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Guidelines for the conduct of pharmacological clinical trials in hand osteoarthritis: Consensus of a Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

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ABSTRACT

Objectives: To gather expert opinion on the conduct of clinical trials that will facilitate regulatory review and approval of appropriate efficacious pharmacological treatments for hand osteoarthritis (OA), an area of high unmet clinical need.
Methods: The European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal diseases (ESCEO) organized a working group under the auspices of the International Osteoporosis Foundation (IOF) and the World Health Organization (WHO).

Abbreviations: ACR, American College of Rheumatology; AUSCAN, Australian/Canadian hand OA Index; CHFS, Cochin Hand Functional Scale; CMC, carpometacarpal; ESCEO, European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal diseases; FIHOA, Functional Index for Hand Osteoarthritis; IA, intra-articular; IP, interphalangeal; KL, Kellgren–Lawrence; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; SYSADOA, symptomatic slow acting drugs for OA.

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Results: This consensus guideline is intended to provide a reference tool for practice, and should allow for better standardization of the conduct of clinical trials in hand OA. Hand OA is a heterogeneous disease affecting different, and often multiple, joints of the thumb and fingers. It was recognized that the various phenotypes and limitations of diagnostic criteria may make the results of hand OA trials difficult to interpret. Nonetheless, practical recommendations for the conduct of clinical trials of both symptom and structure modifying drugs are outlined in this consensus statement, including guidance on study design, execution, and analysis.

Conclusions: While the working group acknowledges that the methodology for performing clinical trials in hand OA will evolve as knowledge of the disease increases, it is hoped that this guidance will support the development of new pharmacological treatments targeting hand OA.

Introduction

Osteoarthritis (OA) is the most common of the musculoskeletal disorders, affecting joints of the hand, knee, hip, and spine. Hand OA as a subtype receives relatively little attention compared with hip and knee OA, and yet estimates show a higher prevalence of hand OA than other joint sites [1]. Hand OA is a heterogeneous disease with involvement of different joints of the thumb and fingers, varying degrees of symptoms including asymptomatic disease, and a more severe subset with radiographic evidence of central erosions [2,3]. Epidemiologic studies of the prevalence of hand OA offer wide ranging estimates due to differences in disease definitions, types of populations, and/or risk factors such as genetic factors or environmental exposures across cohorts. Radiographic hand OA prevalence estimates range from 38% to 44% in the United States to 61% in the Netherlands; although a sizeable proportion of people with radiographic evidence of OA have no symptoms or disability [1,2]. Symptomatic and self-reported definitions present similar estimates of hand OA prevalence at 7–14% and 4–6%, respectively [1,2]. The prevalence of OA increases with age, and the prevalence of hand OA across 6 European countries is estimated at 17% among people aged 65–80 years, which is associated with fair to poor self-rated health [4,5].

Much has been done to better understand the clinical course and structural progression of hand OA. In recent years the number of clinical trials in the field is increasing leading to new research data, although few treatments have produced strong evidence of efficacy in hand OA [6,7]. There is currently no pharmacological therapy approved in the EU specifically for the indication of hand OA; while in the United States, one topical non-steroidal anti-inflammatory drug (NSAID), diclofenac 1% gel, is approved for use in treating pain associated with OA in joints amenable to topical treatment, such as the knees and those of the hands.

Recommendations from the Osteoarthritis Research Society International (OARSI) issued in 2015 on the design and conduct of clinical trials for hand OA provide a systematic review with limited guidance regarding outcome measures, length of follow up and other practical aspects of trial conduct [8]. Consequently, the aims of a working group organized under the auspices of the International Osteoporosis Foundation (IOF) and the World Health Organization (WHO), held in Geneva, Switzerland on February 1, 2017, and this resulting consensus statement from the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal diseases (ESCEO) are to provide a practical reference tool for the conduct of clinical trials that will facilitate regulatory review and approval of appropriate efficacious pharmacological treatments for hand OA.

Methods

The ESCEO working group consisted of clinical scientists expert in the field of OA in academia and consulting for drug development within the pharmaceutical industry, and representatives of national or European licensing authorities giving their contribution on a personal basis.

