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EUROVISCO Guidelines for the Design and Conduct of Clinical Trials Assessing the Disease-Modifying Effect of Knee Viscosupplementation

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Abstract

Objectives. Hyaluronic acid viscosupplementation is a commonly used intra-articular treatment for osteoarthritis (OA). Some recent preclinical and clinical trials have demonstrated a potential for its disease-modifying effects. The goal of this expert opinion, consensus-driven exercise is to provide guidelines for the design and conduct of clinical trials assessing the disease-modifying effect of viscosupplementation in the knee. *Methods*. The EUROVISCO group constitutes 10 members who had expertise in clinical research methodology in the field of OA and viscosupplementation. They initially drafted issues through an iterative process and had to vote on their degree of agreement on these recommendations. The scores were pooled to generate a median agreement score for each recommendation. *Results*. The document includes 31 recommendations regarding study population, imaging, clinical and biological assessment of disease-modifying effects of viscosupplementation. Agreements were reached on some recommendations. In particular, the experts reached unanimous agreement on double-blind study design, imaging primary outcomes, time interval between 2 radiographs, x-ray procedure standardization, and the combined use of imaging and biological markers. The group did not recommend the use of ultrasonography, computed tomography (CT) scan and CT arthrography as a tool for OA diagnosis or to assess progression over time. *Conclusion*. In summary, the working group identified 31 recommendations that represent the current best practices regarding clinical trials that target the assessment of viscosupplementation disease-modifying effects in patients with knee OA. These recommendations integrate new imaging technologies and soluble biomarkers.

Keywords

hyaluronic acid, viscosupplementation, osteoarthritis, guidelines, MRI, radiographs, biomarkers, structure-modifying effect, cartilage, knee

Introduction

Osteoarthritis (OA) of the knee and hip has been ranked 11th among causes of overall disability.[1] In the United States, more than 9 million adults suffer from symptomatic OA of the knee[2] and more than 1 out of 3 adults older than 60 years have radiographic evidence of the disease.[3] In the AGES-Reykjavik Study, a prospective study of 5,764 men

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and women, aged 66 to 96 years, based on a representative sample of the population of Reykjavik followed for 5 years, the prevalence of having at least 1 joint arthroplasty due to OA was 13.6 % and the yearly incidence was 1.4%/year during the 5-year follow-up.[4] Hyaluronic acid intra-articular injections, also named viscosupplementation, is used in hundred thousands of patients each year worldwide for the symptomatic treatment of painful OA of the knee and its effectiveness is evidenced by results in numerous placebo-controlled clinical trials.[7-10] Viscosupplementation has recently been ranked as the most effective treatment for knee OA.[11-13] Despite, these recent evidence of its efficacy coming from meta-analysis, the position of intra-articular hyaluronic acid (IAHA) in recent guidelines for knee OA management remains controversial. Initially recommended by the Osteoarthritis Research Society International (OARSI),[14] the European League Against Rheumatism[15] and the American College of Rheumatology (ACR),[16] Hyaluronic acid (HA) is now not recommended by the American Academy of Orthopaedic Surgeons[17] and conditionally recommended by the ACR[18]; the OARSI recently provided an uncertain recommendation.[19] Expert opinion from these international societies was mainly based on results from meta-analyses, which included some randomized controlled trials of low methodological quality. In contrast, the most recent meta-analyses were restricted to trials of IAHA with the lowest risk of bias. Indeed, such a meta-analysis is considered to provide the highest level of evidence available for evaluating an intervention. In addition, risks of IAHA treatment failure have been identified, which increases the success rate of this intervention.[8] These latest advances explain changes in current opinion of expert and physicians.

Even though the clinical efficacy is now proved, at least in selected patients, the structure-modifying effect remains to be demonstrated. Two recent studies have suggested that repeat intra-articular injections of HA may delay the time to prosthetic replacement.[5,6] Total knee replacement (TKR) is a valuable surrogate marker of severe OA and a possible endpoint for clinical trials, but unfortunately, is neither a reliable marker of the lack of treatment efficacy nor of the anatomical progression of the disease. Indeed, TKR is highly dependent on intrinsic problems such as access barriers due to geographical and financial considerations, the availability of the resources for TKR and in the willingness of patients to be operated.[4] The mechanisms by which HA acts on joint tissues is not fully understood and probably very complex as demonstrated by numerous *in vitro* and animal studies.[20-26] All these properties make HA a good candidate for disease-modifying therapy.[27] However evidences for a clinically relevant efficacy and to slowdown articular cartilage breakdown are still lacking, despite 2 clinical studies in knee OA that have demonstrated a reduced serum level of Coll2-1, a specific marker of type II collagen catabolism suggesting that HA injection may reduce cartilage degradation.[28,29]

