CARTILAGE
2020, Vol. 11(1) 47–59

DOI: 10.1177/1947603518783455
journals.sagepub.com/home/CAR
SAGE

EUROVISCO Recommendations for Optimizing the Clinical Results of Viscosupplementation in Osteoarthritis

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Abstract

Objectives. The 3 aims of the work were to identify population subgroups that can benefit the most from viscosupplementation (VS), to provide recommendations on injection techniques, and to discuss VS appropriateness in clinical situations that are commonplace in daily practice. *Methods*. The task force members voted on their degree of agreement on 27 statements, 36 recommendations, and 22 clinical scenarios using a 9-point scale. The strength of agreement/appropriateness/recommendation (SOA/SOR) was classified as strong if the median agreement score was ≥8. The level of consensus (LOC) was also obtained. *Results*. Among the assumed predictors for VS failure, obesity, radiographic severity, large synovial fluid effusion, severe patellofemoral involvement, major malalignment, and gross joint instability received a large majority of agreements. The lateral mid-patellar approach was recommended for knee injection. Imaging guidance was unanimously recommended for hip and ankle. Agreement was achieved to strictly respect the dosing regimen proven by controlled trials. There was agreement for treating with VS patients with mild to moderate knee and hip OA, with normal weight or moderate overweight, insufficiently improved by first-line therapies, or who do not wish get oral treatment or who have contraindications to pain killers. The group considered the patient's wishes as a key element in therapeutic decision making. *Conclusion*. Based on literature data and clinical experience, the EUROVISCO group proposed a set of recommendations for optimizing the results of VS, aimed to help practitioners, especially in some cases in which the patients' specificities make the therapeutic decision difficult.

Keywords

hyaluronic acid, viscosupplementation, osteoarthritis, knee, hip, ankle, trapeziometacarpal, recommendations, appropriateness, intraarticular injection

Osteoarthritis (OA) is the most common joint disorder affecting millions of people, significantly affecting the quality of life of the affected patients and responsible for an alarming increase in health expenditure.[1-4] Treatment of OA is based on a combination of nonpharmacological and pharmacological modalities reviewed in detail in a plethora of published articles.[5-8] Viscosupplementation by intraarticular (IA) injections of hyaluronic acid (HA) or its derivatives

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is recommended in the management of symptomatic knee OA, for appropriate patients, by many scholarly societies of rheumatology and orthopedics,[5,8,9] sport medicine,[10] and geriatrics,[11] and is generally considered as an efficient and reliable therapy as evidenced by recent systematic reviews and meta-analyses.[12-18] Beyond its clinical efficacy in appropriate patients, it has also been suggested that repeat IA injections of HA may sometimes delay the time to arthroplasty.[19,20] A task force of clinical experts has recently developed and published an Appropriate Use Criteria (AUC) of viscosupplementation in knee OA, aimed to aid practitioners in the decision making of viscosupplementation and to help insurance agencies to determine cases where reimbursement could be considered.[21] However, the authors highlighted the fact that despite the level of evidence in particular situations, each practitioner has to individualize his/her clinical care, by taking into account patient's specificities and wishes. For example, among patients with knee, hip, or other joint OA, many of those who are candidates for joint replacement prefer not to have surgery and prefer treatments that avoid surgery for as long as possible. Consequently, although viscosupplementation is indicated mainly in subjects with mild to moderate OA, it could also be proposed to patients with more advanced disease who cannot (i.e., comorbidities, contraindications, difficulties of gaining access to care, financial reasons, etc.) or who do not want (i.e., fear of surgery, personal or professional reasons, etc.) to undergo joint replacement. Because of its very good safety profile, viscosupplementation can be used in elderly and frail patients[11] because of a favorable benefit/risk ratio, even if the efficacy to be expected is only small or marginal. However, this particular situation, commonly encountered in daily clinical practice, is never mentioned in the different published sets of recommendations.

The goal of the present work was (1) to identify the population subgroups that can benefit the most from viscosupplementation, (2) to provide recommendations on techniques of injection that will optimize the chance of success of HA injections, and (3) to discuss the appropriateness of using HA in several clinical situations that are commonplace in daily practice but have not been yet the subject of specific recommendations.

Methods

Working Group

The 11 members of the EUROpean VIScosupplementation Consensus group (EUROVISCO)[22,23] come from 7 European countries (Belgium, France, Germany, Italy, Spain, Turkey, and the United Kingdom). They constitute a multidisciplinary panel of health care providers in the field of musculoskeletal disorders. Seven were rheumatologists, 2 orthopedic surgeons, 1 rehabilitation physician, and 1 physical therapist. All had expertise in clinical research methodology in the field of OA and viscosupplementation. The working group, which was constituted in 2014, gathered in Lyon from September 7 to 8, 2017, as it previously did in 2014, 2015, and 2016. One member acted as a chairman: He guided the discussion and acted as a moderator in case of opinion discrepancies among the working group members. The chairman and 2 co-chairs drafted the document before all other members participated to the elaboration of the final manuscript.

