

Systematic Literature Review and Expert Opinion for the Use of Viscosupplementation with Hyaluronic Acid in Different Localizations of Osteoarthritis

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Abstract: Osteoarthritis (OA) is a significant cause of disability. Considering the increasing diffusion of the viscosupplementation (VS) with hyaluronic acid (HA), the International Symposium Intra Articular Treatment (ISIAT) appointed a Technical Expert Panel (TEP) to identify the criteria for successful VS with a specific HA in OA; this through a systematic literature review (SLR), performed following the PRISMA guidelines interrogating Medline, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grey Matters and American College of Rheumatology (ACR/EULAR) databases and the opinion of international experts. The research included only studies on adults and humans without limitations of language or time of publication. Researchers extracted both quantitative and qualitative data from each study. Mixed Methods Appraisal Tool (MMAT) was used to perform quality analysis for the level of evidence. The SLR retrieved 385 papers, 25 of which were suitable for the analysis. The TEP focused on the different formulations of the product Sinovial® [HA 0.8%, HA 1.6%, HA 2%, 800–1200 kDa, HA 3.2% (1400–2100 kDa/65–110 kDa)]. The choice was due to the vast amount of evidence available. The TEP weighed the evidence in two rounds of a Delphi survey; the results, and any disagreement, were discussed in a final session. Three domains were considered: 1) the patients' characteristics associated with the best results; 2) the contraindications and the conditions linked to increased risk of failure; 3) the clinical conditions in which VS is considered appropriate. The TEP concluded that VS with HA is safe and effective in the treatment of knee and hip OA of grades I to III and that it is possible to undertake VS in other situations (eg grade IV Kellgren-Lawrence – KL); a comprehensive examination of the patient should be performed before the procedure.

Keywords: appropriateness, osteoarthritis, personalized medicine, viscosupplementation

Introduction

Osteoarthritis (OA) is the most common disabling arthropathy, impairing the quality of life of patients and imposing a heavy burden on healthcare systems. Hand, knee, hip and spinal facets are the most affected joints, with an increasing prevalence with the age of the patients. Women are more affected than men, especially for hand and knee OA. Hunter and Bierma-Zeinstra¹ found a prevalence between 10% and 30% of the population according to sex and the joint affected. The incidence of OA increases steeply after the age of 50 with a peak around 75 years.¹ Roddy and Menz² reported similar results in their review on foot OA. Peyron and Balazs³ first proposed viscosupplementation (VS) with Intraarticular Hyaluronic Acid (IAHA). The

rationale is based on the mechanical and physiological properties of HA, an essential component of the joint tissues and the synovial fluid. Despite the large body of evidence on the safety and efficacy of VS-IAHA, this procedure is still an object of controversial by international guidelines.⁴ Osteoarthritis Research Society International (OARSI)⁵ and European League of Associations for Rheumatology (EULAR)⁶ guidelines granted IAHA a low-grade recommendation, while the National Collaborating Centre for Chronic Condition (NCC-CC)⁷ and American Academy of Orthopedic Surgeons (AAOS)⁸ guidelines recommended against IAHA. The AAOS guideline was criticized by Santilli et al⁹ who pointed out that the guideline was lacking multidisciplinary being prepared mainly by orthopedic surgeons. Other aspects of the above guidelines raised objections: the difference between the highly selected patients enrolled in Randomized Controlled Trials (RCTs), reviewed in the guidelines, and patients in clinical practice; the selection of comparators; the limits of the criterion of the Minimum Clinically Important Improvement (MCII) and the underestimation of the clinical relevance of differences in phenotypes of OA.¹⁰ Maheu et al maintained that OA should be considered as a multifactorial disease requiring a flexible approach and an accurate definition of the most suitable patients for VS.¹¹ The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)¹² guideline recommended a multi-step approach to OA, starting with measures like weight reduction, aerobic exercise, physiotherapy and rehabilitation, followed by Symptomatic Slow-Acting Drugs for Osteoarthritis (SySADOAs), topical or oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), duloxetine or analgesics. The guideline defined VS as an effective treatment for knee OA, with a positive impact on pain and function and as the last step before surgery. Finally, the EUROpean VIScosupplementation Consensus group (EUROVISCO)¹³ issued detailed recommendations for a proper selection of the patients to be treated with IAHA. The International Symposium Intra Articular Treatment (ISIAT), which gathers leading experts on IA treatment every two years, appointed a multinational, multi-disciplinary Technical Expert Panel (TEP), composed by the authors of this paper, to identify predictors of a positive or negative outcome of VS with IAHA. The TEP focused on the different formulations of a single product: Sinovial® (other brand names: Intragel® - Gelsyn-3®) [HA 0.8%, HA 1.6%, HA 2%, 800–1200 kDa, HA 3.2% (1400–2100 kDa/65–110 kDa)]. The choice was made for

four main reasons: the large body of available scientific evidence; the extensive use of the product worldwide; the well-known safety profile and the direct experience of the TEP members. This paper reports the results of the opinion of the TEP to improve appropriate use of VS with HA in clinical practice.

Materials and Methods

The TEP paid great attention to achieving consensus through rigorous scientific methodology. A Systematic Literature Review (SLR) was conducted by a librarian and the papers retrieved were analyzed and weighed by a data extraction form. The steering committee of the TEP (A. Migliore-Scientific Coordinator & Steering Committee, R. Bannuru, X. Chevalier, D. Diracoglou, C. Matucci-Steering Committees) selected 19 statements that were discussed in a first plenary meeting (Lisbon November 2019). During the meeting, the TEP defined 21 statements that were weighed and discussed in two rounds of a Delphi survey; the results, including any disagreements, were further discussed in a final plenary session (Lugano February 2020) where final agreement was reached on the statements.

Systematic Literature Research

The SLR explored the use of HA in all joints affected by OA to identify predictors of a positive or negative clinical response. The steering committee of the TEP identified the clinical questions for the SLR, formulated in the Patient, Problem or Population/Intervention/Comparison, control or comparator/Outcome(s) (PICO) [Timing, duration or date of publication (T)/Study type (S)] format. Table 1 shows the structure of the PICO research.