In 2015, the OARSI had published a set of recommendations for the design, conduct, and reporting of clinical trials for knee OA.[30] The document includes 25 recommendations that represent the current best practices regarding clinical trials that target symptom or structure modification among individuals with knee OA. However, clinical trials on viscosupplementation have some particularities that were not addressed by the OARSI. Herein, we focused on these particularities and propose recommendations for the design and the conduct of clinical trials studying the disease-modifying effect of HA viscosupplementation.

Methods

Experts

The 10 experts constituting the EUROVISCO group[31,32] come from 5 European countries (Belgium, France, Germany, Italy, Spain, and the United Kingdom). This group was composed of 7 rheumatologists, 2 orthopedic surgeons, and 1 physical therapist who had expertise in clinical research methodology in the field of OA and viscocupplementation. The working group congregated in Lyon on September 15-16, 2016.

Issues

Five members of the task force (RR, TC, YH, XC, AM) were tasked to collate an exhaustive literature analysis on the topic. Forty-three statements were selected and discussed during the meeting. For each assertion, the experts had to vote on their degree of agreement, using a 10-point Likert-type scale (1-10), with 1 = *I don't agree at all* and 10 = *I fully agree*. The scores were pooled to generate a median agreement score for each affirmation. Each item was classified as "Agree" if it received a median score of ≥8 and was classified as "Do not agree" if it received a median vote of ≤3. An assertion having received a score between 4 and 7 was classified as "Agree under condition." One member of the working group (TC) was entrusted with the task to select all statements that obtained a median score ≥8, and to rephrase those who obtained a median score of 6 or 7 according to, and to draw up recommendations from the results of the scoring session. All corrections and suggestions by each member were shared with the rest of the task force before coauthoring of final recommendations. A second scoring round of the newly drafted recommendations were achieved and only those that have obtained a median score ≥7 were selected and approved by all members of the working group. For each proposal we calculated the median score, the mean and standard deviation (SD) and range (1-10).

Table 1. Patient Selection.

Recommendation	Strength of Recommendation	Level of Consensus
1. We recommend to well define the study population according to clinical and anatomical phenotypes (Statement).	Strong	High
2. We recommend that clinical trials aimed to demonstrate the disease-modifying effect of viscosupplementation be performed preferentially in patients with knee osteoarthritis (OA). Additionally, patients with hip OA can also be considered.	Strong	High
3. We recommend a randomized controlled double-blind study design for trials to demonstrate the disease-modifying effect of viscosupplementation.	Strong	High
4. To demonstrate the disease-modifying effect of viscosupplementation we recommend that the comparator should be a saline injection with the same volume and the same number of injections as the studied viscosupplement.	Strong	Moderate
5. To ensure true double-blind study design, we recommend that the injector is not the evaluator as the difference of viscosity between saline and hyaluronic acid (HA) can be easily identified.	Strong	Unanimous
6. In trials designed to demonstrate the disease-modifying effect of viscosupplementation, we recommend that patients be treated with HA injection(s) every 6 months with an optimum follow up duration of 24 months. However, a shorter (6-12 months) or longer (36 months) follow up can be considered in particular situations.	Strong	Moderate
7. We recommend a stringent selection involving particular subgroups (i.e., post–anterior cruciate ligament [ACL] injury or postmeniscectomy OA, patients at high risk of OA progression) to obtain a more homogenous population and be able to better demonstrate a structure-modifying effect than a broad selection (i.e., general population).	Strong	High
8. If a broad selection (whose interest is to represent real life and to be generalized to all patients) is chosen, we recommend excluding patients with body mass index (BMI) >30 kg/m^2 due to a demonstrated poor response to viscosupplementation and difficulties in ensuring the intra-articular delivery of the treatment without imaging guidance.	Strong	High
9. Among knee OA patients, we recommend selecting patients only with medial tibiofemoral OA on standard x-rays associated or not with femoropatellar OA, and to exclude patients with lateral tibiofemoral OA, or with both medial and lateral tibiofemoral OA in the same study to ensure consistency and homogenous selection. Isolated patellofemoral OA should be also excluded, excepted if the aim of the study is to demonstrate the effect of intra-articular HA (IAHA) on this particular knee OA.	Strong	High
10. In knee OA, we recommend to preferentially select patients with Kellgren-Lawrence (KL) modified grade 2 and 3. We recommend excluding patients with other KL grades (0, 1, 4).	Strong	Moderate
11. We recommend to preferentially selecting patients with Grade 1 and 2 OARSI joint space narrowing. We recommend excluding patients with other OARSI grades (0, 3).	Strong	High

