Therapeutic Advances in Musculoskeletal Disease

Review

Viscosupplementation for the treatment of osteoarthritis. The contribution of EUROVISCO group

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***Abstract*:** Viscosupplementation (VS) is a symptomatic treatment for knee and other joint osteoarthritis (OA). Despite a long history of use, conflicting opinions remain on the best clinical indications and the most appropriate patients to be treated with intra-articular hyaluronic acid (IA-HA), the optimal dosing regimen and the modalities of retreatment. A multidisciplinary committee of European experts on OA (EUROVISCO) was constituted to formulate recommendations, aimed at helping physicians in the decision-making and the optimal achievement of VS. Before each session members were tasked to collate an exhaustive literature review. Level of evidence and strength of recommendation were based on the level of agreement for each item according to the Delphi method. In 2015, a consensus position was proposed for 24 statements. Among those that obtained a consensual agreement, the working group stressed that VS is effective in mild/moderate knee OA but is not an alternative to surgery in advanced OA, and that dosing regimen must be supported by controlled trials. In 2018, two decision algorithms for the retreatment with IA-HA in knee OA were published. Among the key recommendations, the experts recommended to re-treat every year patients with high risk of OA progression, even if not symptomatic. In 2020, EUROVISCO published two sets of recommendations for the design of clinical trials on the disease-modifying effect of VS and for optimizing the results of VS. The working group underlined that an accurate analysis of radiological features and symptoms and a careful clinical examination may improve the chances of success of VS, as well as good technique of injection and the use of imaging guidance. Based on the exhaustive analysis of the literature and their own clinical experience, the EUROVISCO experts offer a wide range of recommendations intended to help practitioners, particularly in certain cases where the specific characteristics of the patients make the therapeutic decision difficult.

Keywords: viscosupplementation, hyaluronic acid, intra-articular injection, osteoarthritis, knee, hip, recommendations, EUROVISCO

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Introduction

Viscosupplementation (VS), by intra-articular (IA) injection of hyaluronic acid (HA), has been a globally used symptomatic treatment for knee and other joint osteoarthritis (OA) for over a quarter-century.[1] VS is recommended in the management of symptomatic knee OA, for appropriate patients, by many scholarly societies of rheumatology and orthopaedics,[2–6] geriatrics[7] and sport medicine.[8] These recommendations are based on systematic reviews and meta-analyses that consider VS as an efficient and reliable therapy.[9–13] When compared with IA corticosteroids (CSs), IA-HA has been shown to have a more long-lasting effect for relieving knee pain (up to 6 months), while IA-CS is more effective on pain relief in the short term (up to 1 month), with similar safety profiles.[14–16] The good safety of IA-HA is no longer under question.[2–8] However, few authors underline the lack of adverse event

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synthesis standardization that leads to opposite conclusions about the balance of benefits and harms.[17]

Beyond its clinical effectiveness, when administered in appropriate patients, repeat IA-HA injections have also been suggested to delay the time to arthroplasty.[18–20] However, despite positive assessment by clinicians and a high level of evidence, some guidelines continue to fail to recommend VS,[21–23] resulting in a gap between guidelines and practitioners' habits, who continue to use VS in their daily practice.[24,25] Among the reasons that may explain the remaining doubt about the real effect of VS, Printz et al. underlined the importance of conflicts of interest in the studies' outcomes.[26]

In most countries HA viscosupplements are classified as class III implantable medical devices. The mechanisms by which HA acts on joint tissues are not fully understood and probably very complex.[27,28] Hence, the longstanding classification of viscosupplements as medical device has been recently called into question by the American Food and Drug Administration, which decided to reclassify HA as a drug, citing evidences of pharmacological effects.

Despite a long history of use, conflicting opinions remain on the best clinical indications, the most appropriate patients to be treated, the optimal dosing regimen and the modalities of retreatment. In 2017 a task force of US clinical experts developed and published Appropriate Use Criteria of VS in knee OA,[29] aimed to help physicians in the decision making of VS and to help insurance agencies to determine cases where reimbursement could be considered.