The following databases were interrogated: Medline, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grey Matters (<http://www.cadth.ca/>), and American College of Rheumatology (ACR)/EULAR abstracts. The research

Table 1 Formulation of Clinical Questions in PICO Format

P	Human Patients, Adults, Osteoarthritis
I	Hyaluronic acid, infiltrations, viscosupplementation or hyaluronic acid 0.8%, 1.6%, 2%, 800–1200 kDa, 3.2% (1400–2100 kDa/65–110 kDa), infiltrations, viscosupplementation
C	–
O	All

included only studies on adults, humans, without limitations of language or time of publication, this to minimize any risk of bias due to the above factors. An ad hoc extraction module collected the data from the individual studies. The extraction module considered: author, year, publication type, study design and structure, inclusion/exclusion criteria, number of participants, the definition of OA, type of HA formulation [HA 0.8%, HA 1.6%, HA 2%, 800–1200 kDa, HA 3.2% (1400–2100 kDa/65–110 kDa)], a summary of findings. The studies retrieved were reviewed by the panelists who selected a subgroup of studies that were considered worthy of further assessment. Both quantitative and qualitative synthesis of data was performed (Figure 1). The characteristics of the populations enrolled in the selected studies were analyzed with a special focus on patients' subgroups displaying a high or low response rate to VS. Two experts provided each an independent revision of the study: any disagreements were submitted

to a third expert. The quality of the selected papers was assessed by two independent experts using the 2018 version of the Mixed Method Appraisal Tool (MMAT); the appropriateness of study aim, methodology, design, data collection and analysis, and presentation of findings were evaluated.¹⁴

Results

After exclusion of duplicates, the SLR retrieved 385 studies, 25 of which were considered suitable for analysis. The studies were first examined for the exclusion and inclusion criteria. The process of SLR, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement¹⁵ with the number of studies retrieved, excluded, and selected is shown in Figure 1. The quality of the included studies was critically evaluated using the MMAT with scores summarized in Table 2. Tables 3 and 4 summarize the main features of the selected studies.

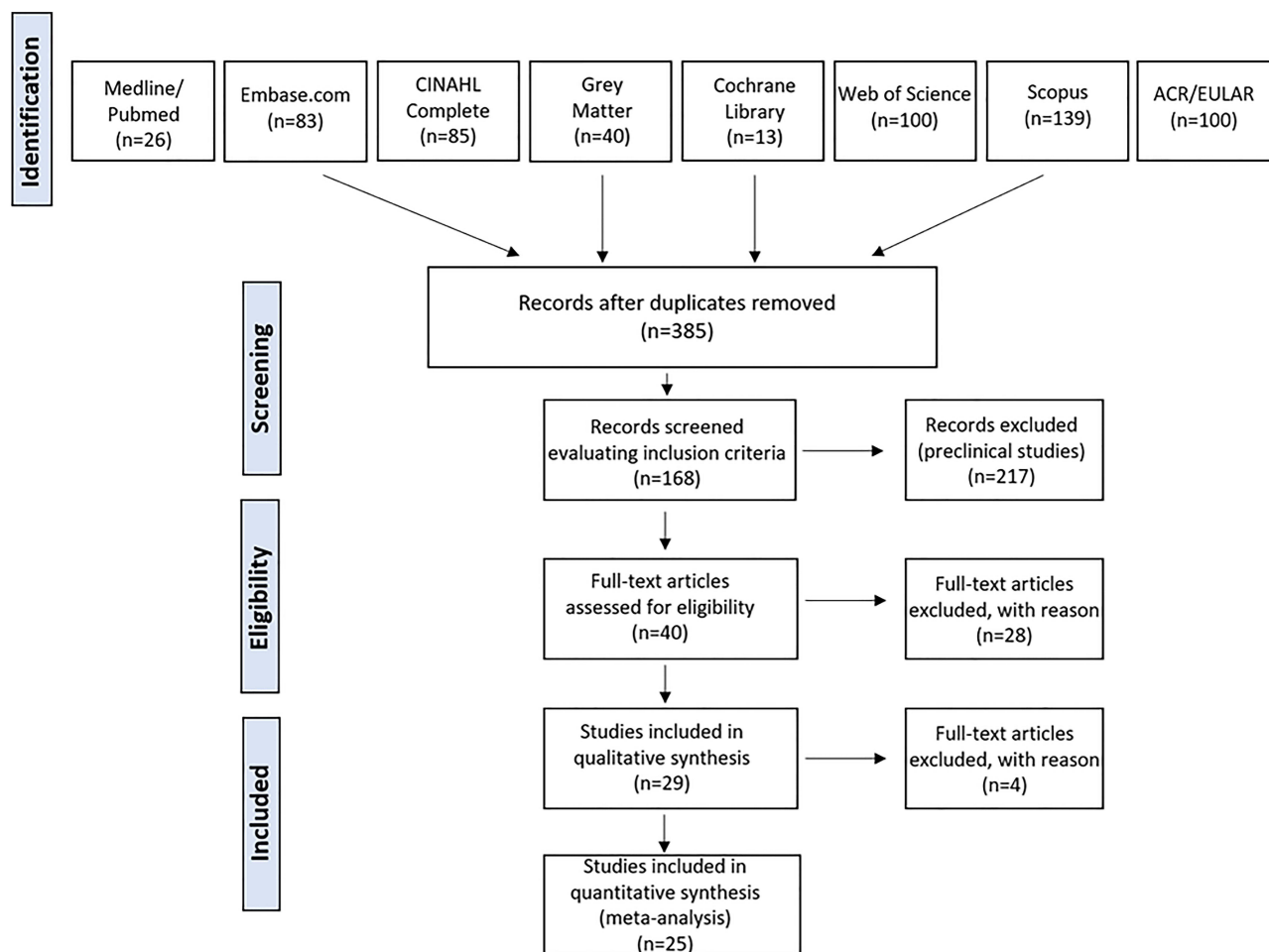


Figure 1 Selection of papers during the SLR.

Table 2 Calculated MMAT Scores for Studies Included in This Systematic Review

Study	MMAT Score
Castellacci 2004 ¹⁶	4
Depont 2004 ⁴⁶	3
Theiler 2005 ¹⁷	5
Pavelka 2011 ²²	5
Polacco 2013 ¹⁸	5
Bottegoni 2014 ²⁰	5
Papalia 2016 ¹⁹	4
Abate 2017 ²⁵	5
Papalia 2017 ²¹	4
Galluccio 2021 ⁴⁷	5
Manciameli 2018 ³⁵	4
Migliore 2018 ⁴⁸	5
Papalia 2019 ²³	5
Migliore 2012 ²⁴	5
Lürati 2015 ³²	3
Abate and Salini 2017 ²⁵	5
Abate 2014 ²⁶	5
La Paglia 2017 ²⁷	5
Busilacchi 2011 ²⁹	3
Gigante 2013 ²⁸	5
D'Avola 2013 ³⁴	3
Bartoloni 2019 ³³	4
Tenti 2017 ³¹	5
Callegari 2011 ³⁶	5
Roux 2007 ³⁰	5

Analysis of the Inclusion/Exclusion Criteria

The analysis of the inclusion/exclusion criteria for each OA localization was the basis for the generation of the statements, which were subjected to two rounds of the survey using the Delphi method. In analyzing the exclusion criteria, the TEP considered that some of them (eg localization and concomitant pathologies) were intended to select the most suitable patients. In contrast, others (eg pharmacological treatments and previous VS procedures) were aimed at allowing a correct evaluation of efficacy. The TEP considered separately knee OA and OA in other joints. The inclusion/exclusion criteria reported in most relevant studies, or recurring more frequently, are commented below; additional criteria are provided in the above [Tables 3 and 4](#).