Strength of Recommendation

The strength of recommendation was classified according to the value of the median score for each issue. It was classified as strong if the median score was 10, 9, or 8 and as moderate if the median score was 7. If lower than 7, the statement was rejected.

Level of Consensus

The level of consensus was obtained according to the number of the panel experts who scored ≥8: It was classified as unanimous if all experts fully agreed with the recommendation. It was considered as high and moderate, respectively, if 9 or 8 and 7 or 6 experts gave a score of ≥8. There was a lack of consensus if 5 experts or less agreed with the proposal and the statement was rejected.

Results

After the 2 rounds of voting, 31 issues were selected by the working group. They were classified into 4 categories: (I) Patients selection, (II) Imaging, (III) Clinical assessment, (IV) Biology

I. Patients selection (Table 1)
   1. We recommend to well define the study population according to clinical and anatomical phenotypes (Statement).
      Median 9; Mean 9.1, SD 1.0; Range 7-10
      Strength of recommendation: Strong; Level of consensus: High
   2. We recommend that clinical trials aimed to demonstrate the disease-modifying effect of viscosupplementation be performed preferentially

in patients with knee OA. Additionally, patients with hip OA can also be considered.
Median 9; Mean 8.7, SD 1.4; Range 6-10
Strength of recommendation: Strong; Level of consensus: High

3. We recommend a randomized controlled double-blind study design for trials to demonstrate the disease-modifying effect of viscosupplementation.
Median 9; Mean 9, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
4. To demonstrate the disease-modifying effect of viscosupplementation, we recommend that the comparator should be a saline injection with the same volume and the same number of injections as the studied viscosupplement.
Median 8; Mean 7.7, SD 2.3; Range 3-10
Strength of recommendation: Strong; Level of consensus: Moderate
5. To ensure true double-blind study design, we recommend that the injector is not the evaluator as the difference of viscosity between saline and HA can be easily identified.
Median 10; Mean 9.4, SD 0.8; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
6. In trials designed to demonstrate the disease-modifying effect of viscosupplementation, we recommend that patients be treated with HA injection(s) every 6 months with an optimum follow-up duration of 24 months. However, a shorter (6-12 months) or longer (36 months) follow-up can be considered in particular situations.
Median 8.5; Mean 8, SD 1.9; Range 4-10
Strength of recommendation: Strong; Level of consensus: Moderate
7. We recommend a stringent selection involving particular subgroups (i.e., post–anterior cruciate ligament [ACL] injury or postmeniscectomy OA, patients at high risk of OA progression) to obtain a more homogenous population and be able to better demonstrate a structure-modifying effect than a broad selection (i.e., general population).
Median 9; Mean 8.6, SD 1.8; Range 4-10
Strength of recommendation: Strong; Level of consensus: High
8. If a broad selection (whose interest is to represent real life and to be generalized to all patients) is chosen, we recommend excluding patients with body mass index (BMI) >30 kg/m^2 due to a demonstrated poor response to viscosupplementation[33] and difficulties in ensuring the intra-articular delivery of the treatment without imaging guidance.
Median 9; Mean 8.2, SD 1.7; Range 5-10
Strength of recommendation: Strong; Level of consensus: High
9. Among knee OA patients, we recommend selecting patients only with medial tibiofemoral OA on standard x-rays associated or not with femoropatellar OA, and to exclude patients with lateral tibiofemoral OA, or with both medial and lateral tibiofemoral OA in the same study to ensure consistency and homogenous selection. Isolated patellofemoral OA should be also excluded, excepted if the aim of the study is to demonstrate the effect of IAHA on this particular knee OA.
Median 8; Mean 8.4, SD 1.6; Range 6-10
Strength of recommendation: Strong; Level of consensus: High
10. In knee OA, we recommend to preferentially select patients with Kellgren-Lawrence (KL) modified grade 2 and 3.[32] We recommend excluding patients with other KL grades (0, 1, 4).
Median 8; Mean 7.7, SD 1.9; Range 5-10
Strength of recommendation: Strong; Level of consensus: Moderate
11. We recommend to preferentially selecting patients with grade 1 and 2 OARSI joint space narrowing.[33] We recommend excluding patients with other OARSI grades (0, 3).
Median 9; Mean 8.5, SD 1.3; Range 6-10
Strength of recommendation: Strong; Level of consensus: High

