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REVIEW

A Review of the Clinical Effectiveness and Safety of Hybrid Cooperative Complexes in Intra-articular Viscosupplementation

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ABSTRACT

Viscosupplementation by intra-articular (i.a.) injection of the non-sulfated glycosaminoglycan (GAG) hyaluronic acid (HA) is a conservative therapy widely accepted in clinical practice for the management of osteoarthritis (OA) and joint diseases. The aim of viscosupplementation is to restore the rheological properties of the synovial fluid to relieve joint inflammation and pain and improve joint function through a chondroprotective effect. However, there is a range of hyaluronic acid products for OA that differ in preparation, molecular weight, rheological characteristics and concentration, and different i.a. formulations are more suited to particular patient populations and clinical situations, in part because of anatomical differences between joints. This paper focuses on innovative hybrid cooperative complexes of high and low molecular weight hyaluronic acid (HA-HL) and hyaluronic acid plus sodium chondroitin (HA-SC) that have been developed. Both products are formulated with pharmaceutical-grade, highly purified hyaluronic acid obtained with a multi-step biofermentation process, with properties that make them suitable across a range of degenerative joint diseases. They represent progress in building on the symptomatic and functional benefits of viscosupplementation in joint disease, with the additional beneficial effect of treating the patient with a high concentration of GAGs by a low number of injections. Here, we review the clinical evidence for the efficacy of a hybrid cooperative compound of HA-HL in various degenerative joint diseases, which suggests a synergistic effect of the different molecular weight hyaluronans that together more closely mimic the physiological composition of synovial fluid. Similarly, the evidence shows that HA-SC is safe, effective, and well tolerated in hip OA, with rapid and clinically significant improvements in pain symptoms and functionality. Such innovations in viscosupplementation expand the usefulness of the modality in the management of OA and other joint diseases, complemented by a lack of systemic or local side effects that allow the concurrent use of other drugs if needed.

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Key Summary Points

Hyaluronic acid-based viscosupplementation therapy has become established as a valid and consolidated therapeutic approach in the management of osteoarthritis and other joint diseases.

Innovative hybrid cooperative complexes of high and low molecular weight hyaluronic acid (HA-HL) and hyaluronic acid plus sodium chondroitin (HA-SC) have been developed to improve the usefulness and the efficacy of intra-articular viscosupplementation in osteoarthritis and other joint diseases.

HA-HL and HA-SC can deliver a high concentration of GAGs to affected joints accompanied by a lack of systemic or local side effects.

INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint disease that frequently compromises overall health and quality of life, imposing a high burden of global disability related to increasing pain and functional impairment [1]. The prevalence of OA has been increasing globally, driven by an aging and overweight population [2]. The direct medical cost related to OA is estimated to account for up to 2.5% of the gross domestic product of high-income countries [3]. However, indirect costs related to loss of productivity, premature retirement, and adverse effects on mental health further increase the individual and socioeconomic burden of OA [3–5].

The pathogenesis of OA is now recognized as a complex and multifactorial process involving mechanical, inflammatory, and metabolic factors, leading to progressive damage of the articular cartilage matrix and affecting subchondral bone and the synovium, capsule, and ligaments [6, 7]. This complexity limits the therapeutic approaches for managing OA, which range from weight loss, activity modification, physiotherapy, and other supportive therapies to analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, pharmaceutical-grade symptomatic slow-acting drugs in osteoarthritis (SySADOAs; e.g., chondroitin sulfate) and, ultimately, joint replacement therapy [6–8]. Recent research has provided insights into the molecular and clinical phenotypes underlying OA [9] which, taken with the distinct molecular mechanisms that underlie the disease, suggest new targeted therapies and advances the potential for precision medicine approaches that identify patients who may benefit the most from therapeutic intervention to prevent or delay the progression of this disabling disease [10].

The optimal management of OA should be individualized for each patient and requires non-pharmacological and pharmacological approaches, initially for reducing pain and stiffness and, subsequently, focused on maintaining physical functioning [8, 11]. Surgical approaches such as arthroplasty should be reserved for those who have not achieved adequate symptom and pain control with conservative therapy [6, 7].

Among the current conservative management modalities available for the treatment of OA, intra-articular (i.a.) viscosupplementation with hyaluronic acid (HA) has become increasingly accepted in clinical practice, both for demonstrated real-world effectiveness and patient satisfaction in pain reduction and improvement in joint function without clinically relevant adverse events or concerns about the tolerability and long-term adverse effects associated with analgesic/anti-inflammatory therapies [12–22]. Viscosupplementation aims to restore the physiological and rheological functioning of the damaged joint to mitigate pain, preserve the range of motion and improve joint function.