Knee OA

Inclusion Criteria

Age between 18 and 82 years and symptomatic knee OA confirmed by X-rays were the inclusion criteria defined by Castellacci.¹⁶ Theiler¹⁷ considered age between 18 and 85

years; pain on walking >30 mm measured by a 100 mm Visual Analogue Scale (VAS). Polacco¹⁸ included patients with symptomatic knee OA with a Western Ontario Mc Master University (WOMAC) score between 0 and 15 (mean 8.8) and with OA of Kellgren & Lawrence (KL) grades from II to III. As for concomitant administration/ comparison to Platelet Rich Plasma (PRP), Papalia¹⁹ compared HA 3.2% with PRP in a particular set of patients (professional soccer players) with lower age, from 34 to 39. Bottegoni²⁰ included patients above 65 years only. Another study by Papalia²¹ considered patients with symptoms lasting for more than three months and with OA of KL grades I to III.

Exclusion Criteria

Castellacci¹⁶ excluded patients with local or systemic inflammatory conditions; Theiler¹⁷ considered exclusion criteria chondrocalcinosis, gout, crystal arthropathy, excessive joint effusion, severe axis deviation or other inflammatory diseases (Paget disease, history of knee surgery or intraarticular steroid injection in the last three months, chronic assumption of steroids). BMI > 32, secondary OA and KL grade IV hip OA were among the exclusion criteria defined by Pavelka.²² For the evaluation of efficacy, the most common exclusion criteria were the use of systemic steroids and SySADOAs in the last three months and VS and treatment with IA steroids before enrollment.^{17,18,20,22} The TEP also considered studies comparing HA with PRP or association of HA with PRP. Such studies excluded patients below 45 or above 75 years. Additional exclusion criteria were medical conditions contraindicating the use of PRP, especially alterations of coagulation or immunodepression (see [Table 2](#)).^{19,23}

Other Joints

Inclusion Criteria

For hip OA, a cohort study of 114 patients included patients aged >40 years, with symptomatic hip OA according to the American College of Rheumatology (ACR) criteria, and KL grades II or III.²⁴ Abate and Salini²⁵ selected patients with KL II and III, clinically symptomatic for more than three months. For hip impingement, the pain was the most common inclusion criterion.^{26,27} For shoulder localizations, Gigante²⁸ included patients aged between 35 and 70 years, affected by shoulder impingements of various degrees from bursitis to eccentric OA. In the study by Busilacchi,²⁹ the inclusion criteria allowed patients with cuff pathology of grades I–IV of Neer's

Table 3 Results of Systematic Literature Research for HA in the Treatment of Knee OA

First Author Year Design	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Castellacci ¹⁶ 2004, Observational, retrospective.	18–82 years with primary or secondary symptomatic Knee OA (confirmed by X rays < 1 year before enrolment).	Acute synovitis, joint effusion, knee prosthesis, RA or other inflammatory diseases, severe osteoporosis, skin disease near the inj. site.	Patients: 40 Treatment: HA 0.8% Procedure: Weekly IA inj. for a total of 5 inj.	None.	Tolerability, LI (baseline, 3, 5 weeks and final visit), pain level, analgesic consumption with follow up at seven weeks.	Tolerability excellent/good- LI from 7.9 to 3.2 at the final visit, similar decrease for pain.
Depont ⁴⁶ 2004, Observational, retrospective.	>20 years knee OA treated with HA 0.8% between Jan. 1, 2003 and Mar. 31, 2003 never treated previously with VS.	Not reported.	Patients: 408 Treatment: HA 0.8% Procedure: IA inj.	None.	Pain at Likert scale, tolerability, consumption of NSAIDs, analgesics and gastro protectors. Total of 12 months.	64.5% of the patients reported improvement of function—better improvement in patients with low BMI and < 5 years Knee OA. The lack of treatment with NSAIDs before injections was also associated with a better response.
Theiler ¹⁷ 2005, Prospective, open-label.	18–85 years, symptomatic knee OA (KL II–I), pain on walking > 30 mm at 100 mm VAS.	Chondrocalcinosis, crystal arthropathies, synovitis or effusion, axis deviations, arthritis, metabolic diseases of the bone, symptomatic hip OA, knee surgery or IA injection of steroids in the last three months, steroid therapy.	Patients: 63 Treatment: HA 0.8% Procedure: weekly IA inj. of HA 0.8% for five consecutive weeks.		Primary endpoint: AE; secondary endpoint WOMAC score, additional follow up at 19 weeks.	WOMAC score was significantly reduced within the first two weeks of treatment, further decreased by the end of the inj. series (week 6) and maintained during the follow-up (week 24). WOMAC subscores significantly decreased from week 4 for “pain” and from week 6 for “stiffness” and “physical function”. Most frequent AE was pain at the inj. site (5.8% of the inj.).

(Continued)

Table 3 (Continued).

First Author Year Design	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Pavelka ²² 2011 RCT.	40–81 years with symptomatic knee OA (KL grades II–III), non-responder or intolerant to analgesics and/or NSAIDs. Mean WOMAC pain sub-score >40mm and <80mm, and <30mm in the contralateral knee.	BMI > 32, secondary OA, femoral patellar OA, KL -IV, hip OA, varus/valgus deformity, arthritides, rheumatic disease, previous knee injury or surgery, allergy to HA. Venous or lymphatic stasis, systemic or IA steroids, concomitant SySADDA, anticoagulant or pain killers.	Patients: 192 Treatment: HA 0.8% Procedure: 1 IA inj. weekly for three weeks.	Patients: 189 Treatment: HA 16mg/2mL Procedure: 1 IA inj. weekly for three weeks	Follow up at 4, 12 and 26 weeks. Primary endpoint: WOMAC Index pain subscore at 26 weeks. Secondary endpoints: Stiffness and function LI, PGA.	HA 0.8% and HA 16mg/2mL treatments were equivalent, both in terms of efficacy and safety.
Polacco ¹⁸ 2013. Open-label, double-blind.	Symptomatic knee OA, classified into moderate, severe and very severe according to WOMAC Index and the KL scales.	Use of systemic steroids or SySADDA within the previous three months; IA inj. of steroids or HA within three months. Sepsis or arthritides.	Patients: 21 (24 knees) Treatment: HA 2% Procedure: 1 IA inj.	None	Primary endpoint: WOMAC score. Secondary outcomes: 1) Pain at rest; 2) Walking distance increase; 3) joint range increase; 4) walking upstairs 5) walking downstairs. At 30, 60, 90, and 120 days.	At four months, there was an improvement in clinical parameters in 77.6% of the 24 treated knees, particularly in patients with moderate and severe OA (improvement in 100% and 66.7%, respectively).
Bottegioni ²⁰ 2014, Observational.	>65 years; moderate or severe knee OA.	Not reported.	Patients: 60 Treatment: HA 1.6% Procedure: 3 inj.	Patients: 60 Treatment: PRP Procedure: 3 inj.	Knee Injury, KOOS score, EQ-VAS baseline, 2 and 6 months.	Significant improvement in both groups Better results of PRP than HA 1.6% at two months; better results of HA 1.6% at six months. Worst results in aged > 80 and higher grade of OA (in this class better results of HA 0.8%).
Papalia ¹⁹ 2016, RCT.	Professional soccer players with unilateral pain not responsive to conservative treatment.	Haematological diseases, previous knee surgery, NSAIDs or steroids within two weeks, recent fever, infections, cancer.	Patients: 24 Treatment: HA 3.2% (1400–2100 kDa/65–110 kDa) Procedure: 3 IA inj.	Patients: 24 Treatment: PRP 5.5 mL Procedure: 3 IA inj.	IKDC score, KOOS score, pain assessment by VAS at baseline, 3–6–12 months.	Good response in both groups at three and six months, better response in HA 3.2% (1400–2100 kDa/65–110 kDa) group but a non-significant difference at 12 months.

