Methodology of clinical trials in hand osteoarthritis: conventional and proposed tools

M. G. Lequesne* and E. Maheu†
*Hôpital Léopold Bellan, 75014 Paris, France
†Department of Rheumatology B, Hôpital Cochin, 75014 Paris, France

Summary

Background: Although very common, hand osteoarthritis (OA) is rarely the focus of clinical trials aimed at determining whether a drug is effective on its symptoms and/or anatomical progression. Besides the common difficulties met in trials in OA in general, the highly unpredictable course of hand OA presents specific challenges. However, hand OA is beginning to be considered as a potential model for the study of drugs in OA, since researchers now have at their disposal new clinical tools and radiological methods to assess with better accuracy and sensitivity either its symptomatic activity or its anatomical course.

Method: The now well-known consensual recommendations for the design and conduct of clinical trials in OA are reviewed, and the specific clinical tools and radiological methods available for the assessment of hand OA detailed. Some specific recommendations for the design of clinical trials in hand OA and the selection of patients for such trials are proposed, taking into account the particularities of this location of OA.

Key words: Hand OA, Clinical trials, Methodology, New assessment tools.

Introduction

Methodology of clinical trials in patients with osteoarthritis (OA) has improved over the last 7 years, mainly due to four meetings dedicated to arriving at a consensus followed by papers discussing trials in OA in general terms concerning the three main OA sites: hip, knee and hand.1-4 This paper concentrates on studies specifically targeted at hand OA and expands upon our previous review.5

General considerations

The first attempt to clarify and define slow acting drugs in OA (SADOA), either symptomatic (SY-SADOA) or disease-modifying drugs in OA (DMOADs instead of previously so-called 'chondroprotective' agents) was implemented by WHO and ILAR in 1992-1994.1 Among the proposals were (1) the use of specific outcome measures for DMOADs, especially the measurement of the radiographic joint space width (JSW) and its loss over time, an assessment originally proposed6 and described in detail in 1995,7 and (2) survival curve methodology to highlight the possible retardation of the joint space (JS) narrowing over 2-3 years.1 These methodologies seem suitable to assess radiographic lesions or to count the newly affected fingers joints (FJ) in hand OA over years in well designed, well controlled long-term trials.

Several meetings (1995-1996) of the European Group for the Respect of Ethics and Excellence in Science (GREES)8 and task force of the Osteoarthritis Research Society (now OARSI) in Washington (May 1996)9 stated that the distinction between fast and slow acting drugs in OA trials is not useful and proposed to establish two new classes: symptom-modifying drugs and structure-modifying drugs, the latter to be used instead of 'DMOADs', while maintaining the definition given in 1994: 'an agent able to prevent, stabilize, retard or even reverse cartilage (and other) lesions of OA in humans'.7 Both the European GREES and the OARS group yielded many details on trial methodology for both classes of drug.

Between these two meetings, the OMERACT III meeting (Cairns, Australia), led to a consensus from the audience on outcome measures of pivotal value ('core' set); of lesser value but strongly recommended ('middle core' set) and optional measures ('outer core' set) with regard to hip, knee and hand OA trials. Figure 1 summarizes the results. The report4 lacks detail and some difficulties arise when specific applications have to be drawn from the core set. One is the ambiguity of the statement 'imaging in trials >1 year' as an outcome measure. This comment is suitable for trials of possible disease- or structure-modifying drugs and their effect on the anatomical course of OA. On the other hand, since a deleterious effect of a given NSAID (for instance, indomethacin) or of other drugs on cartilage remains an underlying hypothesis, this comment deals also with such a possible adverse reaction. However, the latter belongs to a distinct category of consequences recorded in a trial. Another difficulty may arise from the generality of the propositions, whereas given locations of OA, especially in the hand, requires certain adaptations. Nevertheless, the OMERACT III guidelines are concise and have utility although they are not detailed. These details may be found in the three other papers mentioned.

