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# Intraarticular Hyaluronic Acid Preparations for Knee Osteoarthritis: Are Some Better Than Others?

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**Abstract**

*Objective*. This literature review summarizes evidence on the safety and efficacy of intraarticular hyaluronic acid (IAHA) preparations approved in the United States for the treatment of osteoarthritis of the knee. *Design*. A systematic literature search was performed in PubMed, Ovid MEDLINE, and SCOPUS databases. Only studies in which clinical outcomes of individual IAHA preparations alone could be assessed when compared to placebo, no treatment, other standard knee osteoarthritis treatments, and IAHA head-to-head studies were selected. *Results*. One hundred nine articles meeting our inclusion criteria were identified, including 59 randomized and 50 observational studies. Hylan G-F 20 has been the most extensively studied preparation, with consistent results confirming efficacy in placebo-controlled studies. Efficacy is also consistently reported for Supartz, Monovisc, and Euflexxa, but not for Hyalgan, Orthovisc, and Durolane. In the head-to-head trials, high-molecular-weight (MW) Hylan G-F 20 was consistently superior to low MW sodium hyaluronate preparations (Hyalgan, Supartz) up to 20 weeks, whereas one study reported that Durolane was noninferior to Supartz. Head-to-head trials comparing high versus medium MW preparations all used Hylan G-F 20 as the high MW preparation. Of the IAHA preparations with strong evidence of efficacy in placebo-controlled studies, Euflexxa was found to be noninferior to Hylan G-F 20. There are no direct comparisons to Monovisc. One additional IAHA preparation (ie, Synovial), which has not been assessed in placebo-controlled studies, was also noninferior to Hylan G-F 20. *Conclusion*. IAHA efficacy varies widely across preparations. High-quality studies are required to assess and compare the safety and efficacy of IAHA preparations.

**Keywords**

osteoarthritis, knee, intraarticular delivery

## Introduction

Osteoarthritis (OA) is a degenerative disease of weight-bearing joints. OA is the most common form of chronic arthritis, and prevalence is expected to increase due to aging of the population and rising obesity.[1] Symptomatic OA most commonly affects the knee, with a 17% prevalence in adults over the age of 45 in the United States.[2] Based on 2000 to 2014 data from the National Inpatient Sample, total knee arthroplasty (TKA) is expected to increase by 85% to 1.26 million procedures by 2030.[3] Available treatments for OA of the knee address symptoms of pain and loss-of-function. There are currently no approved therapies with proven disease-modifying action. The standard of care includes lifestyle changes (eg, physical therapy, exercise, weight loss) and pharmacological therapies, such as non-steroidal anti-inflammatory drugs (NSAIDs) and tramadol. Viscosupplementation with intraarticular (IA) injections of either hyaluronic acid (HA) or corticosteroids are also approved therapies for OA of the knee.

In the healthy knee, HA present in synovial fluid has an average molecular weight (MW) of 6,000 to 7,000 kDa and is present at concentrations of 2 to 4 mg/mL.[4] HA has visco-elastic properties that allow it to function as a lubricant at low shear rates, during slow movements, and an elastic

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**Table 1.** Levels of Evidence for Therapeutic Studies.

| Levels of Evidence | Criteria |
|---|---|
| Level I | • High-quality randomized study<br>○ Appropriately randomized<br>○ Blinded<br>○ Sufficiently powered<br>○ >80% follow-up<br>○ Reported significant differences, or nonsignificant differences with narrow confidence intervals |
| Level II | • Poor-quality randomized studies, either having<br>○ Improper randomization techniques<br>○ Absence of blinding<br>○ insufficiently powered<br>○ <80% follow-up<br>• Prospective comparative studies |
| Level III | • Retrospective cohort studies |

solid at high shear rates, providing shock absorption during rapid movements. HA may also have chondroprotective and anti-inflammatory effects, as well as contribute to proteoglycan synthesis and scaffolding.[5] In OA of the knee, HA synthesis, degradation, and clearance are abnormal, resulting in a reduced MW and concentration of HA at the joint. These pathological changes diminish synovial fluid viscoelasticity, leading to cartilage damage.

Intraarticular hyaluronic acid (IAHA) injections are administered to help restore a higher average MW and concentration of HA in synovial fluid. HA preparations differ in their method of production (purified from rooster comb or synthesized in vitro),[6] MW (500 kDa to >6,000 kDa), and structure (linear, crosslinked), resulting in a wide variation of rheological properties across preparations.[7] This suggests that individual IAHA preparations may have unique efficacy and safety profiles. Indeed, IAHA studies have yielded conflicting evidence, resulting in a body of literature that has been difficult to interpret. This is reflected by inconsistent clinical practice guidelines, with several international associations endorsing IAHA for the treatment of knee OA,[8-13] while others, including the American Academy of Orthopaedic Surgeons (AAOS), consider the evidence insufficient to support a recommendation.[14-17] In meta-analyses of high-quality randomized placebo-controlled studies performed for the AAOS guidelines,[14] improvements obtained with IAHA were statistically significant, but the effect sizes did not reach clinical relevance thresholds. However, the AAOS noted that most statistically significant superior outcomes were from studies using high MW HA preparations, suggesting that meta-analyses pooling all HA preparations into one single class may dilute the effect sizes of more efficacious preparations. Subsequent independent meta-analyses assessing IAHA pain outcomes by MW have confirmed this observation.[18-20] Here, we explore the safety and efficacy profiles of individual US-approved IAHA preparations, and head-to-head trials that have directly compared them.