II. Imaging assessment (Table 2)

12. We recommend that either cartilage changes on magnetic resonance imaging (MRI) or joint space narrowing progression on standard x-rays be the primary outcome variable in evaluating the structure-modifying effect. The KL score continues to be the useful method for eligibility screening for clinical trial on viscosupplementation. We recommend assessing the joint space width (JSW; typically in millimeters) by measuring the distance between the medial femoral condyle and medial tibial plateau on plain radiograph according to international guidelines for x-ray measures.
Median 9; Mean 8.9, SD 0.6; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
13. We recommend MRI acquisition with 2-dimensional (2D) fast spin-echo sequences with intermediate-weighted and/or T2-weighted contrast with fat

Table 2. Imaging Assessment.

Recommendation	Strength of Recommendation	Level of Consensus
12. We recommend that either cartilage changes on MRI or joint space narrowing progression on standard x-rays be the primary outcome variable in evaluating the structure-modifying effect. The Kellgren and Lawrence score continues to be the useful method for eligibility screening for clinical trial on viscosupplementation. We recommend assessing the joint space width (JSW; typically in millimeters) by measuring the distance between the medial femoral condyle and medial tibial plateau on plain radiograph according to international guidelines for x-ray measures	Strong	Unanimous
13. We recommend MRI acquisition with 2-dimensional (2D) fast spin-echo sequences with intermediate-weighted and/or T2-weighted contrast with fat suppression or short tau inversion recovery (STIR). T2-weighted or proton density fast spin echo sequences are best suited for MR cartilage examination.	Strong	High
14. We recommend that MRI evaluation be performed annually. However, a 6-month time interval between evaluations can be considered to evaluate an early action of product.	Strong	Moderate
15. We recommend a time interval of 1 year between 2 consecutive X rays.	Strong	Unanimous
16. We recommend that the MRI/x-rays evaluator(s) be blind to both the time interval and the treatment allocation.	Strong	High
17. In knee OA, we recommend that x-rays be standardized to standing posteroanterior view, Lyon-schuss or semiflexed view, lateral view, and skyline view of the patella.	Strong	Unanimous
18. We recommend that all x-rays be performed using a standardized procedure (patient positioning, X ray beam distance, radiological incidences) and evaluated centrally by a single observer.	Strong	Unanimous
19. We recommend that the joint space width measurement on standard x-rays be performed using an accurate and validated automated measurement software and that the primary measure be performed on the radiograph that is most sensitive to demonstrate change (Lyon-schuss or semiflexed view).	Strong	High
20. We do not recommend ultrasonography, CT scan and CT arthrography as a tool for OA diagnosis and to assess progression over time.	Strong	Unanimous
21. We recommend that joint space narrowing progression on standard x-rays be a secondary criterion if MRI has been chosen as the primary outcome measure	Strong	Moderate
22. In multicenter studies, we recommend that all trial sites must comply with a specified standardized MRI protocol, including the MR technique, spatial resolution, and signal-to-noise ratio.	Strong	High
23. To warrant reproducible assessment of cartilage changes over time, we recommend using preferentially semiquantitative scoring systems that have been shown to be successful in evaluating disease progression in knee OA, rather than quantitative scoring systems that need further evaluation.	Strong	High
24. Articular cartilage biochemical composition can be reliably assessed with dGEMRIC or T1rho relaxation time measurements, but further studies have to be performed before these techniques can be recommended as primary outcome tool for reliably assessing the structure-modifying effect of viscosupplementation.	Strong	High
25. If available, we recommend using 3.0-T imaging systems that provide the best image quality for accurate articular cartilage examination. If not, MRI scanners with a 1.5-T field strength can be used.	Strong	High
26. Excluding knee (i.e., hip, shoulder, ankle, and trapeziometacarpal joint), viscosupplementation should always be achieved under fluoroscopy or ultrasound guidance.	Strong	Unanimous

suppression or short tau inversion recovery (STIR). T2-weighted or proton density fast spin echo sequences are best suited for MR cartilage examination.[34]

Median 8.5; Mean 8.5, SD 1.1; Range 7-10

Strength of recommendation: Strong; Level of consensus: High

14. We recommend that MRI evaluation be performed annually. However, a 6-month time interval between evaluations can be considered to evaluate an early action of product.

