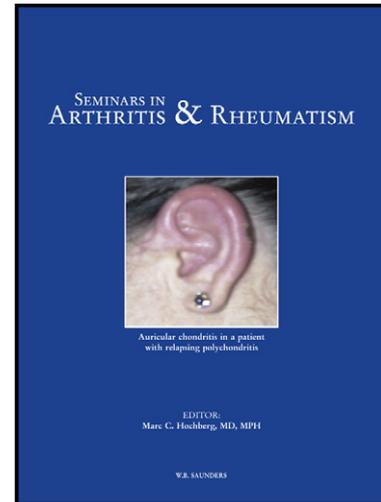


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Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis.

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ABSTRACT

Viscosupplementation (VS) with hyaluronic acid is currently used by physicians to treat osteoarthritis. However, many aspects of this treatment remain questionable and subject of controversy. A group of 8 experts in this field, from European countries, met to debate on 24 statements previously listed by this group members. Based on an extensive research of the literature and expert opinion, a consensus position has been proposed for each statement. Agreement was achieved on some recommendations. In particular the expert achieved unanimous agreement in favour of the following statements: VS is an effective treatment for mild to moderate knee OA; VS is not an alternative to surgery in advanced hip OA; VS is a well tolerated treatment of knee and other joints OA; VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs; VS is a "positive" indication but not a "lack of anything better" indication; the dosing regimen must be supported by evidence based medicine; cross-linking is a proven means for prolonging IA residence time of HA; the best approach to inject accurately knee joint is the lateral mid-patellar one; when VS is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid viscosupplement dilution. These clear recommendations have been established to help practitioners in the use of viscosupplementation.

INTRODUCTION

In the early 90s EA Balazs hypothesized that intra-articular (IA) injections of exogenous hyaluronic acid (HA) could restore visco-elasticity of the osteoarthritic synovial fluid (SF). This concept of "viscosupplementation" (VS) [1, 2] has been developed, based on the finding that the visco-elastic properties characterizing the healthy SF are altered in osteoarthritis (OA) and that these changes were directly related to the quantitative and qualitative HA decline in SF. Indeed, HA plays a major role in lubrication, shock absorption, and visco-elastic behavior of SF [3] as a result

of HA molecules and proteins/HA electrostatic interactions. The visco-elastic property of SF, which is directly related to both molecular weight (MW) and concentration of HA [3-5], gives it the ability to reduce mechanical stress on the joint. At low shear, such as occurs during a slow movement, the linear chains of HA align slowly in the direction of flow and behave like a viscous fluid. When the joint is subjected to fast impact (i.e., running or jumping) HA molecules do not have time enough to realign and exhibit elastic behavior thus allowing shock absorption. In OA, SF visco-elasticity, and consequently its ability to protect cartilage is dramatically lowered because of the decrease of both HA molecular weight (MW) and concentration [2]. Beside these physical properties, HA also exerts biological activities such as promotion of endogenous high MW HA production [6], interaction with pain receptors, and inhibition of pro-inflammatory mediators synthesis by joint cells [7–13].

After more than 20 years of use, VS is usually recognized as a safe and effective treatment of knee OA [14-21], safety being a major issue in the treatment of this condition. However, despite this positive assessment by practitioners and a high level of evidence, recent guidelines fail to recommend this therapeutic modality. This is mainly due to conflicting results of meta-analyses [22-24] that may arise from methodological differences and from possible differences in efficacy between products that widely vary in concentration, molecular weight, molecular organization (linear or cross-linked HA) and protocol of injection. Furthermore the indications, protocol of injecting and economic impacts of VS have yet to be specified [25, 26]. To provide clarification to prescribers and users of VS, a task force of European experts on OA has been brought together in order to propose a consensual approach on VS in knee and other joints OA.

METHODS:

Experts: Eight European experts from Belgium, France, Germany, Italy and UK, were selected according to their expertise in the field of OA and especially VS and were invited to participate at a task force on VS with HA (Lyon, France, June 2014). The expert panel was made of 5 rheumatologists (AM, HB, PR, TC, XC), 2 orthopedic surgeons (JJ, RR) and one physiotherapist (YH). The board members have experience in both academic medicine and private practice, and have expertise in clinical research methodology.

Issues: Twenty-four statements on HA and VS were discussed during the meeting. After extensive debate and discussion, the expert panel had to give their opinion on each of the 24 affirmations. For each assertion the organizing committee and the chairman proposed an extensive review of literature, with particular focus on systematic reviews and meta-analyses as well on randomized controlled trials (RCTS) of highest quality. One member of the task force (TC.) was entrusted with the task to collect a complete literature search on the field. The MEDLINE (PubMed) database was used with the following key-words: "hyaluronic acid" OR "hyaluronan" OR "viscosupplementation" AND "osteoarthritis" OR "joint". Afterwards, an initial list was compiled, and the most relevant papers for each of the discussed items were selected by 2 readers, both rheumatologists.