Hyaluronic acid products for OA that differ in preparation, molecular weight, rheological characteristics, and concentration are used in various clinical situations and patient populations. Although there is a long history of

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viscosupplementation for symptomatic relief in the management of OA of the knee and other joints in appropriate patients and general agreement among clinicians for its effectiveness, there is no definitive consensus regarding the differences in the clinical efficacy of the various available i.a. hyaluronic acid products or consensus among clinical practice guidelines on the appropriateness of using hyaluronic acid viscosupplementation in the different clinical scenarios related to OA [23]. However, increasing evidence from systematic reviews and meta-analyses showing that viscosupplementation is effective and reliable, with an excellent safety profile, supports the inclusion of i.a. hyaluronic acid in numerous expert guidelines in the fields of rheumatology, orthopedics, geriatrics, physical and rehabilitation medicine, and sports medicine [23].

Variations in study design, hyaluronic acid preparations, doses and regimens, clinical endpoints, patient populations, OA phenotypes, and evaluation methodologies explain, to some extent, the discrepancies between the clinical practice of physicians using the modality in their daily practice and practice guideline recommendations, not all of which support viscosupplementation in all OA indications [23]. Notably, the broad differences between products available for viscosupplementation mean that the results of clinical trials of a particular hyaluronic acid cannot directly be extrapolated to others.

A number of expert working groups have developed guidelines to identify best practices for the design and conduct of clinical trials targeting the assessment of viscosupplementation in OA [24–28]. Adopting their recommendations when designing clinical trials in OA will strengthen the evidence base for viscosupplementation and increase the comparability and reproducibility of results demonstrating functional changes over time.

In the meantime, further study is ongoing to take advantage of and better understand the mechanisms underlying the therapeutic benefits of i.a. hyaluronic acid preparations to improve the effectiveness of viscosupplementation in joint disease, especially considering what is new in terms of new products/new technologies. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SCOPE OF THIS REVIEW

The objectives of this review are to examine the recent innovations in the field of viscosupplementation, a Hybrid Cooperative Complex (HCC) of high and low molecular weight hyaluronic acid (HA-HL), and hyaluronic acid plus sodium chondroitin (HA-SC). Although this is a narrative review, it was based on a thorough search of the general scientific literature and clinical studies about the new two formulations to identify all papers relating to the candidate therapies and provide background data relevant to the review focus.

HYALURONIC ACID VISCOSUPPLEMENTATION IN OSTEOARTHRITIS

The glycosaminoglycan (GAG), hyaluronic acid (hyaluronan), is a linear polymer of glucuronic acid *N*-acetylglucosamine disaccharide that in its endogenous form is a major component of healthy synovial fluid, together with other lubricant molecules such as lubricin (proteoglycan 4) [29]. Secreted in the joints by synovial cells, fibroblast-like cells present in the synovial membrane [29], hyaluronic acid acts as a shock absorber and lubricant to reduce friction between the articular cartilage during movement while maintaining the structural and functional properties of the cartilage matrix [29].

The unique hygroscopic, rheological, and viscoelastic properties of hyaluronic acid in synovial fluid, together with additional anti-angiogenic, anti-inflammatory, analgesic, and chondrogenic properties, are, in part, a function of the presence of different molecular weight hyaluronans with distinct biological and rheological characteristics [19, 30]. In OA, the concentration of hyaluronic acid is reduced and the viscoelastic properties of synovial fluid become attenuated, reducing the protective and shock absorption action in joints. Thus, the goal of

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viscosupplementation with hyaluronic acid is to restore the viscoelastic properties of synovial fluid, and it is widely recognized as an effective, minimally invasive treatment option for OA with an excellent benefit/risk profile [17, 18, 23, 31]. Although i.a. corticosteroids when utilized for OA therapy may provide more effective pain relief in the short term (up to 1 month), with noticeable local and general side effects, the therapeutic benefit with i.a. hyaluronic acid is prolonged, with the effect size shown to peak by around 8 weeks and persist for at least 6 months [23, 32]. Because of its favorable benefit/risk profile, hyaluronic acid viscosupplementation is particularly suited for frail or elderly patients where, supported by the clinical evidence, the experience of the care provider and the specificity of the patient should always be considered [31].

In addition to pain relief, there is also evidence that hyaluronic acid viscosupplementation can delay the need for total joint replacement surgery [11, 16, 19, 20, 33, 34].

Recent recommendations from the EUROpean VIScosupplementation COnsensus group (EUROVISCO) for optimizing the clinical results of viscosupplementation in arthritic joint disease provide a valuable resource to guide practitioners in daily clinical practice [31]. They provide guidance on the appropriateness of viscosupplementation in various clinical situations, identify the population subgroups most likely to benefit, make recommendations on image guidance and approach and techniques of injection, and outline predictors of success and failure [31]. Their proposals are based not only on clinical trial evidence but also on extensive clinical experience, and consider the patient's wishes and involvement as a key part of therapeutic decision-making.