Abate and Salini ²⁵ 2017, Observational.	Symptomatic Knee OA (KL I-II-III) for more than three months.	Knee surgery, recent trauma, lower limb length discrepancy, rheumatic pathologies, systemic endocrinopathies, systemic diseases. IA injection or treatments with steroids or NSAIDs within the previous three months.	Patients: 15 Treatment: HA 1.6%, HA 2% Procedure: Weekly IA inj. of HA 1.6% for three weeks. Then, at 4, 8 and 12 months, one inj. of HA 2%.	None.	Pain at rest and during activities, LI, KOOS score, and monthly NSAIDs consumption. Follow up at 1, 4, 6, 8, 12 and 14 months, and patient satisfaction (five-points Likert scale).	Persistent positive results in terms of reduced pain and improved function.
Papalia ²¹ 2017, RCT.	Knee OA Patients with BMI > 30, KL> III, not responsive to conservative treatments. No-inj. treatment.	Previous knee surgery or IA inj., knee instability, axial deformity, osteochondral lesion, general or haematological disorders.	Patients: 24 Treatment: HA 3.2% (1400–2100 kDa/65–110 kDa) Procedure: 2 IA inj.	Patients: 24 Treatment: HA 1.6% Procedure: 2 IA inj.	IKDC score, pain assessment by VAS at baseline, 3 and 6 months.	HA 3.2% (1400–2100 kDa/ 65–110 kDa) improved function and pain of the knee, the treatment with a hybrid HA showed better outcomes than high molecular weight HA in obese patients.
Galluccio ⁴⁶ 2017, Prospective comparative.	Patients with KL grades I/II Knee OA.	Not reported.	Patients: 30 Treatment: HA 2% Procedure: 1 IA inj.	Patients: 30 Treatment: HA 20mg/ 2mL; Procedure 5 IA inj. Patients: 30 Treatment: HA 1.6% Procedure 3 IA inj.	WOMAC score, NHS and social costs.	The three treatments resulted equally effective without statistically significant differences. HA 2% is as clinically effective as the other two regimens but with a very efficient efficacy/cost profile.

(Continued)

Table 3 (Continued).

First Author Year Design	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Manciameli ³⁵ 2018, Observational.	Symptomatic Knee OA confirmed by X rays.	Systemic or local infections, local inflammation or skin diseases near the inj. site.	Patients: 35 Treatment: HA 3.2% (1400– 2100 kDa/65– 110 kDa) Procedure: 2 IA inj. 2 weeks apart.	None.	Pain measured by VAS, WOMAC score, ROM, NSAIDs or analgesics consumption at baseline and 1–3–6 months	The results are long-lasting with good outcomes also over six months, with reduction of VAS pain, WOMAC total score, consumption of NSAIDs and improvement of ROM.
Migliore ⁴⁸ 2018, Observational, retrospective.	≥ 18 years active football players; symptomatic Knee OA confirmed by X rays (KL grades I–II)	Arthritis < 18 years. Allergy to HA.	Patients: 17 Treatment: HA 0.8% Procedure: 1 inj. at time T0, one after two weeks.	None.	Pain measured by VAS at time 0, 1 and 2 days after the 1st injection; at two weeks; 1 and 2 days after the 2nd inj., and at 4, 12, and 24 weeks. LI and PGA assessed at baseline, at 1, 4, 12, and 24 weeks.	The use of HA 0.8% in football players affected by knee OA seems efficacious and safe and resulted in a stable improvement of the symptoms.
Papalia ²³ 2019, RCT.	40–70 years with Knee OA (KL II and III), not responsive to pharmacologic treatment, rehabilitation, or physical therapy.	<45 >70 years KL >III, diabetes, RA, previous IA injections, cardiovascular diseases, coagulopathies, immunodepression, varus > 20° or valgus > 20° morphotype.	Patients: 30 Treatment: HA 3.2% (1400– 2100 kDa/65– 110 kDa) Procedure: 3 inj.	Patients: 30 Treatment: HA 3.2% (1400– 2100 kDa/65– 110 kDa) plus PRP Procedure: 3 inj.	KOOS score, pain assessment by VAS at baseline, 3–6–12 months.	PRP and HA 3.2% (1400–2100 kDa/65–110 kDa) are safe and resulted in being more effective than HA 3.2% (1400–2100 kDa/65–110 kDa) injective therapy alone.

Abbreviations: Inj, injection(s); KL, Kellgren-Lawrence; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; HA, Hyaluronic Acid; IA, Intra Articular; LI, Lequesne Index; NHS, National Healthcare Service; NSAID, Nonsteroidal anti-inflammatory drug; OA, Osteoarthritis; PGA, Patient's Global Assessment; PRP, Platelet Rich Plasma; RA, Rheumatoid Arthritis; ROM, Range of Motion; WOMAC, Western Ontario and Mac Master University score.

Table 4 Results of Systematic Literature Research for HA in the Treatment of OA in Other Joints

First Author Year Design	Joint (Condition)	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Migliore ²⁴ 2012, Observational Prospective.	HIP (OA).	>40 years; symptomatic hip OA (ACR criteria); KL grade II or III.	Oral anticoagulant; no articular space; previous IA CS or HA; significant co-morbidities; allergy to HA and systemic CS.	Patients: 114 Treatment: HA 1.6% Procedure: 4 mL (2 vials) IA inj.	None.	Follow-up every three months, for a total of 6 months (pain VAS), LI score, NSAID use AEs.	Statistically significant reduction in LI score, VAS pain score and NSAID intake were observed at all time-points ($p < 0.05$). No systemic, severe, or even moderate side effects were observed.
Lurati ³² 2015, Observational.	KNEE AND HIP (OA).	Bilateral knee or hip OA (ACR Criteria), with a 2 and 3 KL and Pain VAS ≥ 50 .	RA or other arthritides, pregnancy, allergic to HA, knee, or skin infections. Polyarticular OA.	Patients: 24 knee; 13 hip Treatment: HA 1.6% Procedure: 3 inj. at weekly intervals.	Patients: 35 knee and 14 hip OA; 24 healthy subjects Treatment: None Procedure: None.	Flow cytometry was performed from blood samples to assess T cells subpopulations at baseline and 3-months visit.	The presence of activated T cells confirms that OA is a disease with an immunological- inflammatory involvement. These preliminary results seem to show that HA 1.6% could lower the levels of activated T cells, and thus regulate the articular milieu.
Abate and Salini ²⁵ 2017, Observational retrospective.	HIP (OA).	Patients with moderate-severe hip OA (K-L grades II– IV), symptomatic for more than three months.	Recent hip trauma; IA CS, HA, or PRP and/or oral CS or NSAIDs within the previous three months (paracetamol allowed); rheumatic pathologies, and severe systemic diseases (renal, hepatic, cardiac, etc.).	Patients: 20 Treatment: HA H-L 3.2% (HMMW 1400–2100 kDa- LMW 65–110 kDa) Procedure: US- guided IA inj. 2 mL HA H-L 3.2% (HMMW 1400–2100 kDa- LMW 65–110 kDa) at baseline and after 40 days.	Patients: 20 Treatment: HMMW HA Procedure: US-guided IA inj of 2 mL HA at baseline and after 40 days.	Demographic and anthropometric data, pain at rest and during activities in the previous week VAS, Lequesne Index (LI), HHS, and monthly consumption of NSAIDs baseline, 3 and 6 months.	Combination of LMW and HMMW HA provides better therapeutic results in comparison with HMMW HA. In both groups at 3 and 6 months, VAS scores at rest and during activities decreased significantly, as well as disability (LI) with an improvement of HHS; better results were observed in patients treated with the new hybrid compound, both in terms of pain and improved function.