In 2014, a task force of European experts on OA was brought together in order to propose a consensual approach on VS in knee and other joint OA. The working group was named EUROVISCO (EUROpean VIScosupplementation COnsensus group). The 11 members come from seven European countries (Belgium, France, Germany, Italy, Spain, Turkey and UK). They constitute a multidisciplinary panel of physicians in the field of OA (seven rheumatologists, two orthopaedic surgeons, two physical therapists). All have experience in both academic medicine and private practice, and expertise in clinical research methodology. Before each session three or four members of the task force were tasked to collate an exhaustive literature review on a topic and to prepare the statements to be discussed. At each working session, one member acts as a chairman: he guides the discussion and plays the role of a moderator to iron out opinion discrepancies among the working group members. For each issue raised, the experts must give a degree of agreement, using a numerical Likert scale, ranging from 'I don't agree at all' to 'I fully agree'. The scores are then pooled to generate a median agreement score for each statement, which allows calculating the strength of recommendation. The number of voters who strongly agree obtains the level of consensus: unanimous if all experts fully agreed with the recommendation, high and moderate respectively if 9/10 and 8/7 experts highly agree.

The working objective of the EUROVISCO task force is to publish simple and clear recommendations aimed to provide clarification and advice to prescribers and users of VS. The first set of recommendations was published in 2015.[30] A consensus position based on an extensive research of the literature and expert opinion was proposed for 24 statements on VS of the knee and other joints. In 2018 the task force proposed two decision algorithms for the retreatment with IA-HA in patients with knee OA.[31] In 2020, EUROVISCO published a set of recommendations for the design and conduct of clinical trials on the disease-modifying effect of knee VS[32] and another set focused on the different ways for optimizing the clinical results of VS.[33] The aim of the present article is to briefly summarize the main conclusions of these four publications and to discuss the contribution of EUROVISCO group.

Consensus statement on VS with HA for the management of OA[30]

The aim of this first meeting was to set the record straight on the 'art' of VS and to provide clear and concrete answers to the questions frequently asked by the care-providers. Twenty-four statements exploring the entire field (i.e. effectiveness, safety, injection techniques, imaging guidance) of VS were discussed. Issues addressed included OA of not only the knee but also hip, tapezio-metacarpal joint (TMJ), ankle and shoulder VS. A high level of agreement was achieved for 16 statements or recommendations. In particular the expert achieved unanimous agreement in favour of nine issues. Among them the working group stressed that (1) VS is effective in mild and

moderate knee OA, (2) VS is a well-tolerated treatment of knee and other joint OA, (3) VS is not an alternative to surgery in advanced hip OA, (4) VS can be proposed in all symptomatic patients, even in those who adequately respond to analgesics or non-steroidal anti inflammatory drugs (NSAIDs) if they prefer receiving IA-HA to taking pain-killers, (5) the dosing regimen must be supported by the results of well conducted controlled trials. Statements that received unanimous or strong level of agreement are summarized in Table 1. A strong level of between-expert agreement was also obtained on the fact that VS may also be helpful in advanced stages of knee OA and also that when administered at early stages of OA it might have a chondroprotective effect. Furthermore, the working-group members strongly agreed not to consider HA viscosupplements as a 'single class' due to the wide difference between products. Hence the results of clinical trials of a particular VS cannot be extrapolated to others. They also stressed that a single-injection regimen must be performed with products specifically developed for this irrespective of the joint to be treated. In contrast, the experts could not find a consensus answer regarding the effectiveness of VS in OA of the shoulder and TMJ and on the mandatory use of an imaging guidance when performing VS in non-knee OA. Likewise they did not agree among themselves on the interest to combine HA and CS during the same injection session and on the poorer tolerance of animal-derived HA compared with HA of bacterial origin. Statements on VS use that obtained a unanimous or strong level of consensus are given in Table 1.

Decision algorithms for the re-treatment with VS in patients suffering from knee OA[31]

In daily clinical practice the re-treatment algorithms vary a lot from country to country and even between physicians. Some re-treat patients when pain returns to baseline level. Others opt for a repeat HA injection systematically, every 6 or 12 months. Although systematic reviews of IA-HA repeat injections showed favourable benefit/risk ratio,[34] the criteria for re-treatment had never been published before. The goal of the meeting was to examine two frequent clinical situations: re-treatment in patients successfully treated with VS 6 to 12 months ago and in those in whom previous VS failed or caused adverse effects. At the end of the debates the EUROVISCO group proposed two decision algorithms for the management of knee OA patients previously treated – successfully or otherwise – with VS. The expert panel had to give opinion on 88 issues within 18 statements. The first step was to give an accurate definition of 'success' and 'failure' of the treatment. The second step was to determine when and how to re-treat patients successfully treated by a previous VS. The third step was to determine when and how to re-treat patients in whom VS previously failed. The fourth step was to propose management options in patients who experienced adverse reaction following previous VS.