There is unanimous consensus among the EUROVISCO group that viscosupplementation is an effective treatment for mild-to-moderate knee OA and is a well-tolerated treatment in OA of the knee and other joints [23]. Because of its safety profile, the use of viscosupplementation should not be restricted to patients failing to respond adequately to other treatments, such as analgesics and NSAIDs, but should be a 'positive' indication rather than an option to be considered in the absence of other alternatives. Viscosupplementation could also be appropriate in situations where comorbidities, contraindications, access difficulties, or other concerns constrain treatment options, and may be preferred by patients with more advanced OA wishing to avoid joint replacement surgery as long as possible. However, the dosing regimen should be supported by evidence-based medicine [23].

The EUROVISCO recommendations for the use of viscosupplementation in OA are designed to help practitioners formulate a treatment algorithm for optimizing the results of viscosupplementation [31]. Their main recommendations are summarized in Table 1. More specific guidance on patient eligibility for viscosupplementation, based on a recent consensus report by a Technical Expert Panel appointed by the International Symposium Intra Articular Treatment (ISIAT) [35] is provided in Table 2.

It is recommended that retreatment with i.a. viscosupplementation should be systematically undertaken every year in patients with a high risk of OA progression, even in the absence of symptoms, and patient-reported outcomes (PROs) provide useful and relevant tools for assessing the success or failure of treatment in other patients [36]; retreatment should be undertaken as soon as pain reaches the patient acceptable symptom state (PASS) threshold [23].

Finally, to ensure accuracy of administration and success of viscosupplementation, the practitioner has to be skilled in the use of the modality; it is not enough to have a proven product if it is not correctly administered. Ultrasound guidance during i.a. administration is the most suitable and practical approach for the majority of joints.

INNOVATIVE HYBRID COOPERATIVE COMPLEXES OF HYALURONIC ACID

Although a considerable number of hyaluronic acid-based products are marketed for use in OA, some recent innovations have been developed

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Table 1 Considerations for the use of viscosupplementation in osteoarthritis according to recommendations from the EUROVISCO group [31]

Main items
VS is an effective treatment for mild to moderate knee, hip, ankle, shoulder, and trapeziometacarpal joint OA
VS may also be helpful in advanced stages of knee OA
VS is not an alternative to surgery in advanced hip OA
VS when administered at the early stages of OA may have a chondroprotective effect
Owing to its safety profile, VS should not only be used 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
Because hyaluronic acids differ widely from each other, results of clinical trials with a particular VS cannot be extrapolated to others
The dosing regimen must be supported by evidence-based medicine
A good technique of injection and/or the use of imaging guidance may enhance the success of VS
Obesity (BMI $>$ 30) may influence the response of VS in the knee
Joint space narrowing severity may influence the response of viscosupplementation in the knee and hip
Characteristics of pain may influence the response of viscosupplementation in the knee and hip
Appropriateness for the use of viscosupplementation
Patients with symptomatic, mild to moderate knee or hip OA (joint space narrowing grade 0–2, KL score I–III), with normal weight or moderate overweight (BMI $<$ 30), not sufficiently improved by non-pharmacological interventions and analgesics/NSAIDs or with contraindication to analgesics/NSAIDs

EUROVISCO EUROpean VIScosupplementation COnsensus group, *HA* hyaluronic acid, *KL* Kellgren–Lawrence, *OA* osteoarthritis, *VS* viscosupplementation

to further improve the efficacy and acceptability of hyaluronic acid viscosupplementation. The portfolio of hyaluronic acid-based medical devices for i.a. viscosupplementation manufactured by IBSA comprises a range of preparations designed for use in the range of joints affected by OA and other joint diseases. The IBSA i.a. hyaluronic acid products are formulated with pharmaceutical-grade, highly purified hyaluronic acid obtained with a patented multi-step biofermentation process and are not chemically modified.

Here, we focus on hybrid cooperative complexes of high and low molecular weight hyaluronic acid (HA-HL) and hyaluronic acid plus sodium chondroitin (HA-SC) that IBSA has developed.