As a general methodology, the group reviewed the OARSI recommendations on the design and conduct of clinical trials for hand OA in detail [8], along with the current version of the Committee for Medicinal Products for Human Use (CHMP)/European Medicines Agency (EMA) guideline of clinical investigation of medicinal products used in the treatment of OA [9], and the recommendations for an update of the CHMP/EMA 2010 guidelines from a previous ESCEO working group [10].

The members of the working group were asked to assess the appropriateness and applicability of these documents to the specific area of practical conduct of clinical trials in hand OA, in order to identify areas requiring modification and further clarification. Members of the group (N.A., I.K.H., D.U., D.P.A., G.H.B., and J. B.) prepared a full review of the literature on the design of studies in hand OA, which were presented to the group at the meeting on February 01, 2017. After the presentations, a comprehensive discussion was held within the group and shared conclusions were reached. Following the meeting, members of the writing group (N. A., I.K.H., E.C., F.R., and C.C.) drafted a first report on the meeting consensus, which was reviewed and commented on by all authors.

As is the case for a recent algorithm for the management of knee OA developed by the ESCEO [11], guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) for the management of hand OA recommend both non-pharmacological and pharmacological measures [12,13]. However, non-pharmacological measures of benefit in hand OA were not included for consideration in this consensus, and may form the basis of another paper.

This resulting guidance document is intended to provide recommendations, not rigid rules, and should allow for better standardization of the conduct of clinical trials of pharmacological agents. These recommendations are outlined in Table 1 and further details are discussed herein.

Hand OA phenotypes

Hand OA is a heterogeneous disease with various presentations and several phenotypes, including thumb base [first carpometacarpal (CMC-1) joint and scapho-trapezio-trapezoidal (STT) joint], vs. interphalangeal (IP) (proximal and distal) OA and erosive vs. non-erosive OA, which may involve different pathophysiological mechanisms [3]. However, patients rarely have disease in one anatomical location only. The working group recognized that it would be unlikely that a drug would be licensed in a phenotypic hand OA sub-indication, for example, thumb base or IP; thus, for regulatory approval the unit to be considered would be the hand. However, enrichment of the study population with certain hand OA phenotypes may increase the likelihood of detecting a treatment effect, depending on the mode of action. As an example, in

Table 1
Summary of practical recommendations for the conduct of randomized clinical trials in hand osteoarthritis

Aspect	Symptom modifying trial	Structure modifying trial
Inclusion criteria		
Diagnosis	ACR criteria	ACR criteria
Phenotype	All: thumb base, IP or erosive	All: thumb base, IP or erosive
Clinical disease state	Pain: minimum 40 mm VAS Function: no minimum level	NA
Radiographic disease state	NA	Kellgren–Lawrence grade 2 or 3
Exclusion criteria	Secondary OA	Secondary OA
Pre-trial drug wash-out period	Analgesic—5 × drug half-life No SYSADOA for 6 months No IA CS for 6 months No IA HA for 6 months No prednisolone (PO/IM) for 6 months	NA (unless assessing symptom burden)
Design	RCT, double/triple arm: Placebo Active comparator: paracetamol or NSAID Investigational agent	RCT, double arm: Placebo Investigational agent
Duration	Fast acting drug: minimum 3 months Slow acting drug: minimum 6 months	Minimum 2 years
Assessment intervals	1–6 months	At baseline and after a minimum of 2 years' treatment
Concomitant therapies	Rescue analgesia, for example, paracetamol up to 3 g/day	Rescue analgesia e.g. paracetamol up to 3 g/day Physical/OT permitted
Therapy exclusions	Physical/OT	Drugs/interventions likely to affect joint structure
Outcomes		
Primary	Co-primary endpoint Pain: VAS, AUSCAN pain subscale Function: AUSCAN function subscale, CHFS, or FIHOA	Effect on joint structure: plain X-ray
Secondary	Pain and function subscales, PROs, HRQOL	Symptomatic improvement
Other measurements	Long-term safety data to 12 months Absence of deleterious effect on joint structure over 12 months	
Biomarkers	None identified as relevant to symptoms	Validated biomarkers able to assess cartilage structure

Abbreviations: ACR, American College of Rheumatology; AUSCAN, Australian/Canadian hand OA Index; CHFS, Cochin hand functional scale; CS, corticosteroid; FIHOA, functional index for hand osteoarthritis; HA, hyaluronic acid; HRQOL, health-related quality of life; IA, intra-articular; OT, occupational therapy; IM, intramuscular; NA, not applicable; OA, osteoarthritis; PO, per os; PRO, patient-reported outcome; RCT, randomized controlled trial; SYSADOA, symptomatic slow-acting drugs for osteoarthritis; VAS, visual analog scale; NSAID, non-steroidal anti-inflammatory drug.

trials of anti-inflammatory treatments the inclusion of erosive hand OA patients, who often demonstrate high inflammatory activity, should be considered.