For evaluating success or failure of VS the patient's satisfaction and the patient acceptable symptom state (PASS)[35] were rated as the most useful tools in clinical practice. The patient's opinion being the primary outcome, the task force emphasized the importance of the patient's satisfaction with respect to the treatment, regardless of the results of PASS. There was a strong level of consensus to recommend re-treat in patients in whom pain occurs again and not to re-treat systematically symptom free or minimally symptomatic patients. Furthermore, consensus was obtained on recommending adapting the frequency of treatment to patients' individual situation. Young age, early-stage OA, risks factors of rapid progression and professional sportsmen were identified as clinical situations that can potentially justify re-treating patients earlier. Contra-indications to certain drugs or surgery, due to severe co-morbidities, were also considered as arguments in favour of an earlier re-treatment.

In patients in whom previous VS failed several reasons have obtained a full consensus: wrong clinical diagnosis of the source of pain (i.e. aseptic osteonecrosis, meniscal lesion, tendinopathy, subchondral bone micro-cracks, chondrocalcinosis), inappropriate protocol or inaccurate IA injection, obesity and very advanced OA (i.e. radiographic Kellgren–Lawrence grade IV). The experts consensually agreed that to improve accuracy of IA injection in the knee, the lateral mid-patellar route of injection has to be preferred to anterior approach and imaging guidance has to be preferably used in difficult cases such as obese patients. In normal weight patients imaging guidance is not mandatory. However, in normal-weight subjects, imaging guidance can be used according to the physician's habits. However, although imaging techniques are not necessarily

Table 1. Statements on viscosupplementation use that obtained a unanimous or strong level of consensus.[21]

Statements on viscosupplementation	Level of consensus
VS is an effective treatment for mild to moderate knee OA	Unanimous
VS is not an alternative to surgery in advanced hip OA	Unanimous
VS is a well tolerated treatment of knee and other joints OA	Unanimous
Owing to its safety profile, VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs	Unanimous
Viscosupplementation is a 'positive' indication but not a 'lack of anything better' indication	Unanimous
The dosing regimen must be supported by evidence based medicine	Unanimous
Cross-linking is a proven means for prolonging intra-articular residence time of hyyaluronic acid	Unanimous
The best approach to inject accurately viscosupplement into the knee joint is the lateral mid-patellar one	Unanimous
When VS is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid viscosupplement dilution	Unanimous
VS may also be helpful in advanced stages of knee OA	Strong
VS, when administered at early stages of OA, may have a chondroprotective effect	Strong
Physician education influences the success of VS treatment	Strong
Because viscosupplements differ widely from each other, results of clinical trials with a particular VS cannot be extrapolated to others	Strong
A single-injection regimen must be performed with products specifically developed for this, whatever the joint	Strong
Predictive factors of response to VS are poorly known and remain to be studied	Strong
VS is a cost effective treatment for knee OA	Strong

NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; VS, viscosupplementation.

recommended, they are not contraindicated in any situation of VS. In the case of a previous non-serious local adverse reaction to VS, the experts recommended to change the viscosupplement (i.e. bacterial instead of animal origin) and/or the injection protocol. No consensus was obtained on the proposal of adding CS to HA.

EUROVISCO guidelines for the design and conduct of clinical trials assessing the disease-modifying effect of knee VS[32]

The goal of this consensus driven expert meeting was to provide guidelines for the design and conduct of clinical trials assessing the disease-modifying effect of VS in knee OA.

The mechanisms of action of HA on joint tissues (synovium, cartilage, subchondral bone) are very complex and not fully understood. However, there is increasing data suggesting HA might have disease-modifying properties.[27] However, human trials evidencing a clinically relevant efficacy of VS to slow down articular cartilage breakdown are still lacking.

Thirty recommendations were made regarding adequate study population, imaging and clinical tools, and soluble biomarkers assessing the joint tissue metabolism. Unanimous agreement was reached on both the need for a randomized, double-blind trial and for combining imaging data and soluble biomarker assays.

Among the 30 recommendations only seven obtained both a strong and unanimous agreement: (1) 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. (2) 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. (3) We recommend a time interval of 1 year between two consecutive X-rays. (4) In knee OA, we recommend that X-rays be standardized to standing postero-anterior view, Lyon-schuss or semi-flexed view, lateral view and skyline view of the patella. (5) We recommend that all X-rays be performed using a standardized procedure (patient positioning, X-ray beam distance) and evaluated centrally by a single observer. (6) We did not recommend the use of ultrasonography, computed tomography (CT) scan and CT arthrography as tools for OA diagnosis or to assess progression over time. (7) To demonstrate the disease-modifying effect of VS we recommend a combination of imaging and biological outcome measures. A decrease of soluble biomarkers of cartilage degradation over time alone does not prove the chondroprotective effect of the treatment if this effect is not complemented by the imaging examinations.