Median 9; Mean 8.3, SD 1.6; Range 5-10
Strength of recommendation: Strong; Level of consensus: Moderate

15. We recommend a time interval of 1 year between 2 consecutive x-rays.
Median 9; Mean 9, SD 0.5; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
16. We recommend that the MRI/x-rays evaluator(s) be blind to both the time interval and the treatment allocation.
Median 10; Mean 9, SD 1.7; Range 5-10
Strength of recommendation: Strong; Level of consensus: High
17. In knee OA, we recommend that x-rays be standardized to standing posteroanterior view, Lyon-schuss or semiflexed view,[35] lateral view, and skyline view of the patella.
Median 9; Mean 9.3, SD 0.7; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
18. We recommend that all x-rays be performed using a standardized procedure[36,37] (patient positioning, x-ray beam distance, radiological incidences) and evaluated centrally by a single observer.
Median 10; Mean 9.5, SD 0.7; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
19. We recommend that the joint space width measurement on standard x-rays be performed using an accurate and validated automated measurement software and that the primary measure be performed on the radiograph that is most sensitive to demonstrate change (Lyon-schuss or semiflexed view).[38]
Median 9; Mean 9, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
20. We do not recommend ultrasonography, computed tomography (CT) scan and CT arthrography as a tool for OA diagnosis and to assess progression over time.
Median 10; Mean 9.5, SD 0.7; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous
21. We recommend that joint space narrowing progression on standard x-rays be a secondary criterion if MRI has been chosen as the primary outcome measure.
Median 9; Mean 8.2, SD 2.0; Range 4-10
Strength of recommendation: Strong; Level of consensus: Moderate.
22. In multicenter studies, we recommend that all trial sites must comply with a specified standardized MRI protocol, including the MR technique, spatial resolution, and signal-to-noise ratio.
Median 9; Mean 9.0, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
23. To warrant reproducible assessment of cartilage changes over time, we recommend using preferentially semiquantitative scoring systems that have been shown to be successful in evaluating disease progression in knee OA,[38] rather than quantitative scoring systems that need further evaluation.
Median 8; Mean 8.2, SD 0.8; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
24. Articular cartilage biochemical composition can be reliably assessed with dGEMRIC (delayed gadolinium enhanced magnetic resonance imaging of cartilage) or T1rho relaxation time measurements,[39] but further studies have to be performed before these techniques can be recommended as primary outcome tool for reliably assessing the structure-modifying effect of viscosupplementation.
Median 9; Mean 8.9, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
25. If available, we recommend using 3.0-T imaging systems that provide the best image quality for accurate articular cartilage examination. If not, MRI scanners with a 1.5-T field strength can be used.[40]
Median 8.5; Mean 8.5, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High
26. Excluding knee (i.e., hip, shoulder, ankle, and trapeziometacarpal joint), viscosupplementation should always be achieved under fluoroscopy or ultrasound guidance.
Median 10; Mean 9.5, SD 0.7; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous

III. Clinical assessment (Table 3)

27. We recommend that a clinical assessment be performed every 3 to 6 months throughout the follow-up duration.
Median 9; 8.6, SD 1.2; Range 6-10
Strength of recommendation: Strong; Level of consensus: High
28. We recommend using a combination of validated outcome measures (including pain on a 10-point rating scale and/or WOMAC [Western Ontario and McMaster Universities Osteoarthritis Index] score[41] and/or KOOS [Knee injury and Osteoarthritic Outcome Score] score,[42] and/or patient global

Table 3. Clinical Assessment.

Recommendation	Strength of Recommendation	Level of Consensus
27. We recommend that a clinical assessment be performed every 3 to 6 months throughout the follow-up duration.	Strong	High
28. We recommend using a combination of validated outcome measures (including pain on 10-point rating scale, and/or WOMAC score, and/or KOOS score, and/or patient global assessment on 10 points rating scale, and/or OMERACT-OARSI response criterion, and/or PASS, and/or MCII) for clinical evaluations.	Strong	High

Table 4. Biological Assessment.