Issues

Four members of the task force (JM, YH, XC, AM) were tasked to collate an exhaustive literature analysis on 4 issues, leading to 4 presentations to the expert panel: (1) imaging factors predicting failure or response to viscosupplementation in osteoarthritis of the knee and other joints; (2) Clinical factors predicting failure or response to viscosupplementation in osteoarthritis of the knee and other joints; (3) imaging guidance and injection techniques for optimizing the results of viscosupplementation in osteoarthritis of the knee and other joints; and (4) do soluble biomarkers allow to predict the response to viscosupplementation in osteoarthritis of the knee and other joints? Each presenter conducted an extensive literature review, from the analysis of several database (Medline, Cochrane Database of Systematic Reviews, Google Scholar) and selected the more relevant publications in the field of research that they were responsible for. One month before the meeting, the presenters had to send the results of their research as well as 10 to 20 suggestions of questions to the chair who prepared the questions. During the meeting, after presentations to the expert panel and discussions, the members of the taskforce had to vote on their degree of agreement on 31 issues prepared by the chair, using an 9-point Likert-type scale (1-9), scores 1 to 3 meaning "I don't agree," scores 4 to 6 "I agree under conditions only," and scores 7 to 9 meaning "I agree." Furthermore, 38 recommendations were also put to the vote of the participants, using the same format, scores 1 to 3 meaning "I do not recommend," scores 4 to 6 "I recommend under conditions only," and scores 7 to 9 "I recommend." Finally, the task force had to vote on the appropriateness of using viscosupplementation in 24 scenarios corresponding to 24 clinical situations frequently encountered in clinical practice. As previously described, scores 1 to 3 meant "not appropriate," scores 4 to 6 meant "uncertain," and scores 7 to 9 meant "appropriate." The scores were pooled to generate a median agreement score for each issue/recommendation/appropriateness. The strength of recommendation (SOR) and agreement/appropriateness (SOA) was classified according to the value of the median score for each issue. It was classified as strong if the median score was ≥8 and as moderate if the median score was ≥7 and <8. The level of consensus (LOC) was obtained

according to the number of the panel experts who gave a score of ≥7: It was classified as unanimous if 11 experts out of 11 agreed with the issue. It was ranked as high when 10 or 9 agreed, and moderate when 8 or 7 agreed. LOC was ranked as low if only 6 members were in agreement with the issue. There was lack of consensus if only 5 experts or less agreed with the proposal. After each vote, discussion and occasional heated debates led to some changes in the wording of the question and consequently to a second round of voting.

The working sessions were divided in 5 rubrics: (1) Prerequisite; (2) Clinical, imaging, and technical factors that may influence the viscosupplementation effectiveness; (3) Recommendations for optimizing the rate of success and the safety of viscosupplementation; (4) Appropriateness of the viscosupplementation use in several clinical scenarios; and (5) Interest and limits of using biomarkers to manage clinical trials on viscosupplementation.

Manuscript

Three members drafted the manuscript after taking into account all suggestions and comments of the working group. The final version of the manuscript was amended accordingly and approved by all the experts in the task force. The present recommendations and AUC are intended to help practitioners in the decision making with viscosupplementation in patients with knee and other joint OA.

Results

1. Prerequisites
   - 1.1. A good indication, based on both an accurate analysis of signs, symptoms, and clinical history and a careful clinical examination may improve the chances of success of viscosupplementation.
     Agree, SOR Strong
     Median 9, range 7-9, LOC Unanimous
   - 1.2. A good indication based on a precise analysis of the radiological features may improve the chances of success of viscosupplementation.
     Agree, SOR Strong
     Median 9, range 7-9, LOC Unanimous
   - 1.3. A good technique of injection and/or the use of an imaging guidance may enhance the chances of success of viscosupplementation.
     Agree, SOR Strong
     Median 9, range 7-9, LOC Unanimous
2. Demographic, clinical, imaging, and technical factors that may influence the effectiveness of viscosupplementation
   - 2.1. Increased age may influence the response of viscosupplementation in the knee.
     Uncertain
     Median 3.5, range 1-7, LOC No consensus
   - 2.2. Female sex may influence the response of viscosupplementation in the knee.
     Disagree
     Median 3, range 1-6, LOC No consensus
   - 2.3. Overweight (30 < BMI > 25) may influence the response of viscosupplementation in the knee.
     Uncertain
     Median 5, range 1-8, LOC No consensus
   - 2.4. Obesity (BMI >30) may influence the response of viscosupplementation in the knee.
     Agree, SOA Strong
     Median 8, range 1-9, LOC High
   - 2.5. Radiological severity (Kellgren-Lawrence score IV vs. I-III) may influence the response of viscosupplementation in the knee.
     Agree, SOA Moderate
     Median 7.5, range 7-9, LOC Unanimous
   - 2.6. Joint space narrowing severity (OARSI score 3 vs. 0-2) may influence the response of viscosupplementation in the knee.
     Agree, SOA Strong
     Median 8, range 6-9, LOC High
   - 2.7. Large synovial fluid effusion may influence the response of viscosupplementation in the knee.
     Agree, SOA Moderate
     Median 7.5, range 4-9, LOC High
   - 2.8. Little synovial fluid effusion may influence the response of viscosupplementation in the knee.
     Disagree
     Median 3, range 1-5, LOC High
   - 2.9. Major mal-alignment (i.e., >15°) may influence the response of viscosupplementation in the knee.
     Agree, SOA Moderate
     Median 7, range 4-8, LOC No consensus
   - 2.10. Patellofemoral involvement may influence the response of viscosupplementation in patients with tibiofemoral OA.
     Agree, SOA Moderate
     Median 7, range 5-8, LOC Moderate
   - 2.11. Failure of a previous viscosupplementation (same physician, same joint) may influence the response of viscosupplementation in the knee.
     Agree, SOA Moderate
     Median 7, range 5-8, LOC Moderate
   - 2.12. Gross joint instability may influence the response of viscosupplementation in the knee.
     Agree, SOA Moderate
     Median 7, range 3-9, LOC Moderate
   - 2.13. Characteristics of pain (i.e., pain due to meniscus extrusion, bony pain due to bone marrow