## Methods

### *Literature Search Strategy*

A systematic literature search was performed in PubMed, Ovid MEDLINE, and SCOPUS using terms for hyaluronic acid and osteoarthritis of the knee (see Supplementary Tables 1–3, available online). Searches were limited to randomized and observational studies conducted in humans. The literature search was supplemented by searches of article bibliographies. Only articles in English that were searchable in PubMed or Ovid MEDLINE were considered for inclusion. The article selection criteria included studies with safety or efficacy clinical outcomes, in which the effects of individual IAHA preparations alone could be assessed (see Supplementary Table 3 for study selection criteria).

The level of evidence was determined according to the definition used by the AAOS, the North American Spine Society, and several orthopedic journals (**Table 1**).[21-23] A study was labeled as level I if it was appropriately randomized, and reported significant differences, or nonsignificant differences with narrow confidence intervals. Poor-quality randomized studies and prospective comparative studies were labeled as level II. A poor-quality randomized study was defined as a study with improper randomization techniques, absence of blinding, insufficiently powered, or <80% follow-up. Retrospective cohort studies were labeled as level III.

## Structure and Characteristics of IAHA Preparations Compared in Head-to-Head Trials

For this review, we have categorized IAHA preparations with an average MW of less than 1,000 kDa as low MW preparations, 1,000 kDa to less than 3,000 kDa as medium MW preparations, and preparations of 3,000 kDa or greater

as high MW preparations. A summary of the IAHA preparations approved in the United States is provided in **Table 2**. Two low MW preparations of IAHA have been approved by the Food and Drug Administration (FDA). Hyalgan[24] (sodium hyaluronate; 500 to 730 kDa, 3 to 5 injections) was the first IAHA approved as a class III medical device for treatment of OA of the knee in the United States. Hyalgan is extracted from rooster comb and is linear chain. Supartz/Supartz FX[25] (sodium hyaluronate; 620-1,170 kDa, 5 weekly injections; previously US brand names Artz or Artzal) was approved in 2001 and is also linear chain. Adant has been formulated to be a generic drug equivalent of Supartz/Supartz FX. In the United States, Adant was developed under the brand name GenVisc 850, and approved as a biosimilar based on the demonstration of equivalent chemical composition, physical characteristics, and noninferior clinical performance to Supartz/Supartz FX.[26,27] Supartz/Supartz FX is extracted and purified from rooster comb whereas Adant/GenVisc 850 is produced with bacterial fermentation.

The medium MW IAHA Orthovisc[28] (hyaluronan; 1,000 to 2,900 kDa, 3 to 4 injections) was approved in 2004. Orthovisc is a linear chain sodium hyaluronate derived from bacterial fermentation. Monovisc (hyaluronan; 1,000 to 2,900 kDa, 1 injection)[29] is a single injection IAHA preparation approved in 2014. The HA used in Monovisc is of the same grade and specification that is used in Orthovisc, but it is crosslinked and therefore hydrophobic. Monovisc delivers an amount of HA that is comparable to the 3-injection Orthovisc preparation. Neflexxa/Euflexxa[30] (BioHA [sodium hyaluronate]; 2,400 to 3,600 kDa, 3 injections) was approved in 2004/2011. BioHA is a purified HA synthesized by bacterial fermentation, and contains straight chain HA. Sinovial/gelsyn-3 (sodium hyaluronate; 1,400 to 2,100 kDa, 3 injections) is obtained from bacterial fermentation.

The high MW IAHA preparation Synvisc (Hylan G-F 20 [hylan A, hylan B]; 6,000 kDa, 3 injections [2 mL])[31] was approved in 1997. A single-injection preparation of Hylan G-F 20 (Synvisc-one [6 mL][32]) was later approved by the FDA in 2009. Hylan G-F 20 is extracted and purified from rooster comb hyaluronan. Hylan G-F 20 is distinguished from other HA preparations by its higher MW and chemical structure. Hylan G-F 20 is composed of 2 hylan polymers (ie, crosslinked hyaluronan). Two crosslinking processes produce a mixture of the 2 different hylan polymers in an 80:20 ratio of hylan A to hylan B. Hylan A is a soluble high MW molecule HA (6,000 kDa) and hylan B is an insoluble gel.[33] Durolane (NASHA [stabilized hyaluronic acid], 100,000 kDa, 1 injection) was approved in 2017. NASHA is derived from biofermentation. A process is used to stabilize HA molecules through the introduction of a minimal number (~1%) of synthetic crosslinks, slowing their rate of degradation.[34,35] These linear HA molecules are incorporated into a 3-dimensional gel matrix, and are resistant to degradation with a half-life of ~1 month.[36]