Scoring and voting methods: For each assertion, the experts voted on their degree of agreement with it, using an 11-point Likert scale (1– 10), number 1 meaning « I don't agree at all » and number 10 meaning « I fully agree ». The scores were pooled to generate a median agreement score for each affirmation. Finally, each item was classified as "Agree" if it received a median score of ≥ 7 and was classified as "Do not agree" if it received a median vote of ≤ 3 . An assertion having received a score between 3 and 7 was classified as "Agree under condition".

Recommendations: The present set of recommendations (Table I) was drafted after a face-to-face meeting that followed the vote session by 3 experts (YH, RR, TC) and was subsequently amended then approved by all members of the working group. All corrections and suggestions by each member were shared with the rest of the task force and included till final consensus.

RESULTS

For each out of the 24 issues, the average voting score, standard deviation, median, range and global opinion (Disagree, Agree under condition, Agree) are given.

1-Viscosupplementation is an effective treatment of mild to moderate osteoarthritis of the knee.

Average 9.1; SD 1.1; Median 9.5; range 7-10.

There was a consensus among the experts in considering that VS was effective for treating mild to moderate OA of the knee. They highlighted that the average effect-size on pain of the treatment from the most recent meta-analyses (0.34; 0.22-0.46 and 0.63; 0.39 to 0.88) [15, 27] was similar or better after 4 weeks than other OA pharmacological modalities such as cox-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid intra-articular injections and significantly better than paracetamol [27]. They agreed with the findings of Miller et al [15] and Bannuru et al [20] substantiating the effectiveness of VS to reduce pain and moderately improve function. On the contrary they did not endorse conclusions by Rutjes et al [22], who suggested that the improvement from this treatment was not sufficient enough to be clinically relevant. They also questioned the reasons that led the ACR [28] and OARSI [29] experts to classify HA injections as an "uncertain" treatment for knee OA and especially those that drove the AAOS [30] for recommending no longer to use HA injection. It wasn't even deemed "uncertain" by this association. They concluded, as the ESCEO experts did [31], that VS must be considered in the management of knee OA, not only because of its effectiveness in a large number of cases but also as alternative solutions are limited.

Experts' opinion: Agree

2-Viscosupplementation may also be helpful in advanced stages of knee osteoarthritis.

Average 7.2; SD 1.0; Median 7.5; range 5-8

The original issue was viscosupplementation may also be effective in advanced stages of knee osteoarthritis". The experts chose to replace the word *effective* with *helpful*, considering that in advanced stages of the disease, such as Kellgren-Lawrence grade IV, VS could be proposed as an adjunctive therapy to relieve pain in patients who do not want or cannot, because of co-morbidities, undergo surgery. In patients with co-morbidities, particularly those with arterial hypertension or on anticoagulant medications, VS may be used for its NSAIDs sparing effect, since it

has been demonstrated that IA HA is not significantly different from continuous oral NSAIDs up to 12 weeks [21].

Experts' opinion: Agree under condition

3-Viscosupplementation is effective for treating mild to moderate hip osteoarthritis.

Average 6.6; SD 1.7; Median 6.5; range 4-9

Unlike the consensus achieved for knee OA, the experts had differing views about VS in hip OA. They concluded there is insufficient evidence to determine whether VS can be recommended to treat hip OA. However those who had the largest clinical experience in this field (AM, TC) did not share this view. They emphasized that a careful analysis of literature shows that most of the negative studies were performed with an inadequate number of injections [32] and/or in inappropriate indications [33, 34], volume injected or product concentration. They stressed the results of the Italian cohort [35], including 1906 patients (4002 injections) strongly suggest a long lasting beneficial effect of ultrasound-guided injections of HA in a large proportion of patients. All the experts concluded that prospective randomized controlled trials remained to be performed, particularly with cross-linked single injection products that seem to give rather good results in non-controlled pilot trials [36-41]. Predictive factors of response according to the OA phenotype must also be studied [42].

Expert' opinion: Agree under condition

4-In severe hip osteoarthritis, viscosupplementation is not a valuable alternative to total hip arthroplasty.

Average 9.2; SD 1.0; Median 9.5; range 7-10

This matter provided a consensual response. Based on literature review [34, 41] and practical experience VS is not recommended in patients with severe hip OA awaiting hip replacement. In a large cohort of 191 patients, it has been shown that only 1 out of 4 patients waiting for surgery was satisfied with VS. In contrast, those who did not consider surgery in the short term had a high satisfaction rate (66.6%), similar to that of patients fulfilling the Minimal Clinically Important Improvement in an uncontrolled trial, performed in patients with mild to moderate hip OA [36].

Experts' opinion: Agree

5-Viscosupplementation is effective in mild to moderate osteoarthritis of the ankle.