lesion, effusion-synovitis, neuropathic pain, etc.) may influence the response of viscosupplementation in the knee.
Agree, SOA Strong
Median 8, range 3-9, LOC High

2.14. Increased age may influence the response of viscosupplementation in the hip.
Uncertain
Median 3.5, range 1-9, LOC No consensus

2.15. Female sex may influence the response of viscosupplementation in the hip.
Disagree
Median 3, range 1-6, LOC Low

2.16. Overweight (30 < BMI > 25) may influence the response of viscosupplementation in the hip.
Disagree
Median 3, range 3-7, LOC Low

2.17. Obesity may influence the response of viscosupplementation in the hip.
Agree, SOA Moderate
Median 7, range 3-9, LOC Low

2.18. Radiological severity (Kellgren-Lawrence score IV vs. I-III) may influence the response of viscosupplementation in the hip.
Agree, SOA Strong
Median 8, range 7-9, LOC Unanimous

2.19. Joint space narrowing severity (OARSI grade 3 vs. 0-2) may influence the response of viscosupplementation in the hip.
Agree, SOA Strong
Median 8, range 6-9, LOC High

2.20. Patterns of femoral head migration may influence the response of viscosupplementation in the hip.
Agree, SOA Moderate
Median 7, range 4-9, LOC Low

2.21. The presence of femoral head/acetabulum bone marrow lesion on MRI may influence the response of viscosupplementation in the hip.
Agree, SOA Moderate
Median 7, range 3-9, LOC Moderate

2.22. Failure of a previous viscosupplementation (same physician, same joint) may influence the response of viscosupplementation in the hip.
Agree, SOA Moderate
Median 7, range 3-9, LOC Moderate

2.23. Characteristics of pain (bony pain due to bone marrow lesion, effusion-synovitis, etc.) may influence the response of viscosupplementation in the hip.
Agree, SOA Strong
Median 8, range 3-9, LOC High

2.24. Anatomical OA phenotype may influence the response of viscosupplementation in the hip.
Agree, SOA Moderate
Median 7.5, range 3-9, LOC Moderate

2.25. The presence of a synovial fluid effusion may influence the response of viscosupplementation in the hip.
Uncertain
Median 6, range 3-9, LOC Low

2.26. Using imaging guidance rather than anatomical landmarks for performing injection may improve the accuracy of the intra-articular needle positioning.
Agree, SOA Strong
Median 8, range 4-9, LOC High

2.27. Using imaging guidance rather than anatomical landmarks for achieving injection may improve the clinical outcomes of viscosupplementation.
Uncertain
Median 6.5, range 5-9, LOC No consensus

3. Recommendations for optimizing the rate of success and the safety of viscosupplementation

3.1. We recommend withdrawing any synovial fluid by careful aspiration before injecting HA in any joint.
Agree, SOR Strong
Median 9, range 5-9, LOC High

3.2. We recommend respecting the dosing regimen—number of injections and interval between injections—that have been proved by controlled randomized trials regardless the joint to be treated.
Agree, SOR Strong
Median 8, range 7-9, LOC Unanimous

3.3. We recommend, after knee viscosupplementation, complying with a rest period of few hours involving activities of daily living.
Uncertain
Median 5, range 3-9, LOC Moderate

3.4. We recommend, after knee viscosupplementation, complying with a rest period of one day involving activities of daily living.
Agree, SOR Moderate
Median 7, range 4-9, LOC Low

3.5. We recommend, after knee viscosupplementation, complying with a rest period of few days involving activities of daily living.
Uncertain
Median 4, range 1-5, LOC Moderate

3.6. We recommend, after hip viscosupplementation, complying with a rest period of few hours involving activities of daily living.
Uncertain
Median 5, range 2-9, LOC Low