Hymovis and Gel-One are also FDA-approved IAHA preparations, but these have not been compared to other IAHA in head-to-head trials and will not be explored further in this review. Hymovis (HYADD 4, 500-730 kDa, 2 injections) was approved in 2015.[37] It is a modified hyaluronan derived from bacterial fermentation. HYADD 4 is non-crosslinked hygroscopic viscoelastic hydrogel. Our literature search did not identify any placebo-controlled studies for HYADD 4. One positive randomized level I study (150 patients) reported superior effects with HYADD 4 over IA-corticosteroids.[38] Three observational studies were also found.[39-41] Gel-One[42] (1 injection) was approved in 2011. Gel-One is composed of Gel-200, a cross-linked hyaluronate hydrogel that is produced using photo-gelation technology.[43] One level I study (377 patients)[44] reported statistically significant improvements with IA-Gel-200 over IA-placebo in the primary outcome measure (WOMAC [Western Ontario and McMaster Universities Osteoarthritis Index] pain) at 13-week follow-up in the intent-to-treat (ITT) population. An extension study confirmed the safety of retreatment and increased time-to-retreatment in patients receiving IA-Gel-200.[45,46] A pooled analysis of this study and a second unpublished study also reported superior outcomes with IA-Gel-200 compared to placebo up to 26 weeks.[47] A recent subgroup analysis[48] of patients that closely matched the inclusion criteria in other IAHA trials also reported clinical efficacy at 26 weeks.

## Safety and Efficacy Data of Individual IAHA Preparations

### *Low-Molecular-Weight IAHA Preparations Approved in the United States*

*Sodium Hyaluronate (Hyalgan).* Four placebo-controlled studies (2 level I[49,50] and 2 level II[51,52]) with follow-ups ranging from 5 to 52 weeks reported conflicting results, with only 2 studies observing statistically significant improvements in the primary outcome measure with Hyalgan compared to placebo (1 level I[50] and 1 level II study[51]). In these studies, IA-Hyalgan significantly improved visual analog scale (VAS; 100 mm) pain scores up to 23 to 25 weeks, compared to placebo ($P < 0.05$ to $P < 0.002$).

In one level II study (63 patients)[53] comparing IA-Hyalgan to IA-corticosteroids, the ITT analysis indicated no statistically significant differences between treatments in the primary outcome measure (ie, VAS pain on a self-selected activity that aggravated knee pain the most). Notably, the study had a substantial withdrawal rate over the 6-month follow-up period. Five studies assessed the efficacy and safety of IA-Hyalgan as an adjunct to standard

**Table 2.** FDA-Approved Intraarticular Hyaluronic Acid Preparations.

| | Source | Composition | Confirmation | Molecular Weight | Dose and Treatment Schedule |
|---|---|---|---|---|---|
| Hyalgan | Avian | Sodium hyaluronate | Linear chain | 500-730 kDa | 10 mg/mL<br>3 to 5 weekly injections (2 mL) |
| Hymovis | Bacterial fermentation | Hyaluronan (HYADD 4) | Linear chain | 500-730 kDa | 8 mg/mL<br>2 weekly injections (3 mL) |
| Supartz/Supartz FX | Avian | Sodium hyaluronate | Linear chain | 620-1,170 kDa | 10 mg/mL<br>5 weekly injections (2.5 mL) |
| GenVisc850[a] | Bacterial fermentation | Sodium hyaluronate | Linear chain | 620-1,170 kDa | 10 mg/mL<br>5 weekly injections (2.5 mL) |
| Orthovisc | Bacterial fermentation | Hyaluronan | Linear chain | 1,000-2,900 kDa | 15 mg/mL<br>3 to 4 weekly injections (2 mL) |
| Monovisc[b] | Bacterial fermentation | Hyaluronan | crosslinked | 1,000-2,900 kDa | 22 mg/mL<br>1 injection (4 mL) |
| Neflexxa/Euflexxa | Bacterial fermentation | Sodium hyaluronate (BioHA) | Linear chain | 2,400-3,600 kDa | 10 mg/mL<br>3 weekly injections (2 mL) |
| Sinovial/gelsyn-3 | Bacterial fermentation | Sodium hyaluronate | | 1,400-2,100 kDa | 8.4 mg/mL<br>3 weekly injections (2 mL) |
| Synvisc | Avian | 80 Hylan A:20 hylan B (Hylan G-F 20) | Crosslinked | 6,000 kDa | 8 mg/mL<br>3 weekly injections (2 mL) |
| Synvisc One | Avian | 80 Hylan A:20 hylan B (Hylan G-F 20) | Crosslinked | 6,000 kDa | 8 mg/mL<br>1 injection (6 mL) |
| Durolane | Bacterial fermentation | Stabilized hyaluronic acid (NASHA) | Linear chain, ~1% crosslinked | 100,000 kDa | 20 mg/mL<br>1 injection (3 mL) |
| Gel One | Avian | Sodium hyaluronate (Gel-200) | Crosslinked | N/A[c] | 10 mg/mL<br>1 injection (3 mL) |

[a]Generic drug equivalent of Supartz/Supartz FX.
[b]Same grade and specification of HA that is used in Orthovisc.
[c]Not reported as formulation/is highly cross-linked.

treatment (2 level I and 4 level II, 38 to 251 patients).[54-59] Results were inconsistent, with 3 of the 5 studies (1 level I, 26-week follow-up;[58] 2 level II, 1-year follow-up[54]) reporting no improvement in pain or functional outcomes with IA-Hyalgan as an adjunct to treatment in comparison to standard treatment alone.