(Continued)

Table 4 (Continued).

First Author Year Design	Joint (Condition)	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Abate ²⁶ 2014, Open prospective.	HIP (IMPINGEMENT).	Pain for at least three months, as determined by the hip impingement test; in patients with cam FAI (angle $\geq 55^\circ$).	A-angle $\leq 55^\circ$; age > 55 years, history of hip disease (slipped capital femoral epiphysis, Perthes disease, osteotomy, dysplasia), hip surgery, evidence of radiographic hip OA and previous IA injection with CS.	Patients: 20 Treatment: HA 1.6% Procedure: 1 inj. at baseline and after 40 days; same dosing schedule repeated after six months.	None.	Demographic, anthropometric, and clinical data, pain VAS during the previous week, LI, HHS and monthly consumption of NSAIDs (baseline, 6 and 12 months).	HA 1.6% is safe and effective in the treatment of mild femoral- acetabular impingement, with significant pain reduction and function improvement.
La Paglia ²⁷ 2017, Retrospective.	HIP (IMPINGEMENT).	Femoro- acetabular impingement (FAI).	Group I: rheumatic diseases, allergy to HA, recurrent infections, pregnant or lactating patients; besides, for control Group: platelet function disorder, thrombocytopenia, hypofibrinogenemia, septicaemia, history of cancer; HGB < 10 g/dl, platelet count < 105 .	Patients: 16 Treatment: HA 2% Procedure: 1 US-guided injection.	Patients: 16 Treatment: HA 3.2% (1400–2100 kDa/ 65–110 kDa) and PRP Procedure: 1 US-guided inj.	HOOS questionnaire with pain score and function assessed before treatment (T0), at 2 (T1) and 6 (T2) months after treatment. All patients were evaluated by MRI and/or MRA before treatment (T0) and at 2 (T1) and 6 (T2) months after treatment.	Combined hf-HA 3.2% (HMW 1400–2100 kDa-LMW 65–110 kDa) + PRP IA shows early and lasting improvement in younger patients with a low-grade chondropathy. The combined treatment proved to be more effective vs the HMW HA treatment at T1 and T2 ($P < 0.05$). Follow-up in the mild grade arthropathy group and 75% of the high-grade arthropathy group revealed a significant clinical improvement and MRI. In the very high-grade arthropathy group, the combined treatment produced a clinical improvement in only 15% of patients, with MRI stability and similar results in both hf-HA + PRP IA therapy and HMW HA IA therapy.

Busilacchi ²⁹ 2011, Prospective non controlled.	SHOULDER (CUFF PATHOLOGY).	Cuff pathology four groups (Neer classification) with an added fourth group (cuff tear arthropathy).	Not reported.	Patients: 100 Treatment: HA 0.8% Procedure: 3 US-guided inj, one every 15 days.	None.	Follow up every 15 days (T0, T15, T30, T45 e T90), using VAS, OSS and Constant-Murley score.	In grades I and II, at day 30 of FU, a significant reduction of VAS and an increase in Constant-Murley and OSS were recorded. In grade IV, benefits were recorded for the first 45 days, while OSS and Constant Murley scores did not show any improvement.
Gigante ²⁸ 2013 Prospective, open-label, non- controlled.	SHOULDER (PAIN).	Shoulder pain and reduction of ROM, allocated to 4 groups (Neer's classification). X-ray and MRI performed.	<30 or >80 years, shoulder instability, SLAP lesions, arthritis, shoulder trauma, adhesive capsulitis/calcific tendonitis, previous subacromial injection therapies, diabetes, major depressive syndrome.	Patients: 100 Treatment: HA 0.8% Procedure: 1 US-guided inj. through the anterolateral way, one inj. every two weeks.	None.	Follow-up at 0, 15, 30, 45 and 90 days. VAS, OSS and Constant-Murley score.	In grades I and II, at day 45, a significant reduction of VAS and an increase in Constant- Murley and OSS scores were observed. In grade IV, VAS slowly decreased in the first 45 days, while OSS and Constant Murley scores did not improve significantly. Grade III patients had no clinical and subjective benefits. In grades I, II, and IV, the beneficial effect was still maintained at 90 days.
D'Avola ³⁴ 2013, Retrospective.	HAND (CMC OA).	49–70 years, diagnosis of rhizarthrosis.	Not reported.	Patients: 52 Treatment: HA 0.8% (800–1200 kDa) Procedure: 1 US-guided inj./ month for six months received only the IA HA.	Patients: 29 Treatment: HA 0.8% (800–1200 kDa), and oral CS 800 mg/ day Procedure: 1 US guided inj. /month for 6 months CS 800 mg/day for 90 days.	Pain VAS at baseline and 1, 3 and 6 months after the first injection. One month after the end of treatment 6-point Likert scale as a secondary endpoint. Compliance and AE.	The IA injections of HA 0.8% (MW 800–1200 kDa) produced significant relief from pain by restoring the joint function during the whole follow-up. A more marked reduction of symptoms was observed in patients concomitantly treated with US-guided injection of HA and oral CS.

(Continued)

Table 4 (Continued).