Thumb base OA vs. IP OA

Thumb base OA affects primarily the CMC-1 joint and often in conjunction with OA in the STT joint. It may exist alone, but can occur together with OA in the IP joints [14,15]. Heberden's or Bouchard's nodes often are signs of IP OA, which is then referred to as nodal OA [16].

In a population-based study, prevalence estimates for symptomatic hand OA phenotypes in the adult population aged ≥50 years were found to be 22% for thumb base OA, 16% for nodal IP OA, 5% for non-nodal IP OA, 10% for generalized hand OA, and 1% for erosive hand OA [17]. Considerable overlap between the subclassifications were observed, for example, with 9% of the population experiencing both thumb base and IP joint hand OA. Patients with a combination of thumb base OA and IP OA are observed to have more pain and physical disabilities than patients with isolated IP OA [14,18].

The prevalence of radiographic hand OA has been studied in a community-based population finding evidence for radiographic OA in at least one joint in up to 50% of the population with a mean age of 61 years. Radiographic OA was detected most frequently in first CMC joint in 30% of participants, although the second, third and fifth distal IP (DIP) joints were also commonly affected [2]. Radiographic OA was detected in two or more joint groups in 13–17% of the population.

Thumb base OA is a more biomechanically driven phenotype as compared with IP OA and may require distinct treatments such as splints and surgery [19–21]. Thumb base and IP OA may have different risk factors; hypermobility and subluxation of the CMC joint are risk factors for development of OA, while IP OA may be associated with systemic risk factors [22,23]. Hence, it may be appropriate for the study sub-analysis to identify whether patients with thumb base or IP OA were included in the investigation, and whether the thumb base or an IP joint is the most symptomatic joint, as the results may be pertinent to the mechanism of action of the investigational agent. Patients could be stratified based on hand OA location; alternatively post hoc analyses may detect any interaction between OA phenotype and activity.

Erosive vs. non-erosive OA

It is unknown whether erosive hand OA is a separate entity from non-erosive OA or a more severe form or advanced stage of

the same disease process. In the Framingham Offspring and Community cohort population, the prevalence of symptomatic hand OA ranged from 7% in men to 14% in women, and erosive hand OA ranged from 3% in men to 10% in women. The prevalence of both non-erosive and erosive disease increased with age but, in persons between 40 and 84 years, the prevalence of erosive hand OA remained three times more frequent in women as compared with men [2].

Erosions typically occur in the DIP and proximal IP (PIP) joints. Erosive disease is associated with more severe symptoms and lower grip strength, presenting as higher disease burden with more structural damage as well as inflammation [24,25]. In a longitudinal analysis of patients in the Oslo hand OA cohort, incident erosion was found to be the individual radiographic feature that was most strongly associated with development of incident joint pain [26]. In the same cohort, patients with erosive disease were found to have slightly more symptoms, and remarkably lower grip strength [27].

Clinically apparent inflammation is more common in patients with erosive disease compared with non-erosive disease, and is associated with increased pain and predicts disease progression [28–30]. Slow disease progression of hand OA requires lengthy period of follow-up if the aim is to detect a possible disease-modifying effect. In the Framingham study, the period of follow-up was very long at 9 years. In this population, progression of radiographic findings was found in almost every participant ($>$ 90%) with hand OA at baseline, and the amount of progression was substantial. In the Oslo hand OA cohort, patients with erosive hand OA were found to have not only more structural damage at baseline, but they also demonstrated twice as much progression during the 5-year follow-up than the patients with non-erosive disease [27].