Average 6.7; SD 1.0; Median 7; range 5-8

Most of the participants agreed with this issue but there was no consensus. This was especially due to the lack of large controlled trials. The hip OA experts (TC, AM.) were very satisfied with the treatment, because they had also the widest clinical experience in treating ankle OA. The experts insisted on the fact that the injection protocol recommended for one particular product must be applied. In fact, DeGroot et al [43] showed no significant difference between one injection of low molecular weight HA (3-5 doses) and saline serum. Other authors have shown that 3 to 5 injections of a linear HA of intermediate MW was effective [44-48], demonstrating that the smaller size of the ankle joint, compared to that of the knee, does not justify the use less injections than in knee OA. Similar to hip OA, patients with a less advanced stage might be the best responders [45, 47, 49].

Experts' opinion: Agree

6-Viscosupplementation is effective in mild to moderate osteoarthritis of the shoulder.

Average 6.1; SD 1.5; Median 6; range 3-8

There was no consensus for VS in gleno-humeral OA. Only two large, controlled, HA versus saline studies have been published in shoulder OA, both using linear HA and a multi-injection dosing regimen [50, 51]. One [50] included several shoulder conditions such as gleno-humeral joint OA, rotator cuff tear and adhesive capsulitis. The treatment effect through 26 weeks was significant in patients with OA in the three-injection and five-injection groups, with no significant effect for either regimen in patients without OA. The other study [51] included 300 patients suffering from shoulder OA, with or without rotator cuff lesions. At week 26 there was no difference between patients treated with HA and saline except in the subgroup without rotator cuff lesions. A non-controlled pilot trial showed encouraging results in patients with gleno-humeral OA and an intact rotator cuff, treated with 1 or 2 intra-articular injections of a cross-linked HA [52]. The experts recommend limiting VS to primary gleno-humeral OA after excluding adhesive capsulitis and damage to the rotator cuff.

Experts' opinion: Agree under condition

7-Viscosupplementation is effective in mild to moderate osteoarthritis of the trapezio-metacarpal joint.

Average 5.2; SD 1.0; Median 5.5; range 3-6

Most of the literature data suggests a mild to moderate effectiveness of HA injections in OA of the trapezio-metacarpal joint in open or controlled placebo trials [53-58]. Compared to steroid IA injections, HA has been shown to provide a more delayed but more sustained effect. However most of the RCTs are of poor methodological quality: the number of patients are small, the dosing regimen widely varied among studies, the trials were not designed for demonstrating non inferiority or superiority, and in most of them the method of injection and guidance is not detailed. Furthermore it is unlikely that any of the randomized trials were adequately powered to show a difference between treatments. Consequently the experts recommend using VS as a second line therapy after failure of non-pharmacological modalities, such as orthosis [59] only in patients with early stages of the disease, by injecting HA under fluoroscopy or ultrasonography guidance [60].

Experts' opinion: Agree under condition

8-Viscosupplementation, when administered at early stages of OA, may have a chondroprotective effect.

Average 8.1; SD 2.2; Median 8.5; range 3-10

Despite joint structure modification is not an approved indication for VS, numerous *in vitro* studies strongly suggest the potential chondroprotective properties of HA through complex mechanisms involving the enhanced matrix glycosaminoglycan accumulation, chondrocyte proliferation, the decrease of anti-Fas and nitric oxide (NO) induced apoptosis and the decreased production of PGE2, NO, metalloproteases MMP-1, MMP-3, MMP-13 [61]. In animal models of OA, HA has been shown to reduce articular cartilage destruction [61, 62]. To date there is increasing evidence that HA might have a structure modifying effect in humans. Conrozier et al [63] and Henrotin et al [64] showed that repeated hylan GF-20 injections decreased type II collagen breakdown as evidenced by the decrease of urine CTX II, serum Coll2-1 and Coll2-1NO2, 3 months after the injections. In an

open label trial Wang et al [65] demonstrated in 78 patients (39 receiving 4 cycles of 3 × 2.0 ml of intra-articular hylan G-F 20 injections at 6 month intervals and 39 receiving usual care for knee OA without injections) that HA administered to patients with symptomatic knee OA have a beneficial effect on knee cartilage preservation measured by both cartilage volume and cartilage defects size on MRI. The main experts' conclusion was that, despite these encouraging results strongly suggesting structure-modifying properties, there is a paucity of studies, to demonstrate that HA may be able to postpone the need for arthroplasty.

Experts' opinion: Agree

9-Viscosupplementation is a safe and well-tolerated treatment of osteoarthritis of the knee and other joints.

Average 9.4; SD 0.8; Median 9.5; range 8-10

The expert panel fully agreed with the very good risk/benefit balance of VS. As Bannuru and Mc Alindon [66] they did not agree at all with Rutjes et al conclusions which suggests that HA could cause serious side effects [22]. Their opinion was based on both literature (RCTs and meta-analyses) [67, 68] and their own clinical experience, showing VS was far less responsible of serious adverse events than others modalities such as NSAIDs [21, 69], opioids [70, 71] and even paracetamol [71, 72]. Following VS, adverse events are generally limited to mild or moderate knee pain, easily managed with rest, ice, analgesics or NSAIDs [27]. They usually recover in a few days. Pseudo-septic reactions are much more rare adverse reactions, which commonly occur with HA from animal origin and whose triggering is probably related to an immuno-allergic reaction [73-75]. Despite dramatic appearance, such reaction evolves favorably towards recovery and does not affect the long-term outcome of the treatment.