First Author Year Design	Joint (Condition)	Inclusion Criteria	Exclusion Criteria	Patients Treatment Procedure	Control	Assessment	Results
Bartoloni ³³ 2019, Prospective pilot study.	HAND (CMC OA).	Symptomatic CMC OA; pain ≥40 VAS; KL evaluation.	Arthritides, major trauma, NSAIDs or HA and corticosteroid IA inj. within the previous month.	Patients: 12 Treatment: HA 3.2% (1400– 2100 kDa/65– 110 kDa) Procedure: 2 US-guided inj.	None.	Pain on the VAS scale and DASH questionnaire were recorded at T0 and 1, 3 and 6 months.	Reduction of pain and improvement of hand function. Efficacy on articular function was evident as early as the first month and persistent at six months of follow-up.
Tenti ³¹ 2017, Retrospective comparative.	HAND (CMC).	45–75 years, CMC OA, pain score >30 mm on VAS and a FIHOA score >6. Hand OA KL grades II and III.	Arthritides, septic arthritis, trauma or prior surgery of the hand, wrist, and elbow, coagulation disorders, severe co-morbidity. Patients taking SySADOAs, steroids and IA injection of any joint with HA during the previous six months.	Patients: 55 Treatment: HA 3.2% (1400– 2100 kDa/65– 110 kDa) Procedure: 2 inj. TO and after 15 days.	Patients: 45 Treatment: 0.5 mL of triamcinolone acetoneide intraarticular. Procedure: 2 inj.: baseline and after 15 days.	The primary outcome criteria were the change of global hand pain VAS and FIHOA from baseline to month 6. Secondary outcomes were the change of the duration of morning stiffness, HAQ and SF 36 from T0 to month 6.	The hybrid formulation of HA may be more effective than triamcinolone in pain relief and joint function improvement with a rapid and persistent effect, resulting as a valid alternative to steroids in the management of CMC OA.
Callegari ³⁶ 2011, Open-label, randomised study.	HAND (TRIGGER FINGER).	35 and 70 years with US- confirmed diagnosis of trigger finger.	Patients with grade IV TF or diabetes mellitus; RA; hypercholesterolaemia; hypotension; and hypertension.	Patients: 15 Treatment: HA 0.8% Procedure: MPA 40 mg/mL with 0.8mL lidocaine into the flexor sheath plus inj. of 1mL HA 0.8% ten days later.	Patients: 15 Treatment: Surgery Procedure: Surgical release of the first annular pulley.	DASH questionnaire, satisfaction VAS, pain VAS, before treatment and after six weeks, and 3, 6, and 12 months.	Fourteen patients (93.3%) in the treatment group showed a complete symptom resolution at six months, which persisted for 12 months in 11 patients (73.3%); 3 patients experienced recurrences and 1 reported no improvement. The 15 patients in the control group achieved complete resolution by three weeks after surgery; of these, ten patients needed physiotherapy or analgesics for a complete resolution of the symptoms.

Roux ³⁰ 2007, Prospective randomised.	HAND (CMC OA).	VAS < 40 and refractory to other treatment. CMC OA KL grades II to IV, and met ACR criteria for hand OA.	Symptomatic OA in any other digit, use of steroid injection in the previous six months and previous use of HA injection. Subjects with blood coagulation abnormalities, infection, and hand trauma.	Patients: 42 Treatment: HA 0.8% Procedure: allocated to 4 groups: Group 1 (1 inj.); group 2 (2 inj.); and group 3 (3 inj.) at weekly intervals.	None.	Pain on a 100-point VAS. DFA Index for hand OA. Prospective follow-up parameters were pain, tolerability, and function at T0, 1 and 3 months.	No significant differences were found between each group for pain relief and function. However, the intra groups analysis results showed that IA injections into the thumb in OA could be efficacious on pain and function.
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Abbreviations: ACR, American College Rheumatology; CMC, Carpometacarpal joint; CS, Chondroitin sulfate; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; DFA, Dreiser Functional Index; FAI, Femoral-Acetabular Impingement; FHOA, Functional Index for Hand Osteo Arthritis score; HA, Hyaluronic Acid; hHA, hybrid form Hyaluronic Acid; HHS, Harris Hip Score; IA, Intra articular; HAQ, Health Assessment Questionnaire; KL, Kellgren-Lawrence; MRI, Magnetic Resonance Imaging; MPA, Methylprednisolone acetate; OA, Osteoarthritis; OSS, Oxford-Shoulder-Score; RA, Rheumatoid Arthritis; TF, Trigger Finger; CMC, Carpometacarpal Joint; US, Ultrasound.

classification without indication of age. For hand localizations, Roux³⁰ set as inclusion criteria for his study on the carpal metacarpal joint (CMC) a pain score <40 mm measured by a 0–100 mm VAS and lack of response to other treatments. Tenti³¹ included patients aged between 45 and 75 years of age, with hand pain scores >30 mm (VAS 100 mm), with Functional Index for Hand OA (FIHOA) >6 and OA of KL grades II–III.

Exclusion Criteria

For hip OA, in a large cohort study,²⁴ patients with KL grade IV, systemic co-morbidities (rheumatological disease, low back pain, femoral head osteonecrosis), obliteration of intra-articular space, previous intake of oral steroids, VS with HA, or steroids in the hip were excluded. In a retrospective observational study, Lùrati³² excluded patients with rheumatoid arthritis or other rheumatic diseases, current knee infection or skin infection around the injection site. Abate and Salini²⁵ excluded patients with recent hip trauma, rheumatic or other severe systemic diseases, IAHA, steroids or PRP. Low back pain was an exclusion criterion in different studies.^{24,25,32} In hip impingement, Abate²⁶ excluded patients with other hip pathologies, hip surgery or IA treatments. La Paglia²⁷ compared HA 2% alone to the combination of HA 3.2% (1400–2100 kDa/65–110 kDa) and PRP. The exclusion criteria for HA were rheumatic diseases, history of allergy to HA, recurrent systemic or local infections, pregnancy, or lactation. For the patients treated with HA 3.2% (1400–2100 kDa/65–110 kDa) and PRP, additional exclusion criteria were platelet or coagulation disorders, anemia, septicemia, and previous malignancy.

For shoulder OA, in his study on pain, Gigante²⁸ excluded patients under 30 and over 80 years of age with shoulder instability, Superior Labral Tear from Anterior to Posterior (SLAP) lesions; rheumatoid arthritis, amyloidosis, chondrocalcinosis, gout, rheumatological diseases; shoulder trauma within the last year; adhesive capsulitis/calcific tendonitis, previous subacromial injections; diabetes, depression.

For hand OA (CMC), in an RCT comparing HA 3.2% (1400–2100 kDa/65–110 kDa) with IA steroids, Tenti³¹ excluded patients with a history of any inflammatory joint disease, septic arthritis, major trauma or prior surgery of the hand, wrist and elbow, coagulation disorders, severe co-morbidity and those who underwent therapy with chondroitin sulfate, glucosamine, diacerein, steroids by any

route of administration and IA injection of any joint with corticosteroids or HA during the previous six months.

Statements to Be Discussed

Considering the results of the SLR, the steering committee proposed 19 statements and three assessment domains. During the first TEP meeting, the scientific evidence retrieved was presented and discussed. At the end of the meeting, the TEP defined a questionnaire composed of 25 statements grouped into three domains.