Recommendation	Strength of Recommendation	Level of Consensus
29. To demonstrate the disease-modifying effect of viscosupplementation we recommend a combination of imaging and biological outcome measures. A decrease of soluble biomarkers of cartilage degradation over time does not prove the chondroprotective effect of the treatment if this effect is not complemented by the imaging examinations.	Strong	Unanimous
30. We recommend measuring serum and/or urine concentration of type 2 collagen degradation biomarkers (i.e., Coll2-1; Coll2-1 NO_2; CTX II) that are the most tissue specific and the most evidenced biomarkers for assessing cartilage metabolism. Other cartilage/synovium biomarkers (i.e., HA, PIIANP, COMP) may be used in addition to collagen biomarkers.	Strong	Moderate
31. We recommend repeat measurements of serum/urine biomarkers with an optimal time interval of 3 months between each measurement. However, in long-duration trials (24-36 months) a 6-month time interval between assays may be considered.	Strong	High

assessment on a 10-point rating scale, and/or OMERACT-OARSI response criterion,[43] and/or PASS [patient acceptable symptom state],[44] and/or MCII [minimal clinically important improvement][44]) for clinical evaluations.
Median 9; Mean 9, SD 0.9; Range 6-10
Strength of recommendation: Strong; Level of consensus: High

IV. Biological assessment (Table 4)

29. To demonstrate the disease-modifying effect of viscosupplementation, we recommend a combination of imaging and biological outcome measures. A decrease of soluble biomarkers of cartilage degradation over time does not prove the chondroprotective effect of the treatment if this effect is not complemented by the imaging examinations.
Median 8.5; Mean 8.7, SD 0.8; Range 8-10
Strength of recommendation: Strong; Level of consensus: Unanimous

30. We recommend measuring serum and/or urine concentration of type 2 collagen degradation biomarkers (i.e., Coll2-1; Coll2-1 NO_2; CTX II) that are the most tissue specific and the most evidenced biomarkers for assessing cartilage metabolism.[45] Other cartilage/synovium biomarkers (i.e., HA, PIIANP [type IIA collagen N-propeptide], COMP [cartilage oligomeric matrix protein]) may be used in addition to collagen biomarkers.
Median 9; Mean 8.7, SD 1.1; Range 4-10
Strength of recommendation: Strong; Level of consensus: Moderate

31. We recommend repeat measurements of serum/urine biomarkers with an optimal time interval of 3 months between each measurement. However, in long-duration trials (24-36 months), a 6-month time interval between assays may be considered.
Median 9; Mean 8.7, SD 1.1; Range 7-10
Strength of recommendation: Strong; Level of consensus: High

Discussion

The purpose of this article was to develop a set of recommendations to conduct clinical trials aiming to demonstrate the disease modifying effect of viscosupplementation. Recently, OARSI has proposed recommendations for conducting clinical trials in osteoarthritis.[46] These recommendations deal with topics applicable to multiple types of OA

clinical trials and to specific type of OA trials, including nonpharmacological trials, diet and exercise trials, rehabilitation trials, injury prevention trials, surgical trials, and implementation trials. Viscosupplementation trials have specific challenges that were not addressed by the OARSI. In this article, we focused on the particularities of clinical study design assessing the disease-modifying effect of HA viscosupplementation. The current definition of a disease-modifying OA drug is that a treatment that inhibits structural disease progression and ideally also improves symptoms and/or function. Structural disease progression was defined as either the reduction of cartilage loss and/or other findings of OA on the MRI or as the reduction of the radiological joint space on standard x-rays.[47] Based on joint space narrowing (JSN) measured on standard x-rays, a clinically significant relevance is 50% decrease in the reduction of JSW compared with placebo whereas radiological OA progression is defined as a JSN >0.5 mm during the study period.