3.7. We recommend, after hip viscosupplementation, complying with a rest period of one day involving activities of daily living.
Agree, SOR Moderate
Median 7, range 4-9, LOC Moderate

3.8. We recommend, after hip viscosupplementation, complying with a rest period of few days involving activities of daily living.
Uncertain
Median 5, range 1-6, LOC Moderate

3.9. We recommend, after knee viscosupplementation, to advise the resumption of sport activities the very next day.
Uncertain
Median 5, range 1-9, LOC Low

3.10. We recommend, after knee viscosupplementation, to advise the resumption of sport activities after 2 to 3 days.
Agree, SOR Moderate
Median 7, range 5-9, LOC Moderate

3.11. We recommend, after knee viscosupplementation, to advise the resumption of sport activities after 1 week or more.
Uncertain
Median 5, range 1-9, LOC No consensus

3.12. We recommend, after hip viscosupplementation, to advise the resumption of sport activities the very next day.
Uncertain
Median 5, range 1-9, LOC Low

3.13. We recommend, after hip viscosupplementation, to advise the resumption of sport activities after 2 to 3 days.
Uncertain
Median 6, range 1-9, LOC No consensus

3.14. We recommend, after hip viscosupplementation, to advise the resumption of sport activities after 1 week or more.
Uncertain
Median 5, range 1-9, LOC No consensus

3.15. We recommend administering viscosupplementation in the knee through an anterolateral route.
Uncertain
Median 5, range 1-8, LOC No consensus

3.16. We recommend administering viscosupplementation in the knee through an anteromedial route.
Uncertain
Median 5, range 1-8, LOC No consensus

3.17. We recommend administering viscosupplementation in the knee through a lateral patellofemoral route.
Agree, SOR Strong
Median 9, range 7-9, LOC Unanimous

3.18. We recommend administering viscosupplementation in the knee through a medial patellofemoral route.
Agree, SOR Moderate
Median 7, range 1-8, LOC Low

3.19. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the knee.
Disagree
Median 3, range 1-6, LOC Low

3.20. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the hip.
Agree, SOR Strong
Median 9, range 7-9, LOC Unanimous

3.21. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the ankle.
Agree, SOR Strong
Median 8, range 7-9, LOC Unanimous

3.22. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the shoulder.
Agree, SOR Strong
Median 8, range 3-9, LOC Moderate

3.23. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the trapeziometacarpal joint.
Agree, SOR Strong
Median 8, range 6-9, LOC High

3.24. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the first metatarsophalangeal joint.
Agree, SOR Moderate
Median 7, range 5-9, LOC Moderate

3.25. We recommend performing viscosupplementation under fluoroscopy or ultrasound guidance in the temporomandibular joint.
Agree, SOR Strong
Median 8, range 4-9, LOC Moderate

3.26. According to the Euratom recommendations about avoidance of radiations, we recommend to prefer ultrasound than fluoroscopy guidance as often as possible.
Agree, SOR Strong
Median 9, range 4-9, LOC High

3.27. When imaging guidance is needed we recommend use ultrasound guidance rather than fluoroscopy in all patients and all joints.
Uncertain
Median 5.5, range 1-9, LOC No consensus

3.28. When imaging guidance is needed we recommend use ultrasound guidance rather than fluoroscopy in young patients.

Agree, SOR Moderate
Median 7, range 1-9, LOC Moderate

3.29. When imaging guidance is needed we recommend use ultrasound guidance rather than fluoroscopy in all patients with iodine allergy.
Agree, SOR Strong
Median 9, range 6-9, LOC High

4. Interest and limits of using soluble biomarkers for the management of clinical trials on viscosupplementation
   4.1. We recommend to collect and store biological fluids to assess the predictive/prognostic value of biomarker(s) to identify responders to viscosupplementation.
   Agree, SOR Strong
   Median 8, range 6-9, LOC High
   4.2. We recommend considering baseline level and/or short term change and/or time integrated curve of biomarker(s) to determine their predictive value.
   Agree, SOR Strong
   Median 8, range 6-9, LOC High
   4.3. We recommend testing different biomarker combination to identify the best predictive model.
   Agree, SOR Strong
   Median 8, range 6-9, LOC High
   4.4. We recommend qualifying a predictive/prognostic value of biomarker on multiple independent studies investigating the same viscosupplement and the same protocol of injection.
   Agree, SOR Strong
   Median 8, range 5-9, LOC High
5. Appropriateness for using viscosupplementation in different clinical scenarios
   5.1. Scenario 1: Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), not sufficiently improved by non-pharmacological interventions and analgesics/NSAIDs (nonsteroidal anti-inflammatory drugs).
   Appropriate, SOA Strong
   Median 9, range 8-9, LOC Unanimous
   5.2. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with normal weight or moderate overweight (BMI< 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs.
   Uncertain
   Median 6, range 3-7, LOC No consensus
   5.3. Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with severe overweight (BMI > 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs.
   Appropriate, SOA Moderate
   Median 7, range 5-8, LOC Moderate
   5.4. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with severe overweight (BMI > 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs.
   Uncertain
   Median 4, range 2-8, LOC No consensus
   5.5. Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), sufficiently improved by analgesics/NSAIDs at high risk of OA progression.
   Uncertain,
   Median 6, range 3-8, LOC No consensus
   5.6. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), sufficiently improved by analgesics/NSAIDs, at high risk of OA progression.
   Not appropriate
   Median 3, range 2-5, LOC Low
   5.7. Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), sufficiently improved by analgesics/NSAIDs but who do not want to take per oral therapy.
   Appropriate, SOA Moderate
   Median 7.5, range 5-9, LOC High
   5.8. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with normal weight or moderate overweight (BMI < 30), sufficiently improved by analgesics/NSAIDs but who do not want to take per oral therapy.
   Appropriate, SOA Moderate
   Median 7, range 5-8, LOC Moderate
   5.9. Patients with symptomatic and mild to moderate OA (JSN grade 0-2, KL I-III), with severe overweight (BMI > 30), sufficiently improved by analgesics/NSAIDs but who do not want to take *per oral* therapy.
   Uncertain
   Median 6, range 3-7, LOC Low
   5.10. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with severe overweight (BMI > 30), sufficiently improved by analgesics/NSAIDs but who do not want to take per oral therapy.
   Not appropriate
   Median 3, range 2-7, LOC Low