Of the 7 randomized IA-Hyalgan studies that reported on adverse events (AEs),[49-52,55,56,58] the majority described transient mild to moderate local AEs at the injection site, which occurred with similar frequency in the IAHA and placebo groups.[49,50,55,56,58] However, one study reported more local transient pain and swelling with Hyalgan (47%) compared to placebo (22%),[52] and one study reported 3 suspected treatment-related events in the Hyalgan group only ($n = 30$ patients).[51]

The literature search found 13 observational studies,[60-73] with sample sizes that ranged from 31 to 249 patients, that reported conflicting results. One retrospective analysis[72] compared risk of TKA in patients receiving IAHA using IMS Health's PharMetrics Plus Health Plan Claims Database (50,389 patients). In a Cox proportional hazards model (PHM) of time-to-TKA, the risk of TKA was higher by 7% with IA-Hylan G-F 20 compared to a Supartz/Hyalgan cohort (HR = 1.069, $P = 0.0009$). Notably, while the PHM was adjusted for several background covariates, including age and comorbidities, it was not adjusted for other variables shown to affect IAHA outcomes, such as baseline pain and structural disease severity.[74-76]

*Sodium Hyaluronate (Supartz/Supartz FX).* Four studies assessed the efficacy and safety of IA-Supartz compared to IA-placebo, with consistent results.[77-80] Two level I (209 patients;[77] 240 patients[79]) and one level II (95 patients [116 knees])[78] studies reported that pain and functional outcomes (eg, Lequesne index, WOMAC index) were superior with IA-Supartz compared to IA-placebo, with follow-ups ranging from 4 to 18 weeks. These studies either reported no incidence of AEs[78,79] or low rates of transient minor local AEs that were similar between groups.[77] The fourth study was the Amelia trial (306 patients),[80] a level I study that assessed IA-Adant (generic drug equivalent of Supartz) and reported that repeated treatment cycles are safe and maintain superior clinical outcomes relative to IA-placebo. In this study, which had 6-month follow-ups after the first and second treatment cycle and 1-year follow-ups after the third and fourth cycles, reported that there were significantly more OARSI 2004 responders with IA-Adant than placebo from 14-month (after the second cycle, $P = 0.030$) to 40-month follow-up (after the fourth cycle, $P = 0.004$). Similar rates of patients with at least one AE were reported with IA-Adant and placebo.

One level II randomized study (61 patients, 10 patients lost-to-follow-up) reported comparable outcomes for VAS pain on walking and clinical assessment scores with IA-Supartz (5 weekly injections) and IA-corticosteroids (Decadron; 1 injection, 4 mg) at 5-week and 6-month follow-up.[81] One level I study (240 patients)[82] compared IA-Supartz and IA-placebo as an adjunct to standard care and found no differences between the treatment groups at 20-week follow-up in the ITT or PP (per protocol) populations in several pain and function parameters, including Lequesne index and VAS pain.

The literature search found 6 observational studies, with sample sizes that ranged from 30 to 73 patients,[83-88] with inconsistent results. No additional real-world studies based on large registries or claims databases were identified, other than the retrospective study using IMS Health's PharMetrics Plus Health Plan Claims Database described in the Hyalgan section above.[72]

*Section Summary.* Evidence for the efficacy of low MW IA-Hyalgan is inconsistent. IA-Hyalgan was only shown to be superior to placebo in half (one level I[50] and one level II study[51]) of the 4 studies identified.[49-52] Results from studies investigating IA-Hyalgan as an adjunct to standard care were also mixed, with only 2 out of 5[54-58] studies reporting improvements in pain and function outcomes from adding IA-Hyalgan to standard care. Studies investigating Supartz were more consistent in reporting superior outcomes with IA-Supartz compared to IA-placebo across the 4 studies identified.[77-80] However, one level I study reported no treatment benefit of adding IA-Supartz to standard care.[82] Both Hyalgan and Supartz were shown to have similar efficacy to IA-corticosteroids in level II randomized studies.[53,81] Overall, IA-Hyalgan and IA-Supartz were shown to have acceptable safety profiles, with studies mainly reporting mild to moderate local AEs which were present with similar frequency between in IAHA and IA-placebo groups.

## *Medium-Molecular-Weight IAHA Preparations Approved in the United States*

*Hyaluronan (Orthovisc).* Two studies compared the safety and efficacy of IA-Orthovisc and an IA-saline placebo.[89,90] While the level I study (226 patients)[89] with a 27-week follow-up did not find significant differences between IA-Orthovisc and IA-saline in the ITT population, the level II study (41 patients)[90] reported statistically significant superior outcomes with IA-Orthovisc in several pain and function outcomes ($P < 0.001$ to $P = 0.0001$). The level I study was a multicenter, placebo-controlled, double-blind trial that performed analyses for WOMAC index scores, global assessments, and time to walk 50 feet. All treatment-related AEs were mild to moderate, with no difference between treatment groups.

One level I randomized study (372 patients)[91] comparing IA-Orthovisc to an arthrocentesis control procedure also failed to meet the primary efficacy endpoint which

was "proportion of responders," defined as at least a 20% relative improvement and an absolute improvement of at least 50 mm from baseline in WOMAC Pain Score over 4 consecutive assessment points between 8-week and 22-week follow-up. The efficacy analysis was performed on the PP population (336 patients), which was defined as patients who completed all 4 treatments, had at least one follow-up, and had no important protocol violations. Treatment with IA-Orthovisc yielded a statistically significant higher proportion of responders compared IA-placebo, but this was only at the 8-week follow-up. The safety analysis, performed on the ITT population (370 patients), found no significant differences in AEs between the treatment groups.