The questionnaire was discussed in two rounds of Delphi survey to find an agreement among the participants. The agreement with each statement was defined according to the RAND/UCLA criteria, with a vote from 1 (total disagreement) to 9 (total agreement). The agreement and disagreement among the experts were defined as follows: agreement if 80% of the 14 panelists' ratings were concentrated in one of the 3-point regions (1–3; 4–6; 7–9); disagreement if 90% of the 14 panelists' ratings were spread across one of the two extra-wide regions (1–6 or 4–9).

The whole process was carried out using a web platform. The results of the questionnaire were discussed by the TEP during the second plenary meeting. Unanimity was reached in the domains, and 21 items (Table 5) were selected.

Patients' Features: Characteristics of the Patient to Be Considered Before Planning the VS

The TEP agreed that VS provides the best results in patients with primary and secondary knee and hip OA of KL grades I to III. The TEP pointed out the importance of considering that the efficacy of VS is influenced not only by the severity of the condition (eg KL grade) but also by the phenotype of the patient. Patients with OA of KL grades II and III without malalignment or dissymmetry and with BMI < 30 can be successfully treated; on the other hand, in case of severe malalignment of the extremity, instability in the affected joint and meniscal lesion, the outcome of VS could be less favorable.

The TEP also agreed on further advice concerning specific localizations:

Knee: The TEP considered that VS is possible in patients with knee OA of KL grade IV in selected cases: i) persistent, localized knee pain ii) BMI < 30 iii) walking limitation iv) pain when squatting v) patients who failed to respond sufficiently to analgesics and/or NSAIDs taken regularly vi) patients who responded well but who were

unable to tolerate analgesics and/or NSAIDs vii) absence of malalignment viii) absence of lower limbs dissymmetry.

Hip: Patients with hip OA of KL grades II, III, without malalignment, lower limbs dis-symmetry or with BMI < 30 could be treated. The TEP recommended excluding patients with hip OA of KL grade IV confirmed by X-rays, overweight (BMI > 30), with malalignment or lower limb dis-symmetry.

CMC: The TEP concluded that patients with CMC OA of KL grades I-II-III can be treated. VS with HA can be considered in patients with CMC OA of KL grade IV confirmed by X-rays only in selected cases: patients aged between 50 and 75 years with clinical manifestations for more than three months, defined as global hand pain score more than 30 mm on a 0–100 VAS and a Functional Index for Hand OA (FIHOA) score >6.^{31,33,34}

Conditions That are Linked to Increased Risk of Failure

The TEP discussed cases in which VS is contraindicated, or there may be an increased risk of failure. VS with HA and other HA preparations is contraindicated in case of hypersensitivity to HA, in systemic septic conditions, in cutaneous diseases or infection in the area surrounding the injection site. VS is not indicated in patients assuming double antiaggregant or New Oral Anti Coagulants (NOACs). However, some clinicians suggest that during treatment with NOACs, the injection in the knee is possible in the hands of a skilled, senior physician. VS is also contraindicated if the joint is affected by severe inflammation, active or occurring in the previous 3–6 months. Other conditions in which VS is not indicated are active inflammatory arthropathies (rheumatoid arthritis, psoriatic arthritis) and crystal arthropathies (chondrocalcinosis, gout, etc.), accompanied by synovitis. After reviewing the evidence and considering the clinical experience of the panelists, the TEP agreed that VS could be performed in case of isolated femoro-patellar syndrome or severe varus/valgus deformity in the target knee. The clinician should, however, be aware that these conditions are linked to an increased risk of failure.

Conditions in Which VS is Considered Appropriate

The TEP discussed the conditions occurring in daily clinical practice in which VS with HA can be considered appropriate, ie conditions when VS provides specific advantages to patients. This is because, in RCTs, the study population consists of “ideal” patients, without co-

Table 5 Domains and Items Approved After Discussion

Domain	Item	Aggregation (%)		
		7–9	4–6	1–3
1	Patients features. Characteristics of the patient to be considered before starting the VS.			
1.1	Patients affected by primary OA can be a candidate to VS with HA	100	0	0
1.2	Patients affected by secondary OA can be a candidate to VS with HA	100	0	0
1.3	Patients with X-ray KL grades I–II–III are the better categories of patients affected by OA of the knee to treat with HA	92.9	7.1	0
1.4	In patients with X-ray KL grade IV affected by knee OA HA can be used in selected cases.	85.7	14.3	0
1.5	Patients with X-ray KL grades I–II–III hip OA are the most suitable patients for VS with HA	85.7	14.3	0
1.6	Patients affected by OA of the CMC with X-ray KL grades I–II–III–IV can be treated with HA	71.4	28.6	0
2	Risk of failure (Conditions and contraindications that are linked to increased risk of failure)			
2.1	An isolated femoral patellar syndrome at the target knee is a condition linked to increased risk of failure.	64.3	28.6	7.1
2.2	Severe varus/valgus deformity in the target knee is a condition linked to increased risk of failure.	71.4	21.4	7.1
2.3	Viscosupplementation with HA is not indicated in active arthritides with acute synovitis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, etc.).	85.7	14.3	0
2.4	Viscosupplementation with HA is not indicated in crystal arthropathies with acute synovitis (eg chondrocalcinosis, gout, etc.).	100	0	0
2.5	Viscosupplementation with HA is not indicated in patients with active systemic sepsis.	100	0	0
2.6	Viscosupplementation with HA is contraindicated in patients with septic knee arthritis within the previous 3–6 months.	92.9	7.1	0
2.7	Viscosupplementation with HA is contraindicated in patients with hypersensitivity to HA.	92.9	7.1	0
2.8	Viscosupplementation with HA is contraindicated in the presence of an infected or seriously inflamed joint.	100	0	0
2.9	Viscosupplementation with HA is contraindicated in patients with cutaneous disease or infection in the area of the injection site.	92.9	7.1	0
2.10	Viscosupplementation with HA is not indicated in patients assuming double antiaggregant and NOACs. With NOACs, the injection in the knee is possible if performed by a skilled, senior doctor.	57.1	28.6	14.3
3	Clinical situations in which the VS with HA is considered appropriate			
3.1	The use of HA in patients taking systemic NSAIDs is recommended to reduce the assumption of these drugs.	92.9	7.1	0
3.2	The concomitant use of HA in patients taking SySADOAs (chondroitin sulfate, glucosamine, etc.) may improve clinical efficacy.	92.9	0	7.1
3.3	A treatment model associating intra-articular HA to exercise and rehabilitative interventions can be useful to improve joint function.	92.9	0	7.1
3.4	In the case of multiple joint involvement, HA can be considered in different joints (at best step by step starting from the most painful joint).	85.7	7.1	7.1
3.5	The injection of HA after a failure of other viscosupplements, having significantly different characteristics from HA (MW, concentration, and volume), can be given to verify if the change of product is associated to a better clinical response.	85.7	14.3	0

Abbreviations: HA, hyaluronic acid; KL, Kellgren-Lawrence; MW, Molecular Weight; NOAC, Novel Anti Coagulant; NSAID, Nonsteroidal Anti-inflammatory drug; OA, Osteoarthritis; CMC, Carpometacarpal Joint; SySADOA, Symptomatic Slow Acting Drugs for Osteoarthritis; VS, Viscosupplementation.