5.11. Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), with contraindication to analgesics/NSAIDs.
Appropriate, SOA strong
Median 9, range 7-9, LOC Unanimous

5.12. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with normal weight or moderate overweight (BMI < 30), with contraindication to analgesics/NSAIDs.
Appropriate, SOA Moderate
Median 7.5, range 5-9, LOC High

5.13. Patients with symptomatic and mild to moderate OA (JSN grade 0-2, KL I-III), with severe overweight (BMI > 30), with contraindication to analgesics/NSAIDs.
Appropriate, SOA Moderate
Median 7, range 6-9, LOC High

5.14. Patients with symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with severe overweight (BMI>30), with contraindication to analgesics/NSAIDs.
Uncertain
Median 5.5, range 3-9, LOC No consensus

5.15. Patients with very symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with normal weight or moderate overweight (BMI<30) who do not want to undergo TKR (total knee replacement).
Appropriate, SOA Moderate
Median 7, range 6-8, LOC Moderate

5.16. Patients with very symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with severe overweight (BMI > 30) who do not want to undergo TKR.
Uncertain
Median 5, range 3-8, LOC Moderate

5.17. Patients with very symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with normal weight or moderate overweight (BMI < 30), with contraindication to TKR.
Appropriate, SOA Moderate
Median 7.5, range 6-9, LOC High

5.18. Patients with very symptomatic and advanced stage knee OA (JSN grade 3, KL IV), with severe overweight (BMI > 30), with contraindication to TKR.
Uncertain
Median 6.5, range 4-8, LOC Low

5.19. Patients with symptomatic, mild to moderate hip OA (JSN grade 0-2, KL I-III), not sufficiently improved by non-pharmacological interventions and analgesics/NSAIDs.
Appropriate, SOA Strong
Median 8.5, range 5-9, LOC High

5.20. Patients with symptomatic and advanced stage hip OA (JSN grade 3, KL IV), not sufficiently improved by non-pharmacological interventions and analgesics/NSAIDs.
Uncertain
Median 4, range 1-8, LOC No consensus

5.21. Patients with symptomatic, mild to moderate hip OA (JSN grade 0-2, KL I-III), sufficiently improved by analgesics/NSAIDs but who do not want to take per oral therapy.
Appropriate, SOA Moderate
Median 7, range 4-8, LOC Moderate

5.22. Patients with symptomatic and advanced stage hip OA (JSN grade 3, KL IV), sufficiently improved by analgesics/NSAIDs but who do not want to take per oral therapy.
Uncertain
Median 4, range 2-7, LOC No consensus

5.23. Patients with very symptomatic and advanced stage hip OA (JSN grade 3, KL IV), who do not want to undergo THR (total hip replacement).
Uncertain
Median 5, range 3-7, LOC Moderate

5.24. Patients with very symptomatic and advanced stage hip OA (JSN grade 3, KL IV), with contraindication to THR.
Uncertain
Median 6, range 5-7, LOC Low

Table 1 summarizes the issues that obtained unanimous agreement (11/11 experts agreed with them). **Tables 2** to **4** summarize the issues that have obtained strong agreement (median score 8 or 9/9).

Discussion

The recommendations and AUCs discussed in the present work are based on both evidence-based medicine data and on the daily practice clinical experience of the members of the working group. Treatment decision making is a complex process taking into account scientific evidences, patient wishes, provider experience and patient specificity (age, objectives, comorbidities, concomitant therapies, fears and preferences). All the answers cannot be found in the literature and the caregivers have to be respectful of the patients' wishes and requirements, while also being aware of the evidence-based recommendations given by savant societies. The aim of the task force was to propose simple rules for the use of viscosupplementation and to suggest therapeutic choices in complex clinical scenarios that are frequently encountered in daily practice, for which no clear recommendations have been yet published.