Experts' opinion: Agree

10-Local adverse events (pain, swelling, pseudoseptic reaction) are more frequent in viscosupplements from animal origin than in those obtained by biofermentation.

Average 4.8; SD 2; Median 5; range 2-7

Despite the large majority of pseudo-septic reactions have been described after hylan GF-20 repeated injections, the experts considered that there is no evidence that HA products from animal origin are less well tolerated than those obtained from bacterial fermentation [67, 68, 73]. The procedure of cross-linking involved in the manufacture of hylan was determined as the main reason for these reactions and not the animal origin of the device, substantiating that such adverse reactions are exceptionally rare with other products extracted from rooster combs. In fact, most of the studies comparing HAs from animal or bacterial origin failed to demonstrate a difference of safety/tolerability between products, despite of the conclusions of Reichenbach et al [76] and Kirchner et al [77] who reported more painful reactions and effusions in patients treated with hylan G20 than in those treated with other viscosupplements.

Experts' opinion: Agree under condition

11- Owing to its safety profile, viscosupplementation should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs.

Average 9.6; SD 0.5; Median 10; range 9-10

In a consensual manner the experts advised not to limit VS in patients in whom systemic symptomatic drugs are ineffective or poorly tolerated. They recommended VS as a first line treatment of OA, especially in patients with comorbidities, since it may help avoid NSAIDs/analgesics consumption and consequently may decrease the number of adverse events due to the later. Furthermore, in their daily practice experience, the experts emphasized that a large majority of patients express a preference for receiving intra-articular injections than a daily oral treatment. The intra-articular route also allows avoiding the poor treatment compliance, which is one of the main concerns in chronic diseases such as OA [78].

Experts' opinion: Agree

12-Viscosupplementation is a "positive" indication. It is not a "lack of anything better " indication.

Average 9.8; SD 0.7; Median 10; range 8-10

Despite the predictive factors of response to VS are not fully identified, the experts opinion was highly consensual: hyaluronic acid IA injections should be performed

only after careful analysis of the symptoms and imaging to conclude that VS meets the specific needs of the situation to ensure successful treatment. The pain of an osteoarthritic joint is of multi-factorial origin [79] and having knee pain does not necessarily mean a good indication of VS. For example, HA injections are not advised in case of flare that responds to corticosteroid injections, in case of very severe disease needing joint replacement, major joint malalignment, persisting pain due to meniscus lesion, neuropathic phenomena and tendinopathy.

Experts' opinion: Agree

13- *Physician education influences the success of viscosupplementation treatment.*

Average 9.1; SD 1.1; Median 9.5; range 7-10

The experts' opinion was consensually that, to be effective VS must fulfill 3 criteria: i) good clinical indication, ii) adequate dosing regimen, iii) strict IA injection of the HA gel. Consequently physicians who perform HA IA injections should perfectly know indications and contra-indications of the technique, should have a good knowledge of the dosing regimen for each OA location, and must be highly experienced in IA delivery of the agent such as needle positioning and joint access. For this, a targeted training with regular update is recommended.

Experts' opinion: Agree

14- *Viscosupplements differ widely from each other* so the results of clinical trials with a particular viscosupplement cannot be extrapolated to others:***

**Average 9; SD 1.1; Median 9; range 5-10*

***Average 8.1; SD 1.9; Median 8.5; range 7-10*

There are more than eighty marketed HA viscosupplements worldwide, that differ widely in terms of origin (animal or bacterial fermentation origin), molecular weight (from 0.7 to 3 MDa), molecular structure (linear, cross-linked, mix of both), method of cross-linking, concentration (0.8 to 30 mg/ml), rheological behavior (gel or fluid). Some of them are associated with other molecules (mannitol, sorbitol, chondroitin sulfate) at different concentrations. Considering these major differences, the experts decided that it is not possible to aggregate HA viscosupplements as a single "class"

allowing extrapolating the clinical results with a particular HA product to another. To demonstrate both effectiveness and safety, each viscosupplement should be studied in RCTs. In meta-analyses very different HA products should be classified and then assessed separately (i.e. biofermented viscosupplements of middle MW and 1% concentration cannot be analyzed together with high MW cross-linked HAs from animal origin).