Hybrid Association of High and Low Molecular Weight Hyaluronic Acid (HA-HL)

The HA-HL hybrid complex comprises a buffered physiological solution of high molecular weight (H-HA) and low molecular weight (L-HA) hyaluronic acid produced by bacterial fermentation and is not chemically modified. Through a unique patented thermal process [NaHYCO (/Sodium Hyaluronate Hybrid Complex) technology, patent WO 2012/032151], high and low molecular weight hyaluronic acids

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Table 2 Patient eligibility for viscosupplementation with Sinovial according to the consensus findings of a systematic literature review by a Technical Expert Panel using Delphi methodology [35]

Eligibility for VS with Sinovial can be considered according to the following patient features
Patients affected by both primary and secondary OA can be candidate for VS
Patients with radiological OA KL grades I–II–III (knee or hip) are the most suitable patients for VS
Selected cases of patients with X-ray KL grade IV affected by knee OA
Patients affected by OA of the CMC with X-ray KL grades I–II–III–IV can be treated with HA
Clinical situations in which VS with Sinovial is considered appropriate:
The use of Sinovial in patients taking systemic NSAIDs is recommended to reduce the assumption of these drugs
The concomitant use of HA in patients taking SySADOAs (chondroitin sulfate, glucosamine, etc.) may improve clinical efficacy
A treatment model associating intra-articular HA to exercise and rehabilitative interventions can be useful to improve joint function
In the case of multiple joint involvement, Sinovial can be considered in different joints (at best step by step starting from the most painful joint)
The injection of Sinovial after a failure of other viscosupplements having significantly different characteristics (MW, concentration, and volume), can be given to verify if the change of product is associated with a better clinical response

CMC carpometacarpal joint, *HA* hyaluronic acid, *KL* Kellgren–Lawrence, *MW* molecular weight, *OA* osteoarthritis, *SySADOAs* symptomatic slow-acting drugs in osteoarthritis, *VS* viscosupplementation

are mixed to produce a cooperative hybrid complex, where short and long chains are linked by hydrogen bonds, without the use of a cross-linking chemical agent, allowing high concentrations of hyaluronic acid and unique rheological characteristics very similar to that of endogenous hyaluronic acid [37–40].

HA-HL is compatible with platelet-rich plasma (PRP), as PRP does not modify the rheological properties of sodium hyaluronate [41], allowing it to retain its visco-suppletive function. Indeed, in combination with PRP, HA-HL was superior in stimulating extracellular matrix (ECM) synthesis, possibly due to the low molecular weight hyaluronic acid fraction [41, 42]. HA-HL also increased cell viability and proliferation in in vitro models of OA and tendinopathy [41, 43]

The high molecular weight component of HA-HL is responsible for the viscosupplementary effects, whereas the low molecular weight component added to the formulation overcomes the high viscosity and resultant high extrusive force which can render high concentrations of hyaluronic acid difficult to inject. However, in conventional hyaluronic acid preparations, attempts to increase hyaluronic acid content result in an increase in viscosity, which can create difficulties in preparations intended for i.a. injection [37, 38, 41, 44]. In contrast, the formation of the hybrid cooperative complex is characterized by a decrease in dynamic viscosity. HA-HL displays/mimics viscoelastic properties that are within the range of healthy synovial fluid [41].

Despite the absence of chemical cross-linking utilized in some commercial hyaluronic acid preparations, hybrid associations of high and low molecular weight hyaluronic acid fractions show prolonged resistance to enzymatic degradation [37, 44], as the enzyme hyaluronidase is unable to recognize the conformation of these complexes.

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The medical device was granted CE certification in February 2015 and is marketed as Sinovial® HL[1] (IBSA) in Italy, the Czech Republic, Slovak Republic, Switzerland, Hungary, France, Poland, Albania, and Turkey. Sinovial HL® is available as:

- Sinovial® HL 3.2% in a 2-ml pre-filled syringe containing 32 mg H-HA + 32 mg L-HA (64 mg hyaluronic acid in total)
- Sinovial® HL 3.2% in a 1-ml pre-filled syringe 16 mg H-HA + 16 mg L-HA, (32 mg hyaluronic acid in total).

Hybrid Cooperative Complex of Sodium Hyaluronate and Sodium Chondroitin Non-sulfated (HA-SC)

The technological excipient used by IBSA to modulate the viscosity of high concentration, high MW HA solutions is biotechnological or non-sulfated/chondroitin (SC). SC is an endogenous molecule and a precursor of chondroitin sulfate (CS), which is synthesized in vivo as GAG polymers containing *N*-acetylgalactosamine alternating with glucuronic acid. Sulfation of the SC polymer by specific sulfotransferases usually occurs as the polymer is being formed, before release in the ECM [45]. However, sulfation is not always performed, and some SC is also present in the ECM of several tissues and organs, even if in lower quantity when compared to CS and other sulfated GAGs.

SC is produced through a patented biological fermentation process [46–48]. When used as a technological excipient, sodium chondroitin takes advantage of specific rheological properties that modulate the viscosity of high concentration, high molecular weight hyaluronic acid solutions, preserving the viscoelastic characteristics that replicate the desirable characteristics of hyaluronic acid found in healthy synovial fluid. The use of sodium chondroitin allows a higher concentration of hyaluronic acid without a significant increase in viscosity while maintaining a high therapeutic molecular weight [39].