Table 1. Issues on Viscosupplementation that Obtained a Unanimous Level of Consensus.

Issues	Level of Consensus (11/11= Unanimous)
Statements	• A good indication, based on both an accurate analysis of signs, symptoms and clinical history and a careful clinical examination may improve the chances of success of VS. • A good indication based on a precise analysis of the radiological features may improve the chances of success of VS. • A good technique of injection and/or the use of an imaging guidance may enhance the chances of success of VS. • Radiological severity (KL score IV vs. I-III) may influence the response of VS in the knee. • Radiological severity (KL score IV vs. I-III) may influence the response of VS in the hip.
Recommendations	• We recommend administering VS in the knee through a lateral patellofemoral route. • We recommend performing VS under fluoroscopy or ultrasound guidance in the hip. • We recommend performing VS under fluoroscopy or ultrasound guidance in the ankle.
Appropriateness for using VS in daily practice situations	• Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs. • Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), with contraindication to analgesics/NSAIDs.

VS = viscosupplementation; JSN = joint space narrowing; KL = Kellgren-Lawrence score; OA = osteoarthritis; BMI = body mass index; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 2. Issues on the Use of Viscosupplementation that Obtained a Strong Agreement.

Issues on Viscosupplementation Use	Median (1-9)/Strength of Agreement
A good indication, based on both an accurate analysis of signs, symptoms, and clinical history and a careful clinical examination may improve the chances of success of VS.	9/Strong
A good indication, based on both an accurate analysis of signs, symptoms, and clinical history and a careful clinical examination may improve the chances of success of VS.	9/Strong
A good indication based on a precise analysis of the radiological features may improve the chances of success of VS.	9/Strong
A good technique of injection and/or the use of an imaging guidance may enhance the chances of success of VS.	9/Strong
Obesity (BMI > 30) may influence the response of VS in the knee.	8/Strong
Joint space narrowing severity (OARSI score 3 vs. 0-2) may influence the response of VS in the knee.	8/Strong
Joint space narrowing severity (OARSI grade 3 vs. 0-2) may influence the response of viscosupplementation in the hip.	8/Strong
Characteristics of pain may influence the response of viscosupplementation in the knee.	8/Strong
Characteristics of pain may influence the response of viscosupplementation in the hip.	8/Strong
Owing to its safety profile, VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs.	8/Strong
Using imaging guidance rather than anatomical landmarks for performing injection may improve the accuracy of the intraarticular needle positioning.	8/Strong

VS = viscosupplementation; BMI = body mass index; OARSI = Osteoarthritis Research Society International.

First of all, by giving a unanimous agreement on the 3 prerequisite issues, the working group emphasized the major role of the physician in the decision making and performing viscosupplementation and confirmed its previous recommendations[22,23] emphasizing 3 key points. A careful analysis of symptoms (aimed to understand the mechanisms of pain and the level of pain/disability), of the disease history (i.e., disease duration, previous treatments for OA, previous viscosupplementation, etc.), and of the patient specificities (i.e., body mass index [BMI], wishes, treatment preferences, comorbidities and related therapies, life habits, etc.) is the first step of the therapeutic decision. Second, a careful analysis of the standard radiographs is essential for determining the chances of success, since it has been suggested that the rate of response to viscosupplementation may be significantly lower in the advanced stages of the disease in both knee and hip OA.[24-26] Finally, in order to be effective, HA must be injected intraarticularly. There is an absolute need to

Table 3. Recommendations on the Use of Viscosupplementation that Obtained a Strong Agreement.

Recommendation for Viscosupplementation Use	Median (1-9)/Strength of Recommendation
We recommend withdrawing any synovial fluid by careful aspiration before injecting HA in any joint.	9/Strong
We recommend respecting the dosing regimen—number of HA injections and interval between injections—that have been proved by controlled randomized trials regardless the joint to be treated.	8/Strong
We recommend administering VS in the knee through a lateral patellofemoral route.	9/Strong
We recommend performing VS under fluoroscopy or ultrasound guidance in the hip.	9/Strong
We recommend performing VS under fluoroscopy or ultrasound guidance in the ankle.	8/Strong
We recommend performing VS under fluoroscopy or ultrasound guidance in the shoulder.	8/Strong
We recommend performing VS under fluoroscopy or ultrasound guidance in the trapeziometacarpal joint.	8/Strong
We recommend performing VS under fluoroscopy or ultrasound guidance in the temporomandibular joint.	8/Strong
When imaging guidance is needed we recommend use ultrasound guidance rather than fluoroscopy in patients with iodine allergy.	9/Strong
We recommend to collect and store biological fluids to assess the predictive/prognostic value of biomarker(s) to identify responders to VS.	8/Strong
We recommend considering baseline level and/or short term change and/or time integrated curve of biomarker(s) to determine their predictive value.	8/Strong
We recommend testing different biomarker combination to identify the best predictive model.	8/Strong
We recommend qualifying a predictive/prognostic value of biomarker on multiple independent studies investigating the same VS and the same protocol of injection.	8/Strong

VS= viscosupplementation; HA= hyaluronic acid.