Experts' opinion: Agree

15- The dosing regimen (i.e. number of injections) must be supported by evidence-based medicine:

Average 9.5; SD 1; Median 10; range 7-10

There was a consensual answer to that question. Before proposing a new dosing regimen (i.e. serial injections to single injection), controlled non inferiority trial versus comparator and/or superiority versus placebo studies must be performed to identify the best dosing regimen. This process was carried out with a cross-linked high MW HA, hylan GF-20, before the single injection protocol was validated [80, 81]. On the contrary it has been shown, in a randomized prospective trial, that two different dosages of an intermediate molecular weight linear HA (3x 2 ml weekly injections versus one 6 ml injection) do not exhibit the same efficacy, the three-weekly regimen being more effective than the single injection in reducing pain [82].

Experts' opinion: Agree

16-Cross-linking is a proven means for prolonging the intra-articular residence time of hyaluronic acid:

Average 9.5; SD 0.8; Median 10; range 8-10

All the experts agreed with this assertion. It has been demonstrated that HA injected into the joint is rapidly degraded, limiting the intra-articular residence time from few days for linear molecules to few weeks for the solutions of cross-linked HA [83, 84]. Repeated injections are necessary with linear HA whereas cross-linked HA can be used in a single injection dosing regimen. Addition of antioxidant molecules such as mannitol [85] or sorbitol [86] might be another way to reduce the *in situ* degradation of HA. However the *in vitro* findings with these antioxidant molecules remain to be confirmed *in vivo* in clinical trials

Experts' opinion: Agree

17-A single-injection regimen must be performed with products specifically developed for this, whatever the joint.

Average 7; SD 3.2; Median 8; range 2-10

As a consequence of the previous answer the experts agreed on the fact that VS performed through a single injection protocol necessitates the use of a cross-linked product. Some studies support a controversial evidence of a single injection of linear HAs against saline injection [32, 43] and 6 mL of a linear HA has been shown to be less effective than 3 x 2 mL, weekly injections, of the same HA [82]. Only one expert did not agree with this opinion.

Experts' opinion: Agree

18-The best approach to inject accurately viscosupplement into the knee joint is the lateral mid-patellar one.

Average 9.4; SD 0.9; Median 10; range 8-10

Knee joint aspiration and injection is a common, simple, and generally safe procedure. However debate exists among practitioners as to the 'best' approach portal for knee injection [87, 88]. No approach is 100% accurate, and the accuracy of injection of the knee joint may be enhanced by the use of guidance such as ultrasound. However the experts agreed that lateral mid-patellar and supero-lateral approaches must be preferred to the anterior approaches. The latter can be useful when the knee cannot be extended, or when there is only a minimal amount of fluid in the knee joint, because they do not allow aspiration of synovial fluid and can injure the anterior horn of the menisci. Furthermore the accuracy of anterior approaches range from 55% to 75% while that of the lateral mid patellar is from 76% to 93%. It is however necessary that physicians practicing VS, are familiar with the different approaches, in order to adapt to any situation that may present

Experts' opinion: Agree

19- Excluding knee (i.e. hip, shoulder, ankle, trapezio-metacarpal joint), viscosupplementation should always be achieved under fluoroscopy or ultrasound guidance.

Average 6.9; SD 3.2; Median 7; range 1-10

All the experts fully agreed with this issue for the hip and trapezio-metacarpal joints. In these 2 joints, imaging guidance is the only way to ensure that the treatment has been injected intra-articularly despite a trial showing that 29 of the 32 patients injected without imaging guidance for TMC OA had ultrasound evidence of IA HA [89]. Their opinion was divided on the need to use guidance for the shoulder and above all for the ankle. In the latter, a cadaveric study showed that the accuracy rate for US guided injections was 100% versus 85% for non-guided injections [90]. Similar results were obtained on cadavers using non-guided anterolateral or anteromedial routes [91]. However, as a result of a very high level of success with US and fluoroscopy guided compared to landmark-guided injections [92- 94], the experts recommended to use imaging guidance as often as possible, according to the technical capabilities of the physician. They were unable to advice on a specific type of guidance to be used [95]. Two of the experts (AM, HB) stressed that, contrary to fluoroscopic techniques, ultrasound does not require use of contrast, allowing use in patients intolerant to iodized contrasts. It can be repeated without problems of radiation load to either the operator or the patient. Moreover we have to take into account that the European Community "Directive 97/43/Euratom" about the general principles for protection from the radiation exposure requires a sufficient net benefit to allow radiation exposure, weighing the total potential therapeutic benefits against detriments that the exposure might cause. The same European directive rules that, if available alternative techniques having the same objective but involving no or less exposure to ionizing radiation exist, they should be preferred and in the case the exposure cannot be justified, it should be prohibited. In addition ultrasound guidance is cheaper in comparison to the fluoroscopic guidance.

Experts' opinion: Agree under condition

20-Predictive factors of response to viscosupplementation are poorly known and remain to be studied.

Average 8.1; SD 1.8; Median 8.5; range 8-10

To date very few papers have been focused on the predictive factors of response or failure of VS. The only predictive factor of poor response that has been regularly reported in the literature is the advanced stage of the disease [36, 47, 49, 96-98].