Two level II studies (69 patients;[92] 44 patients[93]) compared IA-Orthovisc to an IA-corticosteroid. The first level II study[92] reported on several pain and function outcomes up to 6-month follow-up, including VAS (100 mm) pain, the Lequesne functional index, and range of knee flexion. Statistically significant superior pain ($P = 0.033$ to $P = 0.015$) and functional ($P = 0.045$) outcomes were observed with IA-Orthovisc at 3-month follow-up only. The second level II study[93] reported statistically significant outcomes with IA-Orthovisc over a 6-month period that were superior to IA-dexamethasone for WOMAC pain ($P = 0.03$), stiffness ($P = 0.03$), and physical activity ($P = 0.03$), but not WOMAC total. Superior improvement in knee extensor strength was also reported with IA-Orthovisc compared to IA-dexamethasone ($P = 0.04$).

The literature search identified one real-world study[94] (29,076 patients; 2008-2015, IBM market scan data) reporting that IA-Orthovisc can decrease use of NSAIDs, steroids, and opioids ($P < 0.001$).

*Hyaluronan (Monovisc).* One level I randomized double-blind multicenter trial (369 patients)[95] reported superior outcomes with the single-injection preparation IA-Monovisc compared to IA-saline. The primary efficacy endpoint was treatment success as defined by OMERACT-OARSI in the WOMAC pain score through 26-week follow-up. A greater overall rate of treatment success was observed with IA-Monovisc compared to IA-saline in the ITT population (365 patient, $P = 0.043$) and the PP population (334 patients, $P = 0.038$). Treatment-related AEs were mild to moderate reactions at the injection site. No statistically significant differences in AE frequency were observed between IA-Monovisc (7.1% of patients) and IA-saline (5.4% of patients).

*Sodium Hyaluronate/BioHA (Euflexxa).* Our literature search identified one level I randomized double-blind multicenter trial comparing IA-BioHA to placebo (FLEXX trial; 588 patients),[96] which also had an extension study (433 patients).[97] The FLEXX trial[96] reported superior outcomes with IA-BioHA compared to IA-placebo in the ITT population for change in VAS (100 mm) pain at 26-week follow-up ($P = 0.002$). The rate of any treatment-emergent adverse event (TEAE; BioHA [157 (54%)] vs. Placebo [169 (57%)]) or serious TEAE ($n = 9$, 3%, both group) were similar between the IA-BioHA and IA-saline placebo group. In the extension study,[97] all patients received a new course of 3 weekly injections of IA-BioHA. The number of patients experiencing at least one AE did not differ between patients receiving of IA-BioHA (*FLEXX trial BioHA group*, 96 patients [43.8%]) and those receiving it for the first time (*FLEXX trial placebo group*, 92 patients [43%]). Of these patients, 21 (4.8%) had a mild to moderate local AE that was attributed to treatment with IA-BioHA.

Two observational studies were identified.[98,99] One real-world study using Medicare administrative data (2005-2012)[99] reported that BioHA is associated with longer time to TKA. Propensity score adjustment indicated that in the HA cohort, time to TKA was longer than the non-HA cohort by 8.7 months ($P < 0.001$). A subgroup analysis indicated that the delay to TKA in the non-BioHA HA cohort was 6.8 months ($P < 0.001$), and that there was an additional 1.8-month delay with BioHA ($P = 0.021$).

*Section Summary.* The efficacy data for Orthovisc is inconsistent and predominantly negative. While a small level II study[90] reported statistically significant improvements in pain and function outcomes with IA-Orthovisc over IA-placebo, a level I placebo-controlled study[89] using IA-saline and a second level I study[91] with an arthrocentesis control both failed to meet primary endpoints in ITT analyses. Two level II studies[92] comparing IA-Orthovisc to IA-corticosteroids, with one study reporting superior outcomes with IA-Orthovisc at 3, but not 6, months,[92] and one study[93] reporting superior outcomes with IA-Orthovisc in in WOMAC pain, stiffness, and physical activity subscores, as well as knee extensor strength. Evidence for the efficacy of Monovisc[95] and BioHA[96,97] was provided by placebo-controlled level I studies. The Monovisc study reported superior outcomes with IA-Monovisc compared to IA-placebo in the primary outcome measure, which was OMERACT-OARSI responder criteria. The evidence for BioHA is provided by one level I double-blind multicenter trial (FLEXX trial[96]) and an extension study.[97] The FLEXX trial met the primary endpoint which was change in VAS (100 mm) pain at 26-week follow-up, and the extension study demonstrated the safety of repeated courses of IA-BioHA. All 3 medium MW preparations were associated with mild to moderate transient local injection reactions that were not statistically significantly different from placebo.

## *High-Molecular-Weight IAHA Preparations Approved in the United States*

*Stabilized Hyaluronic Acid/NASHA (Durolane).* Two level I studies investigated the efficacy and safety of IA-NASHA

compared to an IA-saline placebo, with a 6-week follow-up in the first study (218 patients)[100] and a 26-week follow-up in the second study (346 patients).[101] The primary outcome in both studies was WOMAC pain responder rate, defined as an at least 40% reduction in WOMAC pain score from baseline. Both studies failed to find significant differences in the primary outcome measures between the treatment groups in the ITT populations.

