Workshop

How do we best measure the clinical benefit of a structure-modifying osteoarthritis drug?
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Rationale
The aim of the treatment of osteoarthritis (OA) is to improve symptoms and function; ideally, treatment would also prevent the structural progression of the disease. The targets of structure-modifying OA drugs (STMOADs) can be one of the various lesions of OA, including cartilage destruction, osteophytes, bone sclerosis, cysts, and bone attrition. However, prevention of cartilage destruction (chondroprotection) is currently accepted as the most promising target of STMOADs.

The possibility of preventing progression of cartilage damage has been demonstrated in various animal models of OA. Chondroprotection is now being investigated in human OA. Several trials are in progress, and two positive studies have already been reported1,2. The goal of these initial trials was mainly to demonstrate that a reduction of the natural progression of OA joint space narrowing is possible in humans. Today, chondroprotection is no longer considered a myth, and the questions now are whether STMOADs provide a clinical benefit for the patient and how to evaluate that benefit. These new and relevant questions are difficult to answer.

Can we expect a clinical benefit from STMOADs?

Drugs evaluated for a structure-modifying effect may or may not also have symptomatic effects in the short term. STMOADs with a symptomatic effect can be expected to lead to clinical improvement in the OA patient in the long term. Evaluation of the clinical benefit of STMOADs could be possible with the tools presently used for the assessment of symptom-modifying drugs in OA.

The clinical benefit that can be expected from a drug without known symptomatic effects but with a structure-modifying effect and how to measure that clinical benefit are as yet unknown. An effective STMOAD is not expected to induce a repair of the structural lesions of OA, but it is expected to stop or decrease their progression. Such a structural effect in the long term might result in symptom improvement or might only prevent a progression of symptoms. It also might have no clinical effect, since symptoms and lesions are poorly correlated in OA patients.

The time required to demonstrate the clinical benefit of a STMOAD is unknown. It is possible that there may be a long delay (several years) between the beginning of STMOAD efficacy and the realization of any clinical benefit. The extent of clinical benefit could be related to the degree of effectiveness of the STMOAD. If this were true, the delay in clinical benefit could be very long for drugs able to only partially reduce the structural progression of the disease. Finally, the clinical benefit of a STMOAD might be missed by our usual tools and could require new methods of evaluation.

Pain and function measurement for the demonstration of the clinical benefit of a STMOAD

Numerous tools used for the clinical measurement of the OA patient have been validated in short-term trials of symptom-modifying drugs. These tools rely mainly on the measurement of pain and function, either separately or in composite indices (e.g., Lequesne index, WOMAC scale). Their reliability and sensitivity to change in long-term studies are poorly known. However, they represent valid methods for demonstrating the clinical benefit of STMOADs. The use of quality-of-life questionnaires could be of special interest for such trials.

Are there more appropriate tools for the demonstration of the clinical benefit of a STMOAD?

Stabilization of the clinical status of the OA patient by preventing progression of structural lesions of the disease could be the major clinical benefit of a STMOAD. However,
other methods of evaluation of the clinical benefit of a STMOAD could be imagined. The need for other medical treatments of OA, especially invasive or expensive treatments and those with harmful side effects, could be of interest as clinical end-points. Other end-points could include the need to reduce activity because of functional impairment, the need for devices to aid mobility, such as a cane, and the requirement for joint replacement surgery.

Total hip replacement (THR) has been proposed as an outcome measure of hip OA. THR, sooner or later, is the final treatment for a majority of patients with hip OA. THR is indicative of both a high level of painful handicap and a late pathological stage. Requirement for THR is also a simply measured end-point. However, the time for surgery is partially related to various factors independent of OA: patient psychology, physician psychology, age, associated diseases, economic systems. The effect of these factors could be reduced by using the time when the physician or the patient would estimate that surgery would be justified rather than the time of the surgery itself. Total joint replacement is relatively less common in knee OA than in hip OA. Thus, requirement for surgery of the OA knee would probably be a less usable method of evaluation than THR. The design of a study with THR as a primary outcome measure would be complex since only patients expected to need surgery during the course of the study would be selected. This contrasts with chondroprotection trials, which rely on measurement of the progression of joint space narrowing so that patients expected to need surgery must be excluded.

Trial design for the demonstration of the clinical benefit of a STMOAD

A study designed to demonstrate both a structure-modifying effect and a clinical effect will probably differ from a study designed only to demonstrate a structural effect. For example, selection of patients with regard to pain or handicap level would be different. In a chondroprotection trial, the patients studied must have enough cartilage to permit measurement of its destruction rate, clinical status being of marginal interest. A chondroprotection trial that also aims to demonstrate a clinical benefit would require patients who had not only an adequate amount of cartilage but also enough pain and/or impairment to make possible assessment of clinical improvement. In later trials, cessation of any analgesic or non-steroidal anti-inflammatory drug (NSAID) intake prior to clinical evaluation would also be imperative for the accurate evaluation of a clinical benefit.

The method of calculating the number of patients per group would also be different. The number of patients for a chondroprotection study is based on the natural rate of progression of joint space narrowing. Determining the number of patients needed to demonstrate a clinical benefit of treatment would require some knowledge of the natural rate of progression of symptoms in OA patients (e.g., in patients enrolled in a placebo-controlled trial). Definition of a clinically aggravated patient, as well as the percentage of aggravated patients per year, could be of interest for the design of a trial aimed at the demonstration of a clinical benefit of a STMOAD.

Summary

Evaluation of the clinical benefit of a structure-modifying OA drug is a question of major interest. The evaluations performed in a study of both a structure-modifying effect and a clinical benefit will differ from those performed in a simple trial of chondroprotection. Existing tools used for the clinical measurement of OA patients may be of help in evaluating the clinical efficacy of STMOADs, or it may be that the clinical benefits of STMOADs will be missed by conventional tools and require new methods of evaluation.

Appendix

Abbreviations used in the manuscript:

- NSAID: non-steroidal anti-inflammatory drug
- OA: osteoarthritis
- STMOAD: structure-modifying osteoarthritis drug
- THR: total hip replacement

References