Though hand OA does not appear, at first glance, to be as good a model for trials as knee and hip OA, the rheumatology community has progressively accepted that...
hand OA is a valuable model, beside hip and knee OA, provided some relevant alterations suitable to the particular profile of this location are made. We summarize below what appear to be, in our opinion, the main methodological characteristics (for a more detailed statement, please see Maheu et al.5).

Specific considerations

TRIALS OF SYMPTOM-MODIFYING DRUGS

Diagnosis

An American College of Rheumatology (ACR) subcommittee headed by Altman developed the only currently available set of validated classification criteria for hand OA9 (Table I). These criteria are largely accepted9-11 and used. However, the following additional items, proposed in our first review, are strongly recommended: (1) to take into account the Heberden and/or Bouchard nodes of the fourth and fifth fingers (absent in the ACR set); (2) to obtain radiological OA image of the trapezometacarpal (TMC) joint if it appears to be clinically involved. Since X-rays are positive in only one-third of patients with Heberden's nodes, it can not be determined at this time whether radiologic images of other joints should be required. But we strongly recommend to perform an X-ray before entry; (3) to systematically consider some exclusions: rheumatoid and psoriatic arthritis, since each may cause OA or in the case of psoriatic arthritis, can be difficult to distinguish from erosive hand OA; chondrocalcinosis (TMC joint involvement); hemochromatosis; sequelae of algodystrophy of the hand and diabetes mellitus hand lesions.9

Assessment methods

Pain assessment on a visual analog scale (VAS) or using the pain section of the AUSCAN (five questions; see below), patient’s and physician’s global assessments should be performed as usually. The value of sparing NSAID and/or analgesics consumption, as an outcome measure is still debated. Let us consider specific tools for hand OA.

(1) The first validated functional index for hand OA was developed by Dreiser et al. and published in 1995.9 It consists of a 10-item investigator-administered questionnaire (Table II). The total score ranges theoretically from 0 to 30, but in practice, usually varies from 2 to 18 points with regard to severity of symptoms of hand OA. Its validation was based on the difference between patients with ‘painful’ hand OA (i.e. pain on VAS≥40 mm; mean score: 12.41±5.41), those with ‘quiescent’ hand OA (mean score: 4.28±3.87) and controls, defined by the absence of any disease involving the upper limbs (mean score: 0.59±1.23). This index is valid, reproducible, and simple to use (2-3 min to administer). It has been used in several trials. Its sensitivity has recently been studied, as reported by Dreiser in the present issue. In the meantime, its...
Diagnosis and patient selection

In addition to the diagnostic criteria discussed previously, an X-ray showing definite features of OA is necessary for baseline screening.

As far as symptoms are concerned, since the trial will be of long duration (3-5 years), only a few 'flares' or periods of pain in two or more fingers or in TMC joint will be enough to establish a symptomatic or 'painful' hand OA patients.

To summarize, the primary criterion may be either pain on VAS or a functional index. Using the Dreiser's index, a decrease of 3-4 points at the completion of the trial should be the desired endpoint. Duration of the trial depends on the class of drug being tested: with regard to the Sy-SADOAs, 6-9 months, sometimes up to 12 months (plus a 2-3 month post-therapeutic follow-up to assess the possible persistent effect) are desirable even when a fast-acting compound is evaluated. The long length of this type of study is necessary due to the irregularity of the painful phases which are often separated by a span of several weeks and with a minimum duration of 2-3 months.

**Criteria for the selection of symptomatic or 'painful' hand OA patients**

The terms from the ACR criteria 'hand pain, aching or stiffness' (Table I) are not precise enough for hand OA trials: stiffness alone, without pain (quiescent inactive OA), would not be sufficient to assess results in a symptom-modifying drug trial. We propose additional criteria to specify the severity of symptoms defining 'painful' hand OA as follows (partly according to Lequesne et al. and Maheu et al.)