Sodium chondroitin has been shown in vitro to be biologically active with specific activity on chondrocyte inflammation and potential application in medical devices and pharmaceutical preparations designed for treating conditions of cartilage degradation, including OA [49, 50]. This was demonstrated in human chondrocyte models of OA, where sodium chondroitin non-sulfated increased cell proliferation and enhanced cell viability while reducing markers of inflammation [49, 50]. Furthermore, the combination of high molecular weight hyaluronic acid and sodium chondroitin appears to have a synergistic effect; HA-SC was significantly more effective than sodium chondroitin alone or hyaluronic acid alone in decreasing and/or downregulating biological mediators of inflammation in human synoviocytes and chondrocytes, as well as re-establishing an extracellular environment more comparable to a healthy condition [50].

The patented formulation for the HA-SC medical device comprises pharmaceutical-grade hyaluronic acid, a non-chemically modified, linear natural polymer free of cross-linking agents, obtained from a highly productive microbial strain, complexed with sodium chondroitin non-sulfated, which is used as a technological excipient in formulating the cooperative hybrid complex. The hyaluronic acid component closely mimics endogenous hyaluronic acid while providing a favorable safety profile combined with satisfactory viscoelastic properties.

The HA-SC medical device is a sterile 3-ml unit-dose syringe for i.a. administration containing sodium hyaluronate (high molecular weight) 2.4% in a hybrid complex with sodium chondroitin non-sulfated 1.6% of biotechnical origin as an excipient to modulate the viscosity of the hyaluronic acid solution. Each syringe provides 72 mg of sodium hyaluronate and 48 mg of sodium chondroitin non-sulfated.

Under the Sinogel® (IBSA) brand, the product was first launched in Italy in October 2021.

[1] Other available tradenames: Intragel® HL—Ibesia® HL.

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CLINICAL STUDIES

HA-HL

The use of HA-HL has been investigated in OA of the knee, hip, and hand, calcific tendinopathies, femoroacetabular impingement syndrome, and other conditions involving articular cartilage damage (Table 3). To date, most clinical evidence has come from patients with knee OA [51–55]. However, the first study reporting the use of a hybrid complex of high and low hyaluronic acids in OA was, in fact, conducted in 20 patients with radiologically confirmed moderate-to-severe hip OA [30]. Patients received i.a. ultrasound-guided injections of HA-HL at baseline and after 40 days; treatment was repeated at 3 and 6 months. Data were compared from a matched cohort of patients treated with high molecular weight hyaluronic acid.

There was a significant improvement in clinical and functional outcomes in both cohorts at 3 and 6 months; patients treated with HA-HL showed statistically significant better results versus the high molecular weight hyaluronic acid group at 6 months (Table 3). The study was the first to show that the combination of high and low molecular weight hyaluronic acid is safe and effective in OA while providing better therapeutic outcomes, suggesting that the different molecular weight hyaluronans work synergistically in combination.

In addition, in a retrospective study in 32 young patients with clinically and radiologically confirmed femoroacetabular impingement, HA-HL plus PRP was more effective than a high molecular weight hyaluronic acid i.a. injection [56]. The two cohorts of patients received two injections of HA-HL plus PRP 15 days apart (Group 1) or two injections of a high molecular weight hyaluronic acid 15 days apart (Group 2). The groups were further subdivided for analysis. In Group I ($n = 16$), the mean age of patients with mild, moderate, or severe arthropathy was 25, 35, and 40 years, respectively (Groups Ia, Ib, and Ic, respectively). In the corresponding groups in Group II, the mean age was 26, 35, and 41 years, respectively. There was a significant clinical improvement and improvements in magnetic resonance imaging-evaluated stability in all but patients with very severe arthropathy, with the combined treatment more effective than high molecular weight HA at 2 and 6 months (Table 3) [56].

There are six studies of HA-HL in patients with knee arthropathies (Table 3). Degeneration of knee cartilage is a common source of chronic knee pain in athletes, particularly towards the end of their careers [57]. Furthermore, the metabolic and biochemical changes of cartilage degeneration caused by intensive sport activity are similar to those described for the early stages of OA [58]. HA-HL was compared with PRP in 48 end-career professional soccer players with degenerative cartilage lesions of the knee, who were randomized to treatment with three injections of i.a. HA-HL or PRP [58]. All patients had a statistically significant improvement in all clinical scores tested with treatment; HA-HL was significantly superior to PRP at 3 and 6 months (Table 3). There were no adverse injection-related events during treatment and follow-up in either group.