Currently, there is a lack of a uniform definition of erosive hand OA. Recently, Gazeley et al. [31] performed a systematic analysis of 62 papers looking at different definitions of erosive hand OA. In all but one study radiographic appearance was used as the criterion. The definition of radiographic erosive hand OA differed across studies and different scoring systems were used. Radiographic definitions included a threshold for the number of involved joints in 37 of the 62 studies identified. Of those 37 articles, 19 required ≥1 involved joint, 12 required ≥2 involved joints, and 6 required ≥3 involved joints.

The working group considers that erosive hand OA may be defined as having at least one IP joint with erosions [32], which should be identified using a validated radiographic scoring system, for example, the Verbruggen–Veys anatomical phase scoring system and the OARSI atlas [33,34]. However, it is noted that not all researchers define joint erosions in the same way, and thus better standardization of the erosive OA phenotype is required to aid study in clinical trials.

Symptomatic vs. structure modifying drugs

Effective pharmacological treatment of hand OA may be directed toward altering symptoms and/or modifying structure or pathology. Thus, the design and objectives of clinical trials will be dependent on the mechanism of action of the drug under investigation, either: symptom modifying or structure modifying.

Symptom modifying drugs will be directed at control of symptoms, primarily relief of pain and improvement in function. They may have a rapid onset or afford slower onset of symptom control; the latter being referred to as symptomatic slow acting drugs for OA (SYSADOA). Symptom modifying drugs should not have clinically significant adverse effects on joint structure.

Structure modifying drugs may have effects on joint structure independent of any direct effect on symptoms. This includes therapeutic interventions that have the potential to stop or retard progression, or reverse existing hand OA structural abnormalities. Symptomatic improvement may occur in parallel or secondary to structural effects.

Patient selection

Diagnosis of hand OA

For inclusion in clinical trials, subjects should fulfill validated criteria for the diagnosis of hand OA. The ESCEO working group considered the criteria for diagnosis of hand OA published by the ACR as the current best available criteria appropriate for evaluation of entry into clinical trials (Table 2) [35]. However, it was recognized by the working group that the ACR criteria have some limitations as follows:

- ACR criteria do not include all the fingers.
- ACR criteria require signs of hard tissue enlargement and thus focus on medium to late disease and miss early disease (where drug therapies may be more efficacious).
- ACR criteria do not differentiate between thumb base (CMC-1) and IP joint disease.
- ACR criteria do not differentiate between non-erosive or erosive IP disease.

Notably, the ACR criteria from 1990 do not differ between thumb base and IP OA, which are lumped together. In view of the inherent diagnostic limitations, it is proposed that additional criteria for thumb base OA should be developed to allow clinical trials that specifically address this phenotype. Currently, new hand OA criteria are being developed that address thumb base OA and IP OA separately, and will become available in the near future. This project is supported by the EULAR and will provide an update to their existing diagnostic criteria [16].

Besides an ACR diagnosis, a minimal level of involvement of the joints may be considered as a study entry criteria; however, it is not appropriate to specify a cut-off level in this guidance as some investigational agents will be relevant to early-stage disease while others may be more effective in severe OA. Both hands should be investigated as part of the study and other OA joint locations (i.e., hip and knee) should be excluded from the primary analysis. Patients with OA identified as secondary to other disease, such as

Table 2
American College of Rheumatology (ACR) classification criteria for osteoarthritis of the hand

ACR criteria for hand osteoarthritis
Hand pain, aching, or stiffness
AND
3 or 4 of the following features
• Hard tissue enlargement of 2 or more of 10 selected joints
• Hard tissue enlargement of 2 or more DIP joints
• Fewer than 3 swollen MCP joints
• Deformity of at least 1 of 10 selected hand joints

The 10 selected joints are the second and third DIP, the second and third PIP, and the first CMC joints of both hands. CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal. Adapted with permission from Altman (1990).

systemic inflammatory joint diseases, or hemochromatosis, should be excluded from these trials.

The working group recognized that to focus on a phenotypic subpopulation of hand OA within the study population may introduce limitation in the registration indication afforded, and generate some uncertainties with respect to extrapolation of the data to the full hand OA population. Thus, it was proposed that a single large pharmacological randomised controlled trial may be conducted to include all patients with thumb base and IP OA (and erosive/non-erosive OA). However, depending on the objective of the trial, it may be possible to enrich the study population, for example, with an erosive OA subpopulation, although to do so a clear definition of erosive OA would be required and validated study tools should be used.