The first study reported a higher percentage of patients reporting a treatment-related AE with IA-NASHA compared to IA-saline (15.7% vs. 5.5%, $P = 0.0154$). No AEs were reported in the second study.

One level II study compared IA-NASHA, NSAIDs, and PRP (146 patients).[102] The primary outcome measure was WOMAC pain responder rate (ie, 20% reduction on WOMAC pain score from baseline). All treatments improved the primary outcome measure relative to baseline at 26- and 52-week follow-up. However, between-group comparisons indicated that there was no difference in efficacy between IA-NASHA and NSAIDs at either time point. Over the 52-week follow-up, 2 patients in the IA-NASHA group reported local pain and swelling at injection site. No other treatment-related AEs were reported.

Two studies compared IA-NASHA to IA-corticosteroids.[103,104] The first was a level II study (60 patients)[103] that found no significant differences between IA-NASHA and IA-triamcinolone in electromyographic activity patterns, gait analysis, or any of the clinical parameters examined, including VAS pain, Knee Society Score (KSS), Lequesne score, and SF-36 questionnaire. No AEs were reported in either treatment group. The second was a level I study (442 patients)[104] that reported that IA-NASHA was noninferior to IA-methylprednisolone (IA-MPA) in an ITT (LOCF) population for the primary outcome measure, which was WOMAC pain responder rates (40% reduction in WOMAC pain score from baseline) at 12-week follow-up. Sensitivity analysis of WOMAC responder rates indicated that IA-NASHA was noninferior to IA-MPA up to 24-week follow-up. Superiority was not demonstrated at any follow-up. Treatment-related AEs were transient and localized to the injection site, with a frequency of 21.7% with IA-NASHA and 6.8% with IA-MPA. There were significantly more incidences of arthralgia with IA-NASHA (38 [NASHA] vs. 7 patients [MPA], $P < 0.0001$).

*Hylan G-F 20 (Synvisc).* Three studies (1 level I and 2 level II) assessed the efficacy and safety of Hylan G-F 20 compared to an IA-saline placebo,[105-107] and consistently reported statistically significant improvements with Hylan G-F 20. The level I double-blind placebo-controlled multicenter randomized trial (253 patients)[107] compared IA-Hylan G-F 20 (Synvisc-One) to IA-saline. The primary outcome measure was WOMAC pain over a 26-week period. Analysis of the ITT population indicated that improvement in the primary outcome measure was superior with the single-injection preparation of IA-Hylan G-F 20 (Synvisc-One; $P = 0.047$). The rate of treatment-related AEs between the groups, which were of mild to moderate severity, was not statistically significant (Hylan G-F 20, 4/123 [3.3%] vs. saline, 1/130 [0.8%]). In the first level II randomized study (80 patients),[105] 2 different injection schedules of IA-Hylan G-F 20 (ie, 2 IA injections of Hylan G-F 20 vs. 3 IA injections of Hylan G-F 20) were compared to IA-placebo. Improvements in VAS (100 mm) pain with both IA-Hylan G-F 20 groups were significantly better than with IA-saline up to the final 12-week follow-up. Patient global evaluations also indicated that IA-Hylan G-F 20 was more efficacious than IA-placebo from 8-week follow-up onward ($P < 0.05$). One transient local AE was reported in the IA-Hylan G-F 20 group (muscle pain). In a second level II randomized study (30 patients),[106] statistically significant improvements in VAS pain at rest and WOMAC pain were observed with IA-Hylan G-F 20 compared to IA-saline, at 3- and 8-week follow-up ($P < 0.05$). By the last follow-up at 8 weeks, statistically significant improvements were also observed for VAS night pain, VAS pain during walking, WOMAC functional impairment, and paracetamol usage relative to IA-saline ($P < 0.05$).

Several studies have compared Hylan G-F 20 to other standard therapies for OA of the knee. One level I study (102 patients)[108] compared (1) IA-Hylan G-F 20, (2) NSAIDs plus arthrocentesis, and (3) IA-Hylan G-F 20 plus NSAIDs. No difference was observed between the groups in the primary outcome measure, VAS (100 mm) weight-bearing pain on motion, at 12-week follow-up (93 patients). A q-statistical analysis confirmed that Hylan G-F 20 could be considered at least as effective as NSAIDs in all VAS measures of pain and joint function studied, except for activity restriction. Two patients in the IA-Hylan G-F 20 group had mild to moderate local AEs attributed to treatment. A second level I study[109] randomized 165 patients to IA-hylan G-F 20, the NSAID diclofenac retard, or a placebo consisting of placebo capsules and arthrocentesis over 12 weeks. The ITT analysis showed that IA-hylan G-F 20 was superior to diclofenac retard ($P = 0.03$) and placebo ($P = 0.04$). IA-hylan G-F 20 was superior to the other treatment groups for the Lequesne index in the evaluable population. There were more GI-related AEs in the NSAID group (NSAID, 48% vs. IA-hylan G-F 20, 22%; placebo, 11%).