HA-HL has also been evaluated with and without PRP in 60 patients with radiographically confirmed symptomatic knee OA nonresponsive to pharmacologic and rehabilitation therapy [54]. Patients were treated with three injections of HA-HL or PRP at an interval of 1 week for 3 consecutive weeks. Both treatments were effective in relieving pain and improving functional outcomes (Table 3). The combination was statistically significantly better than HA-HL alone at 3 and 6 months, when evaluated by Knee Injury and Osteoarthritis Outcome Score (KOOS) and VAS scales which, although clinically relevant, lost statistical significance at 12 months.

In a recently published study, a total of 692 patients with radiographically confirmed knee OA were randomized to a single i.a. injection of HA-HL or placebo (physiological saline) in a prospective, double-blind study of 24-week duration [52]. There was a rapid decrease in mean visual analog scale (VAS) pain score in both treatment groups (Table 3). However, the

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Table 3 Summary table of clinical trials evaluating the efficacy of injectable hybrid cooperative complexes of hyaluronic acid in joint diseases

Author	Design	Patient characteristics			Intervention			Outcomes
		Joint	No.	Age (mean or range)	Treatment	No. of injections	Follow-up (months)	
High and low molecular weight hyaluronic acid (HA-HL)								
Migliore (2021) [52]	RCT	Knee	692	63.7	HA-HL Placebo (saline)	1	6	VAS pain rapidly decreased. Pain improvement was significantly in favor of HA-HL at 1, 6, 12, and 24 weeks HA-HL improved functionality, OMERACT-OARSI response and HR-QoL
Papalia (2016) [58]	RCT	Knee	48	37.2 (34–39)	HA-HL PRP	3	12	Significantly superior clinical and pain outcomes compared with PRP at 3 and 6 months
Papalia (2019) [54]	RCT	Knee	60	40–70	HA-HL + PRP HA-HL	3	12	Both improved KOOS and VAS pain. HA-HL + PRP significantly better than HA-HL alone at 3 and 6 months (KOOS) and 3 and 12 months. (VAS)
Manciameli (2018) [51]	Prospective	Knee	35 (59 knees)	59	HA-HL	2	6	VAS pain and WOMAC pain and HR-QoL improved by 1 month and kept stable through 6 months

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Table 3 continued

Author	Design	Patient characteristics			Intervention			Outcomes
		Joint	No.	Age (mean or range)	Treatment	No. of injections	Follow-up (months)	
Papalia (2017) [53]	RCT	Knee	48 obese patients	61.5 60	HA-HL HMW HA	2	6	VAS pain, IKDC and KOOS significantly improved at 3 and 6 months in both groups HA-HL was more effective than HMW HA
Scaturro (2021) [55]	Prospective	Knee	37 overweight patients	63 (45–75)	HA-HL	2	3	Pain, WOMAC, 6MWT and QoL improved significantly at 3 months
Abate (2017) [30]	Prospective/ retrospective	Hip	20	63.6 63.3	HA-HL HMW HA	4	6	VAS pain scores at rest and during activities improved at 3 and 6 months HA-HL significantly better than HMW HA at 6 months
La Paglia (2017) [56]	Retrospective	Hip	32	18–55 years	HA-HL + PRP HMW HA	2	6	Combined treatment was more effective that HMW HA at 2 and 6 months, particularly in mild-to high grade arthropathy
Conforti (2020) [59]	Case series	Shoulder	97	54.3 52.7	HA-HL + laser needling ± US-PICT	2–3	3	VAS pain and ASES improved after treatment and at 3 months in both groups; US-PICT did not significantly improve response

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Table 3 continued

Author	Design	Patient characteristics			Intervention			Outcomes
		Joint	No.	Age (mean or range)	Treatment	No. of injections	Follow-up (months)	
Tenti (2017) [42]	Retrospective	Trapezio-metacarpal	100	68.6 65.5	HA-HL Triamcinolone acetonide	2	6	Both treatments improved VAS pain, FIHOA and HR-QoL HA-HL was significantly superior to triamcinolone at 1 and 6 months
Bartolini (2019) [60]	Prospective	Trapezio-metacarpal	12	63	HA-HL	2	6	HA-HL reduced VAS pain and improved hand function by 1 month and persisting for 6 months of follow-up
Hyaluronic acid plus sodium chondroitin non-sulfated (HA-SC)								
Papalia (2021) [61]	Prospective	Hip	48	61.2	HA-SC	1	6	Rapid and significant decrease of VAS pain and LI that was sustained at 6 months

6MWT 6-Minute Walk Test, *ASES* American Shoulder and Elbow Surgeons, *FIHOA* Functional Index for Hand OA, *HA* hyaluronic acid, *HMW* molecular weight, *IKDC* International Knee Documentation Committee, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *LI* Lequesne's Algofunctional Index, *PRP* platelet-rich plasma, *RCT* randomized controlled trial, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Arthritis Index

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mixed-model analysis showed a statistically significant between-groups difference in the VAS pain score at 1, 6, 12, and 24 weeks. HA-HL was also more effective than placebo in improving functionality, health-related quality of life (HR-QoL), and patient-reported treatment response parameters [52]. The study demonstrated that HA-HL effectively provides rapid, sustained, and clinically relevant improvements in pain, physical functioning, and HR-QoL in symptomatic knee OA.