1. At least two IP and/or one TMC joint painful at entry.
2. At least two or three painful flares in a finger joint during the previous 12 months.
3. Pain during at least half of the days in the previous 2 months.
4. Pain for at least 2 days before inclusion or pre-inclusion visit in a radiologically affected joint.
5. Pain achieving 40 mm or more on a VAS.
6. A Dreiser's index score ≥6 points.

How many criteria (three, four or more) should be met?

This is to be established in additional studies.

**Trials of potential structure-modifying drugs**

The primary criterion of a trial assessing structure-modifying drugs should be a measure of the changes in anatomical structure, i.e. today radiography. However, symptomatic effect of the drug must also be assessed. Therefore, some of the above mentioned outcome measures for symptoms should be selected and evaluated in parallel to disease modification throughout the trial duration.

**Table II**

Functional index for hand osteoarthritis developed by Dreiser et al. (modified by the authors with the help of Paul Boulos-Haraoui)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>(1)</td>
<td>At least two IP and/or one TMC joint painful at entry.</td>
</tr>
<tr>
<td>(2)</td>
<td>At least two or three painful flares in a finger joint during the previous 12 months.</td>
</tr>
<tr>
<td>(3)</td>
<td>Pain during at least half of the days in the previous 2 months.</td>
</tr>
<tr>
<td>(4)</td>
<td>Pain for at least 2 days before inclusion or pre-inclusion visit in a radiologically affected joint.</td>
</tr>
<tr>
<td>(5)</td>
<td>Pain achieving 40 mm or more on a VAS.</td>
</tr>
<tr>
<td>(6)</td>
<td>A Dreiser’s index score ≥6 points.</td>
</tr>
</tbody>
</table>

How many criteria (three, four or more) should be met? This is to be established in additional studies.
assess symptomatic effect during the trial. A current painful phase, just before or at baseline, is, while desirable, not mandatory.

Inclusion criteria derived from radiographic images should be fully defined. Patients with few moderate lesions (less than two IP joints involved) or, in contrast, with severely advanced hand OA (more than two-thirds of IP joints involved) ought not to be recruited. Likewise, concerning the stage of OA, the doubtful cases (osteoophyte not clearly visible; no ascertained JS narrowing or no clear subchondral bone radiolucency) should be excluded as well as those with too highly advanced lesions: complete erosive hand OA, or JS completely collapsed in more than four IP (out of 18 IP in both hands). An alternative proposal could be to identify different subsets of hand OA patients according to the existence of erosive lesions at baseline and at the conclusion of the study. Patients with such erosive lesions should be analysed separately. However, the reader(s) should be blinded to the time-sequence order of X-rays.

Radionuclide bone scanning could be useful to select—or to exclude, depending on the scientific committee decision—patients at high risk of active disease which could rapidly lead to severe lesions. It has been shown by some authors that fingers joints with increased uptake were often subject to such a deterioration. However, this procedure might be difficult and costly, and at present, the exact percentage of patients with increased uptake who will develop a rapidly progressive disease is not known. The high cost of this procedure may preclude its use in clinical trials.

**Outcome measures**

The primary efficacy criterion should be the radiographic course of hand OA over 2–5 years. One accurate method was that developed by Buckland-Wright *et al.* They showed an increase in JS width of DIP and PIP joints in patients with early OA compared to healthy controls (over-hydration?). In 33 hand OA patients, JS width did not change enough over an 18-month period to be considered a significant parameter. The two significant changes were those of osteophytes and of juxtaarticular radiolucencies. However, the special device with microfocus X-ray source necessary to perform macroradiographs to conduct such a study is available only in London.