Two studies (1 level I and 1 level II) have reported evidence that Hylan G-F 20 is superior to IA-corticosteroids, while 3 studies (2 level I and 1 level II) have found no statistically significant differences in outcomes between the 2 treatments. Notably, one of the negative studies was a level II randomized study (111 patients [143 knees]; 30 patients lost to follow-up)[110] conducted in patients with advanced disease awaiting arthroplasty, and the clinical outcomes examined only assessed changes in knee function

parameters (Lysholm, KSS functional, KSS total scores). The second study to report no difference between IA-Hylan G-F 20 and IA-corticosteroids (triamcinolone acetonide [TA]) was a level I study (110 patients, 11 patients lost-to-follow-up)[111] that compared improvements in VAS pain, WOMAC score, and active knee joint flexion at 6-month follow-up. However, effects were seen more rapidly with IA-TA, resulting in a statistically superior outcome with TA in the first 7 days ($P = 0.018$), with no difference between the groups thereafter. One treatment-related AE was reported by a patient in the IA-Hylan G-F 20 group who experienced transient pain and swelling at the injection site. The third study[112] to report no significant difference between IA-hylan G-F 20 and IA-corticosteroids (betamethasone sodium) was a level I study that randomized 100 patients 1 of the 2 treatment conditions reported no statistically significant differences in WOMAC, KSS, or VAS scores between the 2 treatments at 6-month follow-up. One level I study (218 patients)[113] reported superior outcomes with IA-Hylan G-F 20 compared to IA-TH. An ITT (LOCF; 215 patients) analysis showed greater improvements with IA-Hylan G-F 20 compared to IA-TH, in the primary outcome measures at 12- and 26-week follow-up: WOMAC pain (12-week follow-up, $P = 0.007$; 26-week follow-up, $P = 0.0129$) and VAS pain ($P < 0.0001$). In the safety analysis (216 patients), no statistically significant differences were observed in the rate of patients with treatment-related AEs (21% [Hylan G-F 20] vs. 14% [TH]), including arthralgia which was the most commonly reported AE (31% [Hylan G-F 20] vs. 32% [TH]). The second was a randomized level II study (82 patients)[114] which examined KSS for pain and function and VAS pain up to 24 weeks. From the 4-week follow-up onward, IA-Hylan G-F 20 was superior to the IA-TH for KSS score ($P < 0.01$). From the 12-week follow-up onward, the IA-Hylan G-F 20 group was superior to IA-TH for VAS pain ($P = 0.03$) and KSS function ($P < 0.01$). In the IA-TH group, 1 patient developed a mild infection, and 3 patients experienced a transient rise in blood glucose levels. One patient in the IA-Hylan G-F 20 group had a transient acute inflammatory reaction at the injection site.

Four studies assessed the safety and efficacy of Hylan G-F 20 as an adjunct to appropriate standard care. All 4 studies were consistent in reporting statistically significant improvements in pain and functional outcomes with the addition of IA-Hylan G-F 20, up to 52-week follow-up. The first level I randomized study (110 patients [117 knees])[115] reported statistically significant improvements with the addition of IA-Hylan G-F 20 as an adjunct to standard care compared to the addition IA-placebo in VAS pain and patient-reported treatment success up to 12-week follow-up in the ITT population. The second study was a level I study (255 patients),[116] which reported statistically significant improvements in WOMAC pain with the addition of IA-Hylan G-F 20 at 12-month follow-up in the ITT population ($P = 0.0001$), compared to standard care alone. The study also reported a statistically significant reduction in the utilization of steroid injections, oral NSAID therapy, and other medications for knee OA in the Hylan G-F 20 group. In the group receiving IA-Hylan G-F 20, 82 transient local AEs were reported in 38 patients, of which 15 were attributed to Hylan G-F 20 treatment and 57 to the injection procedure. Fewer gastrointestinal AEs were observed in the Hylan G-F 20 group (26 vs. 53), including severe GI AEs (5 vs. 22). A post hoc analysis[117] assessed outcomes using 2 different sets of OARSI responder criteria developed for the study of intraarticular drugs in the treatment of knee OA, and a third simplified set of criteria developed by OMERACT-OARSI. IA-hylan G-F 20 was superior to standard care using all 3 sets of criteria ($P = 0.017$). A second post hoc analysis[118] later confirmed the safety of repeated courses of Hylan G-F 20; no statistically significant differences in local adverse events or rates of arthrocentesis were identified between the groups receiving one versus repeated courses of IA-Hylan G-F 20. The third level I study (506 patients),[119] reported superior outcomes in the primary outcome measure, Lequesne index at 9-month follow-up, in the ITT population (LOCF) with IA-Hylan G-F 20 ($P < 0.0001$). The most common adverse event in the IA-Hylan G-F 20 group was pain or swelling at the injection site (37.2%). In the control group, the most common adverse event was gastrointestinal symptoms in 11.9% of patients, compared to 3.5% in the IA-Hylan G-F 20 group. In the recent VISK study (156 patients),[120] the primary outcome was response to therapy at 52 weeks according to OMERACT-OARSI response criteria. Subjects who were lost to follow-up were considered nonresponders in the intervention group and responders in the control group. IA-Hylan G-F 20 was superior to the control group in the 2 different primary outcome analyses that were performed: (1) one using pain at rest for the pain domain ($P = 0.006$) and one using pain during activity for the pain domain ($P = 0.015$).