Patients with radiologically confirmed degenerative arthropathy of the knee (59 knees of 35 patients) were treated with two cycles of i.a. HA-HL at an interval of 2 weeks and assessed at baseline and 1, 3, and 6 months after treatment [51]. There were significant reductions in knee pain in all knees treated, while consumption of rescue medication (NSAIDs; analgesics) declined after treatment (Table 3).

Knee OA has particular implications for overweight patients. Two studies have been conducted on overweight/obese patients with symptomatic knee OA [53, 55]. In the first, a randomized study in 48 obese patients [body mass index (BMI) > 30] with OA, HA-HL was significantly more effective than i.a. injection of a high molecular weight hyaluronic acid in terms of International Knee Documentation Committee (IKDC) score and KOOS (both $P \leq 0.01$) [53]. The between-group difference in KOOS remained statistically significant at 6 months of follow-up; VAS pain relief was also superior with HA-HL at 3 months ($P < 0.001$) (Table 3).

In 37 overweight (BMI > 25) patients with symptomatic knee OA assessed at baseline and 3 months after ultrasound-guided HA-HL, pain symptoms, disease severity, cardiopulmonary capacity, and measures of quality of life improved significantly. The use of rescue analgesic intake for pain control was reduced [55] (Table 3).

HA-HL has been used in combination with high-power, low-thermal impact multi-frequency i.a. laser therapy, a well-established method for treating a range of musculoskeletal conditions in the treatment of calcific tendinopathies of the shoulder. Ninety-seven patients with symptomatic rotator cuff calcific tendinopathies were treated with i.a. HA-HL plus the laser therapy performed at the intra-articular level using a needle-conveyed optical fiber technique, also known as laser needling, with or without first-line treatment with ultrasound-guided percutaneous needle aspiration (US-PICT) [59]. Patients were evaluated at baseline, end-of-treatment (after 2–3 infiltration visits), on return to work or regular activity, and 3 months post-treatment. The laser treatment combined with HA-HL effectively relieved pain and improved activities of daily living, and was in itself sufficient in resolving acute disease without the need for US-PICT [59] (Table 3).

HA-HL has also been shown to provide effective pain relief and improve joint function in trapeziometacarpal OA [42, 60]. In a retrospective comparative study, the medical records of 100 patients with mono- or bilateral trapeziometacarpal OA treated with two injections of HA-HL or of triamcinolone acetonide were reviewed [42]. Change in global pain was assessed by VAS and hand function by the Functional Index for Hand OA (FIHOA). Both treatments were effective in relieving pain and improving joint function (Table 3). However, HA-HL was significantly superior to triamcinolone acetonide 1 month after the first injection ($P < 0.01$), and during 6 months of follow-up ($P < 0.001$). HA-HL was also more effective than triamcinolone in decreasing morning stiffness and improving HR-QoL [42].

Finally, the effect of HA-HL on pain symptoms and articular function was assessed prospectively in a pilot study in 12 consecutive patients with radiologically confirmed trapeziometacarpal OA [60]. Patients received a course of two ultrasound-guided injections at baseline and after 15 days. HA-HL effectively reduced pain and improved hand function, with a rapid effect on articular function evident from the first month and persisting at 6 months of follow-up [60] (Table 3).

Viscosupplementation was well tolerated in these trials, with AEs generally absent or of only mild severity.

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HA-SC

A single viscosupplementation study of the hybrid cooperative complex of sodium hyaluronate 2.4% plus sodium chondroitin non-sulfated 1.6% formulation (HA-SC) in OA has been published to date [61]. In the prospective, multicenter, open-label pilot study, a single 3 ml i.a. injection of HA-SC rapidly and significantly reduced hip pain in 48 patients with radiographically confirmed symptomatic hip OA and moderate-to-severe pain (Table 3). Measures of joint function were also improved, and the majority of patients reported global improvement at all measured time points. Treatment was well tolerated, with injection site pain/localized arthralgia in 20.8% of patients [61].

DISCUSSION

Osteoarthritis is a whole joint disease with a complex pathogenesis and multiple pathological pathways that are not yet fully understood but are currently recognized to involve mechanical, inflammatory, and metabolic factors [6, 7]. The impaired regeneration capability of damaged cartilage matrix and impaired function of chondrocytes as a consequence of biomechanical and biochemical changes substantially contributes to the progressive damage of articular cartilage in OA [28, 62]. Consequently, viscosupplementation with i.a. hyaluronic acid has potential benefits by counteracting the OA-induced deficit of hyaluronic acid in the joint to restore the viscoelastic properties of synovial fluid and alleviate the symptoms of OA.