Harris *et al.* have noted over 10 years that 45–50% of DIP, PIP and MCP OA joints deteriorated, while about 45% did not change and 6–9% improved. However, such long term follow-up is not feasible for a clinical trial. The same remark applies to the 6–7 year duration study by Kallman *et al.* who developed a complete and sensitive grading scale to study the radiographic progression of hand OA. This methodology still requires further studies to assess the other metrologic properties (i.e. clinical relevance, reproducibility, easiness to perform, etc.). Their global score sums the assessment of six radiographic features (osteoophyte size, JS narrowing, subchondral bone sclerosis, subchondral cysts, presence of erosion, deformity) for the DIP, PIP, TMC and scaphotrapezial joints (only five and three signs graded for the two latter locations, respectively). In our experience, it takes 7–8 min for a trained reader to score one radiograph.

In addition to the classic Kellgren and Lawrence 5-grade radiographic assessment, another feasible method implemented in a prospective randomized clinical trial is that of Verbruggen and Veys. In a 5-year follow-up, 36 patients with hand OA were screened for the eight DIP, eight PIP (thumb excluded) and eight MCP per hand. The authors noted that only time frames of 3 and 5 years were relevant to observe significant changes. Osteophytes, JS and subchondral cysts were quantified as shown in Table III. Scores for each of the three parameters were combined. Two parameters exhibited significant increases at 3 and 5 years: the combined score adding each item of Table III, i.e. the worsening of lesions, and the number of DIP, PIP and MCP joints affected by OA in comparison with baseline. Moreover, the authors showed that 30–40% of
their patients developed an erosive OA of some joints, a phase followed by reparative changes, either remodeling or leading to fusion.\textsuperscript{20,21}

Looking at the current proposed radiological methods to assess structure in hand OA, five methods should be considered: (1) Kellgren–Lawrence score; (2) Kallman grading scale; (3) Verbruggen numerical scoring methods; (4) Buckland-Wright macroradiography and (5) global assessment of the presence/absence of OA. No study thus far has compared the respective value of the measures provided with these methods. One study conducted by one of us (Maheu \textit{et al.}) is in progress, but the results are not yet available. For this reason we are not able, at present, to recommend a particular method based on documented evidence. We can give only an overview of each method and refer the reader to the paper on radiographic assessment in this issue. Further studies should elucidate the most appropriate radiographic method to be used in studies assessing the structure-modifying effects of a drug in hand OA.

In the above methodologies, individual data on the TMC joint is not evaluated. We think that this particular location, where OA is very common and is usually associated with more pain and/or discomfort than in DIP and PIP joints, should have separate clinical and radiological outcome measures. Consequently, the TMC joint should perhaps be characterized separately from IP joints with OA in future clinical trials.

Similarly to hip and knee OA, radiographs of the hands should be read blindly by one or two readers previously identified as having a good intrarater reproducibility. Films should be blinded for names and dates, and read in series of 20–30, each series containing in random order, all the radiographs for one given patient.\textsuperscript{9}

Table III

<table>
<thead>
<tr>
<th>Osteophytes*</th>
<th>Joint space</th>
<th>Subchondral cysts</th>
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</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>+1.0</td>
<td>Narrowing</td>
</tr>
<tr>
<td>Disappearance</td>
<td>-1.0</td>
<td>Widening</td>
</tr>
<tr>
<td>Increase in size</td>
<td>+0.5</td>
<td>Increase in size</td>
</tr>
<tr>
<td>Decrease in size</td>
<td>-0.5</td>
<td>Decrease in size</td>
</tr>
</tbody>
</table>

*Small ossification centers at the joint margins were regarded as OA-related changes and they were evaluated as osteophytes.

**Conclusion**

Hand OA deserves to be used for therapeutic trials since (1) patients’ demand for treatment is large; (2) it might not be possible to extrapolate results of trials from hip/knee OA to hand OA, which often progresses differently; (3) we currently have at our disposal a number of specific tools and assessment methods in hand OA which allow us to consider the hand as a valuable ‘model’ to study treatments for OA. These tools and methods are sensitive and provide an acceptable accuracy (even radiologically in the long-term) to lead to conclusive results. The above methodological propositions are obviously opened to discussion and should lead to the constitution of a working group and to an international consensus meeting.

**References**