Several other recommendations obtained a high level of agreement and consensus. In multicentre studies, the task force recommended that all trial sites must comply with a standardized MRI protocol using MRI with a 3.0 Tesla (T) field strength, two-dimensional fast spin-echo sequences with intermediate-weighted and/or T2-weighted contrast with fat suppression or short tau inversion recovery. To warrant reproducible evaluation of cartilage changes over time, the experts favour semi-quantitative scoring systems over quantitative ones, as these still need further evaluation. For clinical evaluation a combination of validated outcome measures was recommended (i.e. pain on 10 point rating scale and/or WOMAC score and/or KOOS score and/or patient global assessment on 10 point rating scale and/or OMERACT-OARSI response criterion and/or PASS and/or MCII).[35–37]

EUROVISCO recommendations for optimizing the clinical results of VS in OA[33]

The primary aim of this work was to vote on the appropriateness of the VS use in several frequent daily clinical situations and to identify phenotypes of patients who can benefit the most from VS. The task force also provided recommendations for optimizing the clinical results of VS. There was a large agreement for using VS to treat patients with mild to moderate knee and hip OA, with normal weight or moderate overweight, in whom pain is insufficiently relieved by first line therapies or who do not wish to take or have contra-indications to pain killers. The experts' opinion was in accordance with the German guidelines for the management of knee OA,[38] which stipulate that subjects with contra-indications to NSAIDs/analgesics should avoid oral medications and opt for IA-HA or CSs. The working group stressed that the patient's decision remains the key element in therapeutic decision-making. For example, in very severe OA requiring surgery, VS can be performed if the patient requests it for postponement of the arthroplasty, provided that he (she) has been well informed of the risk/benefit ratio.

Obesity, severe anatomical joint involvement, large synovial fluid effusion, severe patello-femoral OA, gross joint instability and major malalignment were considered by most of the members as the main predictors of VS failure. Therefore, a good indication based on both an accurate analysis of symptoms and a careful clinical examination must be determined to 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. Thus, for optimizing the chances of success of VS, the lateral mid-patellar approach was recommended for knee injection whilst imaging guidance was unanimously recommended for hip and ankle injection. Issues, recommendations and appropriateness for VS use that obtained a unanimous level of consensus are given in Table 2.

Conclusion

The EUROVISCO group, made up of a multidisciplinary panel of European doctors specializing in the management of OA, proposed four sets of recommendations on VS of the knee, hip and other joints. Based on the exhaustive analysis of the available literature and their own clinical experience, the experts offer a wide range of recommendations intended to help practitioners, particularly in certain cases where the specific characteristics of the patients make the therapeutic decision difficult. Among the statements that obtained a consensual agreement, the working group stressed that VS is effective in mild and moderate knee OA

Table 2. Issues, recommendations and appropriateness for viscosupplementation use that obtained a unanimous level of consensus.[24]

Issues	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 *versus* I–III) may influence the response of VS in the knee. Radiological severity (KL score IV *versus* I–III) may influence the response of VS in the hip.
Recommendations	We recommend administering VS in the knee through a lateral patello-femoral 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 non-pharmacological 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 contra-indication to analgesics/NSAIDs.

BMI, body mass index; JSN, joint space narrowing; KL, Kellgren–Lawrence; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; VS, viscosupplementation.

but is not a viable alternative to surgery in advanced OA, though it could be useful to help relieve pain in patients who cannot undergo arthroplasty. The choice of the viscosupplement and the dosing regimen must be supported by clinical trials, since HA products widely vary between themselves. Among the key recommendations for IA-HA retreatment, the experts recommended to re-treat systematically every year patients with high risk of OA progression, even if not symptomatic. For the others, re-treatment must be discussed as soon as pain reaches the PASS threshold. Among the ways for optimizing the VS outcomes, the working group underlined that a good indication, based on both an accurate analysis of radiological features and symptoms and a careful clinical examination, may improve the chances of success of VS. As well, a good technique of injection and/or the use of imaging guidance may enhance the chances of success of VS.

Conflict of interest statement

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, Pfizer, Labrha, Expanscience, TRB Chemedica

Jörg Jerosch: Received honorarium from Sanofi for speaker services

Thierry Conrozier: Received honorarium from Sanofi, MEDAC, Fidia 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

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