The first part of the work emphasizes the importance of the patient selection and study design. One major concern in viscosupplementation clinical trials is the blinding procedure to prevent disclosure of treatment to patients and study staff. The injector can usually identify the treatment because of unique properties such as viscosity especially if the comparative group is, for example, a saline or corticosteroid solution. For this reason, EUROVISCO group unanimously recommends that the injector is not the evaluator. This is an important precaution as the difference of viscosity between saline and HA is easily identified. As comparator treatments, saline solution must not be considered as sham treatment because synovial fluid is commonly punctured before saline injection. The group also recommends a stringent selection of patients to obtain a more homogenous population to increase the chances to demonstrate a disease-modifying effect. More precisely, the EUROVISCO group recommends excluding obese patients, patients with a severe OA, and recommends selecting patients with only medial tibiofemoral knee OA. Of course, this approach will not allow the extrapolation of the data to the general population. Furthermore, because of a poor correlation between clinical and imaging outcomes, this stringent patient selection based only on structural feature may decrease the chance to observe a symptomatic response.

A large number of EUROVISCO recommendations are dedicated to evaluation of structure modifying effect of OA by imaging techniques. Unanimously, the experts recommend performing either MRI or standard x-rays for JSN annually to evaluate cartilage changes. Image acquisition procedure have been clearly described by OARSI and we recommend reading the article by Hunter *et al*.,[47] which is precise and only focused on knee imaging in clinical trials. It is evident that EUROVISCO recommendations are in line with OARSI clinical trials recommendations.[46] There were no specific recommendations relating to viscosupplementation clinical trials in the OARSI recommendations.

Concerning MRI protocols, the EUROVISCO experts have also stated that 3D acquisition allows best spatial resolution and should be preferred if quantitative volumetric analysis of articular cartilage is to be performed. However, this technique is time consuming. One particularity of EUROVISCO guideline is that the experts do not recommend ultrasonography, CT scan and CT arthrography as a tool for OA diagnosis and to assess progression over time. This is partially in contradiction with the OARSI guidelines that stated that CT arthrography can also be used to provide knee joint assessment in OA research study. The EUROVISCO does not recommend this technique because CT arthrography is an invasive technique requiring radiation exposure and intra-articular contrast administration, which has a limited use in longitudinal OA research study. To evaluate cartilage matrix changes, the EUROVISCO group recommends using MRI protocols T2 mapping, T1rho mapping, or dGEMRIC even though this last technique requires contrast agent administration with a small risk of nephrogenic systemic sclerosis.[48]

To demonstrate the disease-modifying effect of viscosupplementation, we recommend a combination of imaging and biological outcome measures. A decrease of soluble biomarkers of cartilage degradation over time does not prove the chondroprotective effect of the treatment if this effect is not complemented by the imaging findings. This is in accordance with the recommendations OARSI/FDA working group,[30] which provides a guide to the application of biochemical and other soluble biomarkers in the development of drugs for OA. This document describes the process of biomarker qualification applied to a particular biomarker to support its use as a surrogate endpoint in drug discovery, development or postapproval and where appropriate in regulatory decision making. Through the process of qualification, a biochemical biomarker must have a demonstrated link to modifications in clinical or structural outcomes.[49] In the context of structure-modifying effects, a biochemical marker can be linked structural outcomes identified with MRI or x-rays. This justifies the EUROVISCO recommendation of a combination of biochemical and imaging outcomes in OA clinical trials with viscosupplement.

We also recommend testing a panel of biomarkers with repeated measurements every 3 months, excepted in long-duration trials (24-36 months) for which a 6-month time interval between assays may be considered. This approach allows the use of time integrated curve to compare the effect of viscosupplementation effects with comparators or saline solution.

In conclusion, the EUROVISCO working group have developed a set of consensual recommendations for the design and management of clinical trials conducted to demonstrate the disease modifying effect of viscosupplementation in knee

OA. A robust study on disease-modifying effect of HA viscosupplementation requires a good definition of the study population, a randomized controlled versus saline solution double blind study design, a multicentric approach, an assessment of cartilage changes by MRI or JSN on standard x-rays combined with soluble biomarkers measurement, and fluoroscopy or ultrasound for injection guidance. The sample size has to be calculated following recommendations and guidance on statistical principles for clinical trials,[50] considering a minimal variable difference between time points at least equal to the variability of the primary endpoint. This group also provides guidance for the assessment of symptomatic, structural and biological patient responses to viscosupplementation, which complement the other clinical trial recommendations. The intention of the experts was to help academic investigators and industry researchers to design and conduct high quality clinical study.

Authors' Note

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with regard to intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Ethical Approval

Ethical approval is not required for this study.

Informed Consent

Not applicable.

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