Clinical disease state

Symptom modifying trial

For inclusion in a trial of a symptom modifying agent, a minimum level of pain at baseline should be required, for example, of at least 40 mm on a 0–100 mm visual analog scale (VAS) after withdrawal of analgesics/non-steroidal anti-inflammatory drugs (NSAIDs). No minimum level of disability score is specified, for example, as measured on the Australian/Canadian hand OA Index (AUSCAN) function subscale, the Cochin Hand Functional Scale (CHFS), or the Functional Index for Hand Osteoarthritis (FIHOA) scale.

Radiographic disease state

Structure modifying trial

Radiographic information can help to define the disease state and the selection of the study population. Classically, the diagnosis of OA in epidemiologic studies has relied on Kellgren–Lawrence (KL) grading [36]. For inclusion in a trial of a structure modifying agent, it is recommended that patients fulfill the ACR criteria and that the affected joints are assessed as KL grade 2 or 3 at baseline, that is, sufficient remaining interbone distance to permit detection of worsening/progression or a certain pre-defined amount of joint space width (in mm) [9].

Determination of radiographic disease state is achieved by classical methodology, that is, X-ray of a single posterior-anterior radiograph of both hands, parallel on the same cassette. The plain radiograph remains the most widely available and the standardised method for evaluation of hand OA [8]. The radiograph should be taken during the 4 weeks preceding study entry.

For further detailed practical guidance on the application of hand imaging assessments in disease modifying clinical trials the reader is referred to recent OARSI recommendations [37].

Pre-trial drug wash-out

The duration of the pre-trial drug wash-out period should be determined by the time required for the clinical effect to disappear, that is, five times the half-life of the medication for analgesics. The working group recommended the following medication restrictions before entry into the planned clinical studies:

- An analgesic wash-out period of five times the drug half life.
- No SYSADOA in the prior 6 months.
- No intra-articular corticosteroids in the hands in the prior 6 months.
- No intra-articular hyaluronic acid in the prior 6 months.
- No oral or intramuscular prednisolone in the prior 6 months.

The working group considered that inhaled steroids need not be excluded prior to study entry; however, as with all other treatments, the use of concurrent medications should be recorded at baseline and throughout the study.

A wash-out period may not be required in trials of structure modifying drugs; however, if the effect on symptoms is to be tested, the use of a wash-out period should be considered [38].

Study conduct

Symptom modifying trial

Study design

To best investigate a symptom modifying drug, the working group recommended a placebo-controlled trial; while comparison with an active comparator as the relative control is desirable, no medication is currently registered for the management of hand OA. The only active comparator that could be considered currently is for pain, for example, an analgesic (paracetamol) or NSAID at the European registered dose for pain relief [10].

The study duration was considered as dependent on the mechanism of action of the drug, but a minimum of 3 months was deemed appropriate for a fast-acting drug, and not less than 6 months for a slow-acting drug. The timepoint of assessment of the primary endpoint also depends upon the mechanism of action of the drug under investigation, as does the frequency of assessments, which would occur at intervals from 1 to 6 months.

It was agreed that all concomitant treatment for OA should be removed for the duration of the trial and that physical and occupational therapy should be forbidden for the study duration. Rescue analgesic medication may be allowed during the study, for example, paracetamol at a dose of up to 3 g/day.

The working group recommended the collection of long-term safety data for up to 12 months following study commencement. The absence of deleterious effects on joint structure should also be assessed over at least 12 months. Regarding laboratory tests, no specific markers have been identified to be appropriate to symptom modifying trials.

Study outcomes

The working group recommended that trials of symptom modifying agents study the primary endpoint of pain measured on a VAS. The VAS and the AUSCAN pain subscale are the most widely tested in hand OA [39]; however, the AUSCAN is not freely available in the public domain. The AUSCAN includes three subscales specifically concerned with measurement of pain, stiffness, and function, which the scale developers recommend to use individually.