Some biomarkers such as serum hyaluronic acid concentrations and urinary C-telopeptide fragments of type II collagen [63] were suggested to be of prognostic value, but none of them has been proven to be useful at an individual level to predict either OA progression or the efficacy of VS. The experts insisted on the absolute necessity of conducting research specifically designed to accurately determine the factors influencing treatment outcome. The combination of biomarkers and MRI findings seems to be the most promising assessment method. Nevertheless, the way HA is administered (blindly, ultrasound or fluoroscopy guided, routes of injection, arthrocentesis, rest or immobilization after injections) and characteristics of pain (i.e. neuropathic pain) remains to be carefully studied.

Experts' opinion: Agree

21- It is not recommended to inject hyaluronic acid and corticosteroid together into a single joint.

Average 4.7; SD 1.4; Median 5; range 3-7

The data in the literature does not allow a consensus on this matter. The combination of a steroid with HA has an experimental and clinical justification. An animal model of OA showed that the association was more effective than HA alone in the treatment of cartilage degeneration [99] and several clinical trials showed that from the injection date to week 4, IA corticosteroids appear to be relatively more effective for pain relief than HA, by week 4, the 2 approaches have equal efficacy, but beyond week 8, hyaluronic acid has greater efficacy [15]. The combination steroid-HA is clinically justified to obtain pain relief much more quickly than with HA alone. However, many trials were designed to compare HA and steroid injections and very few have compared HA alone and the combination HA-steroid. Despite a suggested synergistic effect of steroids and HA [100-102], the studies were not powered enough to demonstrate the superiority of the association. Moreover the impact of steroids on the HA molecule structure is still poorly understood. A non-published in vitro study suggested a differential impact of IA corticosteroids on the HA molecule, triamcinolone hexacetonide being much less deleterious on the rheological behavior of HA than cortivazol [103].

Experts' opinion: Agree under condition

22-When viscosupplementation is performed under fluoroscopy, the amount of radio-opaque contrast agent must be as low as possible.

Average 9.8; SD 0.5; Median 10; range 9-10

Logically, diluting HA viscosupplement might decrease its efficacy. Hence it is advisable to carefully remove the synovial fluid in case of effusion [104].

Consequently the experts suggest to use the lowest possible volume of contrast agent in case of fluoroscopy-guided injection as a rheological study has demonstrated a dose dependant deleterious effect of meglumine ioxaglate on HA molecules soon a ratio 1/1 [103].

Experts' opinion: Agree

23-A relative rest period of at least 24 hours should be recommended after viscosupplementation.

Average 7.1; SD 2.7; Median 8; range 2-10

To date no published data could support recommendation on rest period after IA HA injections. However the average experts opinion was to advise a short period of relative rest, ranging from 12 to 24 hours, during which patients can walk slowly, avoiding impact activities like running and carrying heavy loads. Indeed this short period of rest might reduce the frequency and/or intensity of post injection pain and might also improve the rate of success by reducing the clearance of HA fragments from the synovial space.

Experts' opinion: Agree

24- Viscosupplementation is a cost effective treatment for knee osteoarthritis.

Average 7.4; SD 1.7; Median 7.5; range 5-9

The majority of experts agreed that there are increasing evidences that VS is a cost effective therapeutic modality to treat OA especially through NSAID/analgesic sparing effect and ability to delay arthroplasty in some cases [105-111]. A very recent trial demonstrated that HA was both cheaper and more effective than conventional care with NSAIDs and analgesics, with ICER QALYs well below the threshold for adopting new technology [105].

Experts' opinion: Agree

DISCUSSION

Viscosupplementation is booming, with an annual growth estimated at 7.1% and more than 17 million treatments sold so far [112]. Nevertheless major controversies persist regarding its efficacy, safety and cost-effectiveness. This reflects a huge gap between those who doubt – some academics, methodologists, and health authorities, and those who believe - practitioners, for whom there is little doubt that VS is a very useful therapeutic modality in the management of OA..

It thus seemed logical to bring together experts from different medical disciplines (rheumatologists, orthopedic surgeons, rehabilitation specialists) within a professional environment (university, hospital, private) to collate their opinion on critical points related to VS. As Sacket et al, we think that Evidence-Based Medicine (EBM) should not discount the value of clinical experience and that the practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research [113]. Hence we have proposed a list of recommendations after carefully analyzing both the literature and the expert opinion. These recommendations are summarized in table I.