Table 4. Appropriateness for Using Viscosupplementation in Different Clinical Scenarios that Obtained a Strong Agreement.

Appropriateness for Using Viscosupplementation	Median (1-9)/Strength of Appropriateness
Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs.	9/Strong
Patients with symptomatic, mild to moderate knee OA (JSN grade 0-2, KL I-III), with normal weight or moderate overweight (BMI < 30), with contraindication to analgesics/NSAIDs.	9/Strong
Patients with symptomatic, mild to moderate hip OA (JSN grade 0-2, KL I-III), not sufficiently improved by nonpharmacological interventions and analgesics/NSAIDs.	8.5/Strong

OA = osteoarthritis; JSN = joint space narrowing; KL = Kellgren Lawrence score; BMI = body mass index; NSAIDs = nonsteroidal anti-inflammatory drugs.

ensure the accuracy of the needle positioning using a good injection technique and/or the use of an imaging guidance. Here again it has been evidenced that the accuracy of the needle positioning, consequently of the IA injection, may influence the clinical outcomes of viscosupplementation.[27,28] This is easily understandable because HA does not have a systemic but a local effect and cannot diffuse into the intraarticular space if injected extraarticularly.

The first part of the work was dedicated to the clinical and anatomical factors that may influence the treatment efficacy in knee OA. Among the assumed predictors for failure, obesity and radiographic severity gathered a large majority of the agreements. The task force relied on the findings of the post hoc analysis of a randomized controlled trial (RCT), which demonstrated a diminishing rate of success in obese patients compared to nonobese subjects.[25] The authors showed that the percentage of responders was only 47% in obese patients, while it was 78% and 75% in normal or overweight but nonobese patients. The negative impact of obesity on the outcome of viscosupplementation was confirmed in another prospective trial, which illustrated that the chance to fulfill the Patient Acceptable Symptom State (PASS) criterion was significantly lower in obese patients.[29] Several other studies

pointed out the importance of the radiological grade[24,25,30] that has led most experts to consider severe joint space narrowing as a factor of poor prognosis, despite having experienced patients with very advanced OA who have greatly benefited from viscosupplementation in daily practice. The mechanism of pain was of major importance for 10 out of the 11 members. Indeed, OA-related pain has complex pathophysiology, including neuropathic peripheral and central abnormalities, together with local inflammation involving all joint structures.[31] The task force felt it was very important to understand well the mechanism of pain (i.e., synovitis, meniscus pain, pain due to subchondral bone involvement, neuropathic pain, etc.) before the decision making for viscosupplementation is done. Unfortunately, to date, evidence is still lacking in the published literature on this front. A large, not a little or moderate, synovial fluid effusion and a severe and/or isolated patellofemoral involvement were also identified as possible predictive factors of poorer outcome based on their clinical experience and the results of a retrospective cohort analysis.[32] Additionally, major malalignment, gross joint instability, and failure of a previous viscosupplementation collected a majority of votes as possible predictive factors of failure. The action to be taken in case of failure of a previous viscosupplementation was discussed in detail in a previous set of recommendations.[22] In hip OA, the conclusions were very similar, despite a level of evidence being even weaker, except for the radiological severity that has been inversely correlated to the clinical outcome.[25,33] The working group has relied on the recent paper of Deseyne *et al*.,[34] who published that both a superolateral femoral head migration and the presence of a femoral and/or acetabular bone marrow lesion on MRI were predictive of a lower response rate 3 months after hip viscosupplementation.

The second objective of the working group was to develop a set of recommendations aimed to optimize the chances of success of viscosupplementation in knee, hip, and other joint OA. Agreement was achieved with a high level of consensus to strictly respect the dosing regimen that has been proven by RCTs, regardless of the joint to be treated, and on the importance of removing synovial fluid effusion by careful aspiration before injecting HA. However, they could not reach consensus neither on the need and time of a rest period after injection nor on the time before resumption of sport activities. Based on their experience and plain common sense they advise to comply with a relative rest period of 1 day after injection and to resume sport activities after 2 or 3 days after knee viscosupplementation. No sufficient consensual agreement was obtained for hip OA on both rest and sport resumption. This shows that additional studies are required to help decision making on this particular issue.