morbidities and concomitant treatments that are common in a real-life setting. Besides, because of the chronicity of the disease, the treatment of real-life patients is longer than that of patients enrolled in RCTs and requires integration or shadowing with other treatments. The TEP considered first that the association of VS, exercise and rehabilitative interventions could be useful to improve joint function. Moreover, VS is a means to reduce the intake of NSAIDs.^{25,36} VS can be performed in conjunction with the use of SySADOAs to obtain a synergistic action. In this regard, the TEP considered is of particular interest the study by D'Avola³⁴ in which 52 patients received HA 0.8% (800–1200 kDa), and 29 received HA 0.8% (800–1200 kDa) plus chondroitin sulfate P.O. A more marked reduction of pain (VAS from 70 to 10 at three months: $p < 0.01$ and at six months: $p < 0.02$) was observed in patients treated with HA 0.8% (800–1200 kDa) and chondroitin sulfate P.O. As the effect of VS becomes evident after a few weeks, while the SySADOAs need a few months before showing an evident clinical effect, the combination of VS and SySADOAs may not be effective in the acute phase. In case of multiple localizations of OA, VS can be performed in multiple target joints (especially bilateral injection in the knee is feasible) when OA is of initial or intermediate grade, while in other cases the concomitant administration of SySADOAs or NSAIDs could be considered. Finally, VS with HA after the failure of other viscosupplements having significantly different characteristics (MW, concentration, and volume) can be tried to verify if the change of product could be associated to a better clinical response.

Items in Disagreement

The TEP discussed conditions in which further research was deemed opportune.

In hip impingement, Abate²⁶ found that VS with HA 1.6% significantly reduced ($p < 0.0001$) the pain measured by VAS, the Lequesne Index (LI) and the Harris Hip Score (HSS) at 6 and 12 months. A retrospective open study conducted by La Paglia²⁷ compared the efficacy of HA 2% with a combination of HA 3.2% (1400–2100 kDa/65–110 kDa) and PRP using imaging and a Hip disability and Osteoarthritis Outcome Score (HOOS) questionnaire exploring pain and function at baseline, 2 and 6 months after treatment. The Authors found that the combination of HA 3.2% (1400–2100 kDa/65–110 kDa) and PRP was more effective than HA 2% alone in the reduction of HOOS and at the MRI imaging. The TEP concluded that this preliminary

evidence required further investigation. In Shoulder localization, VS with HA 0.8% in 100 patients affected by cuff pathology (grades I–IV of Neer's classification) induced reduction of pain measured by VAS at 30 days, as well as improvement of the OSS and Constant-Murley C-M score, the treatment being more effective in grades I and II.²⁹ Similar results were obtained by Gigante²⁸ in patients with OA of grades I and II, HA 0.8% reduced the pain measured by VAS and improved the OSS and the C-M score starting from 15 and up to 90 days. VS proved to be less effective in grades III and IV. The TEP concluded that further studies are needed to assess the efficacy of HA 0.8% and its indication in the treatment of rotator cuff syndrome, shoulder OA, impingement, and pain.

Stenosing tenosynovitis (Trigger finger): Callegari³⁶ compared HA 0.8% + prednisolone and lidocaine (15 patients) with open surgery (15 patients) in the treatment of trigger finger. The patients were assessed before the procedure and at 6 weeks, 3, 6 and 12 months after the procedure. At 12 months, VS had similar efficacy and lower overall burden (time to recovery, care of the surgical wound) on the patient. However, due to the limited number of patients, the TEP considered further research on the subject necessary.

Research Agenda

The statement on which agreement could not be reached would form a “research agenda”, defining topics of interest in future research.

The TEP considered interesting to design future research to assess the efficacy of VS in the prevention of the progression of OA from its early stage; the prospective collection of morphological data could also allow a better understanding of the efficacy of the combination of VS with oral SySADOAs in limiting or slowing the structural progression of OA. A second topic that the panelists also considered worthy of further research is the assessment of the value of imaging (MRI, US, etc.) in the detection of patients most suitable for treatment with VS and in the definition of patients in which VS has the highest possibility of success. More information is needed on Grade IV CMC OA and ankle OA. Further research should be conducted to assess the efficacy of VS in hemophilia and post-acute chondrocalcinosis. Finally, the TEP agreed on the importance of studying phenotypes that are more suitable for each specific HA formulation since, to date, the choice of the formulation to be used is based on the experience of the operator.

Discussion

Among the strengths of this review is the multidisciplinary team that carried over the review. Moreover, a rigorous and well-codified methodology was used for the collection and appraisal of the clinical evidence. MMAT revealed an overall good quality of the selected papers.

As for the limitations of the review, one is the focus on a single product. As discussed above, this choice met two criteria: feasibility, to allow an in-depth analysis of each paper and homogeneity, concentrating the analysis on the medical condition itself and not on the comparison of different products. The second limitation of the review is that the TEP did not include representatives of patients and General Practitioners (GPs). This is because the focus of this review was on the VS technique, yet the TEP considered the patients' and GPs' point of view of primary importance and recommended their involvement in future assessments on VS.

Concerning the results of the review, the TEP reached an excellent level of agreement on the evaluation of available efficacy and safety data. Considering the data discussed above, the authors concluded that HA has a favorable benefit/risk ratio. This evaluation was consistent with the results of a previous review on HA.³⁷

This review cannot be considered conclusive. The field of VS is evolving, and there are many aspects to be studied as mentioned in the research agenda. First, the possibility that VS, in association with SySADOAs, could prevent the progression of OA, as hypothesized in previous reviews.^{38–40} Another key area of study is the role of imaging. While there is a large body of scientific evidence on the use of various imaging techniques to guide the procedure of VS,^{41–43} little is known on the possibility to use imaging techniques to select the patients most suitable for the VS. Finally, the VS in specific medical conditions is still controversial; it is the case of chondrocalcinosis, where IAHA is not recommended.⁴⁴ Further research should focus on the identification of new therapeutic strategies based on the definition of therapeutic sequencing and/or association between VS and other IA compounds, as well as pharmacological and non-pharmacological treatments. The last field worthy of further research is the definition of types of IAHA most suitable in various clinical conditions. There are several types of IAHA, differing mainly for their molecular weight, which influences not only the rheological behavior of the HA but also the interaction of HA with the biological structures.⁴⁵

Conclusion

This systematic literature review and Expert Opinion discuss studies with a sound scientific methodology. The TEP analyzed the use of VS with HA in different localizations of OA. The results of the review can be summarized as follows: i. VS is safe and effective in most cases of knee and hip OA of KL grades I to III; ii. A careful evaluation of the medical history and concomitant conditions should be conducted before undertaking the procedure iii. The evaluation of the patient should not be limited to the assessment of KL grade but should also consider concomitant conditions that could reduce the efficacy of the procedure iv. Specific locations and situations require an additional evaluation from the clinician. v. VS can be usefully complemented by rehabilitation programs and the use of SySADOAs.

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