These recommendations should be helpful for health practitioners to better use VS in the management of OA patient. The task force considers VS as an effective and safe therapeutic modality to treat mild to moderate knee OA. Furthermore, the experts emphasized that VS should not be reserved for patients with therapeutic failure after NSAIDs treatment or for whom NSAIDs are not indicated. Since the VS allows to reduce NSAIDs consumption [114], the experts consider that depriving some patients of VS treatment might result in NSAID overuse by these patients. This could pose a high risk of systemic adverse effects in these patients. Further, since VS contribute to preserve cartilage as demonstrated by MRI [65], the experts also think that VS should be proposed to all patients for whom VS is indicated. The potential structure-modifying effect of HA has also been discussed and, in a consensual manner, the experts' advice was to treat knee OA patients with VS as soon as possible expecting a protective effect of HA on cartilage degradation particularly in those with a high risk of disease progression, though the chondroprotective effect of HA has not been yet proven in humans trials. However long term prospective controlled trials remain to be performed before conclusive evidence on chondroprotection can be provided. Furthermore, VS indication must

remain a "positive" but not a "lack of anything better " one. HA injections should be performed after a careful clinical and imaging analysis, to improve the chances of a successful treatment. In knee OA, VS could also be helpful in advanced stages of the disease in patients who cannot be or do not want to be operated. In contrast, in patients with advanced hip OA, HA injections do not provide substantial benefit and cannot be recommended. Furthermore, an individualized multimodal medical management taking into account the patient's preferences is advocated by most of the recommendations [28, 29, 115, 116]. Studies have suggested that patients with OA may prioritize comorbidities over their OA [115] and that patient's stated preference for a treatment increases compliance to this treatment [117].

Another point of consensus was that HA products are different in terms of origin, MW, structure, concentration and rheological properties such a way that the results of clinical studies with a particular viscosupplement cannot be extrapolated to others. Accordingly they suggested that each viscosupplement must demonstrate both effectiveness and safety through RCTs. Therefore the dosing regimen must also be supported by EBM. Two other issues reached consensus: the lateral- mid-patellar approach in the knee and to use the least amount of contrast medium to avoid HA dilution, when injection is performed under fluoroscopy [103].

Among the issues that did not achieve consensual response, the notable one was regarding the association HA-corticosteroid. The combination steroid-HA can be clinically justified since some trials suggested a synergistic effect of steroids and HA [100-102] leading to a more rapid improvement of pain. However the experts advise not to systematically associate HA and steroids and to reserve the association for patients having high level of pain needing a quick relief, favoring triamcinolone hexacetonide which *in vitro* study does not seem to have a significant deleterious effect on HA properties.

Regarding VS in other joints than knee, opinions were divided on VS effectiveness but there was a consensus with regard to the need of new well designed prospective randomized controlled trials with a particular focus on predictive factors of response according to the patients' characteristics and OA phenotype.

The remaining issues have achieved a general agreement without reaching a true consensus. The expert's, general conclusion was that further clinical and experimental studies remain to be performed in order to better understand the

complex mechanisms of action of VS thus better identifying patients susceptible to effective treatment with VS. Finally, the experts highlighted the importance that can play soluble biomarkers of collagen degradation in the prognosis and evaluation of VS efficacy and the follow-up of response at individual level. The association of VS with a biomarker of efficacy could be also helpful to better estimate the moment of re-injection.

In conclusion, this task force has helped to create consensus on critical points of the use of VS in OA management including the route of injection, the indication, the efficacy and the tolerability. These recommendations should contribute to a better use of VS in the daily practice of physicians.

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Accepted manuscript

Table I: Level of expert consensus on the use of viscosupplementation

| Issues on viscosupplementation use | Level of consensus | Distribution of ratings | | |
|--|---------------------|-------------------------|-----|-----------------|
| | | ≤3 | 4-6 | ≥7 ^b |
| VS is an effective treatment for mild to moderate knee OA | Unanimous in favour | 0 | 0 | 8 |
| VS may also be helpful in advanced stages of knee OA | Strong in favour | 0 | 1 | 7 |
| VS is an effective treatment for mild to moderate hip OA | Moderate in favour | 0 | 4 | 4 |
| VS is not an alternative to surgery in advanced hip OA | Unanimous in favour | 0 | 0 | 8 |
| VS is an effective treatment for mild to moderate ankle OA | Moderate in favour | 0 | 3 | 5 |
| VS is an effective treatment for mild to moderate shoulder OA | Weak in favour | 1 | 3 | 3 |
| VS is an effective treatment for mild to moderate TMC joint OA | Weak in favour | 1 | 7 | 0 |
| VS when administered at early stages of OA, may have a chondroprotective effect | Strong in favour | 1 | 0 | 7 |
| VS is a well tolerated treatment of knee and other joints OA | Unanimous in favour | 0 | 0 | 8 |
| Local adverse events are more frequent in viscosupplements from animal origin than in those obtained by biofermentation | No consensus | 4 | 3 | 2 |
| Owing to its safety profile, VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs | Unanimous in favour | 0 | 0 | 8 |
| Viscosupplementation is a "positive" indication but not a "lack of anything better" indication | Unanimous in favour | 0 | 0 | 8 |
| Physician education influences the success of VS treatment | Strong in favour | 0 | 2 | 6 |
| Because viscosupplements differ widely from each other, results of clinical trials with a particular VS can not be extrapolated to others | Strong in favour | 0 | 2 | 6 |
| The dosing regimen must be supported by evidence base medicine | Unanimous in favour | 0 | 0 | 8 |
| A single-injection regimen must be performed with products specifically developed for this, whatever the joint | Strong in favour | 1 | 0 | 7 |
| Cross-linking is a proven means for prolonging IA residence time of HA | Unanimous in favour | 0 | 0 | 8 |
| The best approach to inject accurately viscosupplement into the knee joint is the lateral mid-patellar one | Unanimous in favour | 0 | 0 | 8 |
| Excluding knee, VS should always be achieved under fluoroscopy or ultrasound guidance | Weak in favour | 1 | 3 | 4 |
| Predictive factors of response to viscosupplementation are poorly known and remain to be studied | Strong in favour | 0 | 2 | 6 |
| It is not recommended to inject HA and corticosteroid together into a single joint* | No consensus | 2 | 4 | 1 |
| When VS is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid viscosupplement dilution | Unanimous in favour | 0 | 0 | 8 |
| A relative rest period of at least 24 hours should be recommended after VS | Moderate in favour | 1 | 1 | 6 |
| VS is a cost effective treatment for knee OA | Strong in favour | 0 | 2 | 6 |