Physical function, as a secondary outcome, may be assessed using the CHFS, the AUSCAN function subscale, or the FIHOA, which are the better validated indices [40–42]. The AUSCAN is a composite of subscales for pain, stiffness and function, for which the group recommended use of the separate physical function subscale for the study primary endpoint and not the total score [41]. The FIHOA is another scale for function assessment which has shown good feasibility, reliability and sensitivity to change [39,42,43]. The Health Assessment Questionnaire (HAQ) may also be considered although it is not hand specific [44]. Other secondary outcomes in trials of symptom modifying agents may be multiple and could include, for example, hand strength, patient-reported outcomes (PROs), and health-related quality of life (HRQOL) [8,45].

The ability to interpret scores from PROs depends on the availability of valid, clinically meaningful benchmarks of response and state attainment, that is, minimal clinically important improvement (MCII) and patient acceptable symptomatic state (PASS). While values of MCII and PASS have been estimated for

some countries using both the FIHOA and AUSCAN scales for hand OA, the cut-off values of MCII and PASS can vary for different diseases and in diverse cultures for the same disease [46]. Thus, without a current clear definition of MCII, the working group considered that "The clinical relevance depends on the magnitude of the effect balanced with the global safety profile of the drug."

Structure modifying trial

Study design

The working group recommended that studies of structure modifying drugs should have a randomized, double blind, placebo controlled, parallel group design, and not include crossover studies. The recommended study duration is of 2–3 years to optimize identification of structural changes. With a cross-over design, a wash-out period is necessary after the initial treatment to avoid carry-over effects. This will increase the length of the study, and despite the wash-out period, the patients may still have changed after the initial treatment, which may affect the results of the subsequent treatments.

For the study duration, concomitant therapies (drugs or other interventions) that are likely to affect joint structure should be excluded, although rescue therapy should be permitted, standardized and carefully recorded and monitored. Paracetamol at a dose up to 3 g/day was recommended as rescue analgesia. Physical and occupational therapy was considered as permissible and should be standardized, balanced between treatment groups, and carefully recorded in structure modifying long-term studies.

Laboratory tests may be useful in long-term structure modifying studies. During progression of OA, many biological markers will be released in synovial fluid, blood and urine, reflecting either degradation or synthesis of cartilage, bone or synovium (e.g., enzymes, matrix fragments, and growth factors). However, further work is still needed on how changes measured correlate with OA disease progression.

Biomarkers for osteoarthritis may be useful to evaluate joint remodeling and disease progression; however, at present collection of biomarker data may be limited to research purposes. The nature of these biomarkers can either be structural molecules or fragments linked to cartilage, bone or synovium, and may be specific to one type of joint tissue or common to them all. They may represent tissue degradation or tissue synthesis and may be measured in synovial fluid, blood, or urine [47]. These biomarkers can either be related to collagen metabolism, aggrecan metabolism, or other processes, such as inflammatory biomarkers, and adipokines [47]. Some biomarkers and methods have been investigated as predictors of pain in knee OA [48]. One member of the ESCEO *E. Cavalier* has also validated some of these biomarkers for use in clinical trials (Supplementary Table A).

Study outcomes

For studies of structure modifying drugs, the working group recommended that the primary endpoint measures the effects on joint structure independent of any direct effect on symptoms. Several tools are available for measuring joint structural changes and it is the responsibility of the applicant to select and validate the tool used in any study. The primary endpoint may be assessed either as radiographic change using semi-quantitative scoring systems such as the KL grading scale, which is a global OA scale, or the OARSI atlas, which assesses individual OA features [49]. Alternatively, change in quantitative joint space width (JSW) or progression quantified as joint space narrowing (JSN) and measured by conventional X-ray can be used [50]. However, JSW assessment has not been fully validated and the optimal analysis of JSW measurement to maximize sensitivity to change is to be determined. It is not yet known whether analysis at the joint level or patient level is more sensitive to change. Most previous studies have analyzed at the patient level using sum scores [51], while there may be occasions where analyses at the joint level could be of greater importance and relevance, for example, looking at progression in joints with certain imaging features such as synovitis or bone marrow lesions.