Viscosupplementation with hyaluronic acid for symptomatic relief is well established and widely utilized in the clinical management of OA, particularly of the knee, although there is increasing evidence for its benefits in joint disease other than the knee. Against the background of evidence from systematic reviews and meta-analyses of clinical trials that show that viscosupplementation is effective, reliable, and safe, reinforced by recommendations and guidance from evidence-based expert consensus, technological innovation continues to improve the efficacy and acceptability of hyaluronic acid viscosupplementation in joint disease.

The hybrid cooperative complexes of high and low molecular weight hyaluronic acid (HA-HL) and hyaluronic acid plus sodium chondroitin non-sulfated (HA-SC) developed by IBSA represent progress in building on the symptomatic and functional benefits of hyaluronic acid viscosupplementation in joint disease, with the additional beneficial effect of treating the patient with a low number of injections, with a consequent increase of compliance. In the studies of HA-HL reported to date [30, 42, 51–56, 58–60], the new hybrid cooperative compound's increased efficacy can best be explained as a synergistic effect of different molecular weight hyaluronans that together aims at mimicking the physiological composition of synovial fluid.

Current data for the use of hybrid cooperative complexes of hyaluronic acid, produced for viscosupplementation through an innovative patented thermal process, are encouraging, although there are potential limitations in some studies related to retrospective or case-series design, small patient numbers, and differences in study endpoints. However, the use of HA-HL is now supported by data from the large randomized placebo-controlled study in 692 patients with painful knee OA [52]. The biocompatible hyaluronic acid source in each of the hybrid cooperative complexes is produced by a patented biofermentation process, which avoids the presence of avian-derived molecules in hyaluronans produced from avian sources, associated with a higher risk of immunogenicity and potentially serious acute inflammatory reactions [63–65]. Furthermore, the hybrid complex of hyaluronic acid in combination with biotechnical sodium chondroitin non-sulfated addresses the anatomical differences between the knee and hip joints in a novel way [61]. Only a few medical devices have been available that are specifically designed for hip viscosupplementation, which, as the largest ball-and-socket joint in the body, requires the use of a large volume of hyaluronic acid. Accommodating a hyaluronic acid concentration sufficient to ensure efficacy without

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increasing the viscosity of the solution for injection to a level resulting in a gel-like solution that would require excessive extrusion force to inject has been a challenge that the innovative HA-SC formulation overcomes. In addition, the deeper localization of the hip joint, and the proximity of femoral vessels and nerves, which necessitates imaging-guided infiltration, has limited the number of studies of i.a. hyaluronic acid viscosupplementation in hip OA.

The study of HA-SC in patients with hip OA shows the hybrid complex of hyaluronic acid plus sodium chondroitin non-sulfated is safe, effective, and well tolerated, resulting in rapid and clinically significant improvements in pain symptoms and functionality [61].

Hyaluronic acid-based viscosupplementation therapy has become established as a valid and consolidated therapeutic approach in the management of OA [54, 66, 67]. The modest effect size for i.a. viscosupplementation observed in some clinical trials should be set against the real-world effectiveness and patient satisfaction seen in everyday clinical practice. Notably, a significant placebo effect is recognized in OA [68, 69], particularly concerning route of delivery and choice of placebo comparator. For instance, i.a. saline, often chosen for the placebo arm, is independently beneficial in OA [69]. However, the prolonged therapeutic effect on the symptoms and outcome of OA, together with the reduction in the use of NSAIDs and other pain medications and reduced AEs associated with hyaluronic acid-based viscosupplementation result in a cost/benefit ratio with the potential to offset any short-term savings with therapies such as i.a. corticosteroids [10, 14, 15, 70].

Identifying the patient groups most responsive to therapy is an ongoing pursuit, as new products expand the indications for viscosupplementation. It is important that therapy is individualized and that the patient's wishes and requirements are taken into consideration in the decision-making process, together with the clinical trial evidence, combining pharmacological and non-pharmacologic approaches as necessary to achieve optimal management of the condition.

CONCLUSIONS

There are opportunities for further research to add to the existing evidence base supporting the use of the hybrid cooperative complexes described in this paper. However, such innovations in hyaluronic acid viscosupplementation expand the usefulness of the modality in the management of OA and other joint diseases, allowing the delivery of high concentrations of active agent to the affected site complemented by, as with other i.a. hyaluronic acid formulations, a lack of systemic or local side effects that allow the concurrent use of other drugs if needed.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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