital, St Leonards, NSW 2065, Australia

Department of Medicine, P M BROOKS
University of New South Wales, St Vincent’s Hospital, Darlinghurst,
New South Wales 2010, Australia

Correspondence to: Professor P M Brooks.


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