On the contrary, a strong agreement was obtained for injection techniques. In the knee, a lateral mid or superolateral route was strongly recommended. Debate exists among physicians as to the more accurate approach portal for knee injection since no approach is 100% accurate. The task force agreed that lateral mid and superolateral patellar approaches must be preferred to the anterior routes, as advised in many publications.[35-38] The experts underlined that providers practicing viscosupplementation have to be familiar with the different approaches to adapt to any situation that may present. Imaging guidance, using either ultrasound or fluoroscopy, was unanimously recommended by the task force for hip and ankle, and strongly recommended for trapeziometacarpal, temporomandibular joint, and for shoulder. It has also been pointed out that ultrasound guidance might be useful not only to check the good positioning but also to inject the optimal volume of HA that can be safely administrated into very small joints, especially the trapeziometacarpal joint. The group concluded that using imaging guidance rather than anatomical landmarks for achieving HA injection improves the accuracy of the intraarticular needle positioning, although the improvement of clinical outcomes still remains to be formally demonstrated in large-scale trials. The strength of recommendation for using imaging guidance was only moderate for the first metatarsophalangeal joint. In the knee, considering the good accuracy of the mid-patellar approach, guidance can be proposed only in specific cases, particularly in obese patients or in the presence of severe patellofemoral OA. When imaging guidance is necessary the group advised the use of ultrasound rather than fluoroscopy where possible, as recommended in the European Community Directive 97/43/EURATOM for avoidance of radiations, particularly in young patients and those with history of iodine allergy.

The third objective of the working group was to evaluate the appropriateness of using HA injections in different clinical scenarios frequently encountered in daily clinical practice. Unsurprisingly, there was unanimous to moderate consensus in favor of the appropriateness for treating with viscosupplementation patients with mild to moderate knee and hip OA, with normal weight or moderate overweight, who are insufficiently improved by first-line therapies (analgesics, NSAIDs, nonpharmacological modalities) or who do not wish to get oral treatment or who have contraindications to pain killers. In normal weight or moderately overweight patients with advanced knee OA or in those with mild to moderate knee OA and obesity, the experts considered the indication of viscosupplementation as appropriate whereas they consider it as not appropriate in those combining the 2 risk factors, basing their conclusions on the findings published by Eymard *et al*.[25] The principal learning point from this session is that most of the members of the group consider the patient's wishes as a key element in therapeutic decision making. If the patient wishes to

postpone arthroplasty or expresses his (her) preference for intraarticular rather than oral treatment, viscosupplementation can be performed, provided the patient has been well informed of the benefit/risk ratio of the procedure. These recommendations enshrine the desire of the caregivers to have patients' wishes at the center of therapeutic decision making. Unfortunately, the analysis of literature does not allow having a formal opinion in many clinical situations, leading the experts to rank the AUCs as uncertain in 10 out of 24 clinical scenarios. However, the general opinion was in accordance with the German guidelines for the management of knee OA, recently published online,[39] which recommend that patients with contraindications to NSAIDS/analgesics should avoid oral medications and go right a way to intra-articular HA or corticosteroids.

Finally, 4 issues were dedicated to the interest of using soluble biomarkers in viscosupplementation treatment. Biomarkers are not available in routine practices and the proposed recommendations apply only to clinical trials. All issues were strongly agreed and received a high level of consensus. The working group highlighted the interest of using combinations of biomarkers to identify responder profiles to viscosupplementation and the need of further research to better understand the mechanisms of action of hyaluronic acid in OA.

In conclusion, based on the available literature data and the clinical experience of its members, the EUROVISCO task force has proposed a set of recommendations and AUCs on viscosupplementation of the knee, hip, and other joints. This is aimed to help practitioners in formulating a treatment algorithm, by taking into account not only data from evidence-based medicine but also experts opinion, especially in some cases where the patients' specificities make the therapeutic decision difficult.

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 respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Acknowledgments and Funding

The authors acknowledge LABRHA SAS (Lyon, France) who kindly organized and funded the meeting.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Yves Henrotin: Received honorarium from Menarini, Flexion Therapeutics, IBSA, BioIberica, Expansciences, Royal Canin, MagPharm, Pfizer, Fidia and LABRHA and Tilman SA for consultant services. Founder and shareholder of KIOmed pharma. Founder and shareholder of Artialis SA. Raghu Raman: Received honorarium from Sanofi and LABRHA for consultant services. Pascal Richette: Received fees from BioIbérica, Fidia, IBSA, Expanscience, Genévrier, Sanofi, Rottapharm, Servier, Flexion Therapics, and Ménarini. Hervé Bard: Received speaker and expert fees from Sanofi, Rottapharm-Madaus, Pfizer, Labrha, Expanscience, TRB Chemedica. Jörg Jerosch: Received honorarium from Sanofi for speaker services. Thierry Conrozier: Received honorarium from Genevrier, Sanofi, Aptissen Bioventus, and LABRHA for expert and consultant services. Xavier Chevalier: Received fees as a Genevrier Board member, Sanofi-Aventis expert, member of the IBSA foundation, speaker in IBSA meetings, Moebius and Flexion Therapics consultant. Alberto Migliore: Received consulting fees from Abbvie, BMS, MSD, Fidia, Sanofi, IBSA, Pfizer and LABRHA for national and international studies and courses. Jordy Monfort: Received consulting fees from Sanofi and Bioiberica. Dominique Baron: Received speaker fees from LCA and Expansciences.

Ethical Approval

Ethical approval is not required for this study.

Informed Consent

Not applicable.

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