The Verbruggen–Veys anatomical phase or the Ghent University Scoring System (GUSS) scoring systems can be useful in cases with erosive hand OA [51,52]. The plain X-ray radiograph is the most widely available and standardized method for the evaluation of hand OA. Further research on the validity of ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) techniques are needed before these imaging methods can replace X-ray as an instrument to assess structural damage in clinical trials of hand OA [53]. MRI scoring systems for hand OA and thumb base OA have been developed [54–56]; however, at this stage, MRI and ultrasound are not yet fully validated for use as primary outcomes measures although they may be considered as secondary endpoints [57,58]. For structure modifying trials, the study population could be enriched, although there is a risk of jeopardizing extrapolation of the results to the whole hand OA population. For each of the radiographic methods, the optimal timing of assessments needs to be determined according to the pathologic rate of change of each lesion in every hand joint, sensitivity to change of the imaging modality, effect size of the intervention and the measurement error of the scoring method [37].

Indirect evidence supports a relation between structural changes and long-term clinical outcome [10,59]. Secondary endpoints in studies of structure modifying drugs may in addition measure symptomatic improvement. Strengthening the earlier statement from the European Medicines Agency/Committee for Medicinal Products for Human Use (EMA/CHMP) guidance, the working group recommends that "If structural changes are chosen as primary endpoint… an improvement of symptoms and/or a correlation between structural outcome and pain and function evolution will support the surrogacy value of X-ray changes" [9].

Radiographic scoring methods

There are a small number of validated tools including the KL, OARSI, Kallman, and Verbruggen–Veys which have been compared in two studies without showing any superiority of one technique over another [49,60]. The KL scale is a global OA score (0–4 scale), for which grade 2 or higher represents definite OA [36]. The KL scale has been criticized for being too dependent on the presence of osteophytes, and modified scales have, therefore, been used in some studies [2]. However, both cross-sectional and longitudinal studies in knee OA have shown that osteophytes are a reliable predictor of early disease [61]. Both the OARSI atlas and the Kallman are scales that assess individual features of OA on semi-quantitative scales, including osteophytes (grade 0–3), JSN (grade 0–3), sclerosis (absent/present), cysts (absent/present), malalignment (absent/present) as well as erosions (absent/present) [34,62]. In order to better capture the progression of erosive hand OA, Verbruggen and Veys developed a scale of anatomical phases, including an early stationary phase with limited changes, a pre-erosive phase characterized by joint space narrowing and subchondral cysts, an erosive phase characterized by destruction of the joint plate and a remodeling phase with reconstruction of the joint plate, reappearance of the joint space and formation of large osteophytes [33]. The GUSS is another more recent scoring system that may enable detection of progression over a shorter period of time in erosive OA of the IP finger joints compared with the other anatomical phase scoring systems [52]. The subchondral plate, the

joint space and the subchondral bone architecture are each scored on 0–100 scales with lower scores indicating more pathology (in total 0–300).

Conclusions

The goal of these recommendations formulated by the ESCEO working party is to provide evidence-based guidelines on the design, execution and analysis of pharmacological clinical trials in hand OA. These recommendations provide guidance, not rigid rules, which should allow for better standardization of the conduct of clinical trials and facilitate registration and approval of new pharmacological treatments for hand OA, an area of high unmet medical need for which there is currently no approved medication in Europe. For inclusion in clinical trials, we recommend that patients fulfill the validated ACR criteria for the diagnosis of hand OA which, although with limitations, are currently the best available criteria. Trials of symptom modifying agents should assess effect on pain as the primary outcome, which could be measured either on a VAS or the AUSCAN pain subscale. Secondary outcomes are multiple, and could include physical function, hand strength, PROs, and HRQOL. The trial should be placebo-controlled and for a minimum duration of 3 months for a fast-acting drug, and not less than 6 months for a slow-acting drug. For structure modifying agents, the optimal study duration is for 2–3 years to identify structural changes. The primary endpoint of structure modifying trials should measure effect on joint structure independent of any effect on symptoms, which can be included as secondary endpoints. The ESCEO working party recognizes that the development of the methodology for performing clinical trials for hand OA is a work in progress and will evolve as more information becomes available. Nonetheless, the guidance provided in this document will support the development of both symptom modifying and structure modifying drugs targeted at alleviating the considerable clinical burden of pain and reduced physical function, and at attenuating the progression of this debilitating, degenerative disorder.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2017.12.003.

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