^[a] n = 7

^[b] Scale ranging from 1 ('strongly disagree') to 10 ('strongly agree')

VS= viscosupplementation; OA= osteoarthritis; HA= hyaluronic acid; TMC= trapezio-metacarpal ; NSAIDs= non steroidal anti inflammatory drugs; IA= intra articular

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Table I: Level of expert consensus on the use of viscosupplementation

| Issues on viscosupplementation use | Level of consensus | Distribution of ratings | | |
|--|---------------------|-------------------------|-----|-----------------|
| | | ≤3 | 4-6 | ≥7 ^b |
| VS is an effective treatment for mild to moderate knee OA | Unanimous in favour | 0 | 0 | 8 |
| VS may also be helpful in advanced stages of knee OA | Strong in favour | 0 | 1 | 7 |
| VS is an effective treatment for mild to moderate hip OA | Moderate in favour | 0 | 4 | 4 |
| VS is not an alternative to surgery in advanced hip OA | Unanimous in favour | 0 | 0 | 8 |
| VS is an effective treatment for mild to moderate ankle OA | Moderate in favour | 0 | 3 | 5 |
| VS is an effective treatment for mild to moderate shoulder OA | Weak in favour | 1 | 3 | 3 |
| VS is an effective treatment for mild to moderate TMC joint OA | Weak in favour | 1 | 7 | 0 |
| VS when administered at early stages of OA, may have a chondroprotective effect | Strong in favour | 1 | 0 | 7 |
| VS is a well tolerated treatment of knee and other joints OA | Unanimous in favour | 0 | 0 | 8 |
| Local adverse events are more frequent in viscosupplements from animal origin than in those obtained by biofermentation | No consensus | 4 | 3 | 2 |
| Owing to its safety profile, VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs | Unanimous in favour | 0 | 0 | 8 |
| Viscosupplementation is a "positive" indication but not a "lack of anything better" indication | Unanimous in favour | 0 | 0 | 8 |
| Physician education influences the success of VS treatment | Strong in favour | 0 | 2 | 6 |
| Because viscosupplements differ widely from each other, results of clinical trials with a particular VS can not be extrapolated to others | Strong in favour | 0 | 2 | 6 |
| The dosing regimen must be supported by evidence base medicine | Unanimous in favour | 0 | 0 | 8 |
| A single-injection regimen must be performed with products specifically developed for this, whatever the joint | Strong in favour | 1 | 0 | 7 |
| Cross-linking is a proven means for prolonging IA residence time of HA | Unanimous in favour | 0 | 0 | 8 |
| The best approach to inject accurately viscosupplement into the knee joint is the lateral mid-patellar one | Unanimous in favour | 0 | 0 | 8 |
| Excluding knee, VS should always be achieved under fluoroscopy or ultrasound guidance | Weak in favour | 1 | 3 | 4 |
| Predictive factors of response to viscosupplementation are poorly known and remain to be studied | Strong in favour | 0 | 2 | 6 |
| It is not recommended to inject HA and corticosteroid together into a single joint* | No consensus | 2 | 4 | 1 |
| When VS is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid viscosupplement dilution | Unanimous in favour | 0 | 0 | 8 |
| A relative rest period of at least 24 hours should be recommended after VS | Moderate in favour | 1 | 1 | 6 |
| VS is a cost effective treatment for knee OA | Strong in favour | 0 | 2 | 6 |

^[a] n = 7

^[b] Scale ranging from 1 ('strongly disagree') to 10 ('strongly agree')

VS= viscosupplementation; OA= osteoarthritis; HA= hyaluronic acid; TMC= trapezio-metacarpal ; NSAIDs= non steroidal anti inflammatory drugs; IA= intra articular