The literature search identified 26 observational studies, including 7 large real-world studies based on large registries or claims databases.[72,121-126] One real-world study[121] confirmed the efficacy and safety of 2 consecutive series of IA injections of hylan G-F 20 preparation (1,263 patients) in clinical practice using the Southwestern Ontario primary care database compared to a reference group (3,318 patients). After 2 cycles of hylan G-F 20 therapy, the average VAS score for pain at rest declined by $3.66 \pm 1.78$ in a 10-point VAS, significantly more than the reduction of $3.12 \pm 2.03$ seen in the reference group ($P = 0.012$). The average VAS score for pain after the 6-minute walk test also decreased by $5.56 \pm 1.74$ points, which is a significantly larger than the change seen in the reference group ($2.99 \pm$

1.85; $P = 0.001$). Two real-world studies of patient registries confirmed the tolerability of IA-Hylan G-F 20, reporting mild to moderate AEs in less than 5% of patients (4,253 patients[122]; 1,047 patients[123]). These studies also reported a reduction in use of analgesics and NSAIDs with IA-Hylan G-F 20 treatment. Two studies provided evidence that IA-Hylan G-F 20 increases time to TKA.[124-126] A retrospective case series of medical records (1997 to 2010; 1,867 knees)[124,125] reported a survival analysis which indicated that TKA was delayed by more than 7.3 years in 75% of the IA-Hylan G-F 20-treated knees. A second study using the Optum Clinformatics data set (2006 to June 2016; 4,027,848 knee OA patients)[126] reported that in the 141,305 patients who had undergone TKA, the adjusted median time to TKA was longer by more than 7 months in patients receiving IAHA ($P < 0.001$), compared to patients who had not received IAHA. In Hylan G-F 20 patients specifically, time to TKA was an additional 1.7 months longer compared with other IAHAs, after adjusting for time to HA and number of injections ($P < 0.001$).

*Section Summary.* The 2 US-approved high MW preparations reviewed had very different efficacy and safety profiles. Treatment with IA-NASHA failed to meet primary endpoints in 2 level I placebo-controlled studies with 6- to 26-week follow-ups.[100,101] Both studies reported no statistically significant differences in WOMAC pain responder rates between IA-NASHA and IA-saline in ITT populations. The safety profile reported for IA-NASHA varied across studies. While 3 studies reported no or fewer than 2% of AEs with NASHA,[101-103] 2 studies reported higher numbers of patients with treatment-related AEs with IA-NASHA compared to IA-saline (level I[100]) and IA-corticosteroids (level I[104]). In the study comparing IA-NASHA to IA-MPA, the higher patient rate of treatment-related AEs was attributed to a higher frequency of arthralgia.

IA-Hylan G-F 20 improved WOMAC pain in the ITT population compared to IA-saline over a 26-week follow-up in 1 level I study.[107] Evidence for the efficacy of IA-Hylan G-F 20 was also reported in 2 smaller level II studies,[105,106] which showed statistically significant improvements in pain and functional outcomes between 3- to 12-week follow-up. In addition, 4 level I studies reported statistically significant superior pain and functional outcomes with the addition of IA-Hylan G-F 20 to standard care at 12- to 52-week follow-up.[115,116,119,120] AEs in placebo-controlled studies were mild to moderate transient injection reactions, and the frequency did not differ between IA-Hylan G-F 20 and IA-Saline. In studies comparing addition of IA-Hylan G-F 20 to standard care reported a decrease in rate of GI-related AEs in patients receiving IA-Hylan G-F 20.

IA-NASHA[102] was reported to have similar efficacy to NSAIDs. One level I study reported that IA-Hylan G-F 20 was superior to NSAIDs,[109] and a second level I found the 2 treatments to be of similar efficacy.[108] Two studies have compared IA-NASHA to IA-corticosteroids.[103,104] In a level I study,[104] IA-NASHA was noninferior to IA-MPA in WOMAC pain responder rates in the ITT population at 12-week follow-up. A smaller level II study[103] echoed these findings, reporting no differences in several pain and functional outcomes. IA-Hylan G-F 20 was superior to IA-TH in pain and function outcomes at 12- to 26-week follow-up in a level I study[113] and a level II[114] study. However, 2 level I studies[111,112] reported no difference between IA-Hylan G-F 20 and IA-TA corticosteroid at 6-month follow-up, and a level II study[110] in patients with severe OA awaiting arthroscopy also reported no difference between IA-Hylan G-F 20 and IA-corticosteroids at 3 or 6 months.

## Head-to-Head Comparisons between IAHA Preparations Approved in the United States

Results from the head-to-head trials are summarized in **Tables 3** to **5**.

### *Low- versus Medium-Molecular-Weight IAHA Preparations*

*Adant versus Monovisc.* One level II randomized study (41 patients, 1 lost to follow-up)[127] compared the efficacy and safety of IA-Adant (3 weekly injections, 2.5 mL) and IA-Monovisc (1 injection, 4 mL). Both treatment groups reported improvements relative to baseline in all outcome measures examined up to the final 6-month follow-up (VAS [100 mm] pain, WOMAC index scores; $P < 0.001$), except for WOMAC stiffness. No between-group differences were observed for any of the outcomes at any follow-up, although improvement in VAS pain at rest was significantly better with IA-Adant compared to IA-Monovisc at the 6-month follow-up only. No adverse events were recorded.

### *Low- versus High-Molecular-Weight Preparations*

*Hyalgan versus Hylan G-F 20.* A level I study (392 patients)[128] compared 5 weekly injections of IA-Hyalgan to 3 weekly injections of IA-Hylan G-F 20. An ITT (LOCF) analysis indicated that the primary outcome measure, VAS pain at 6 months, was significantly reduced from baseline with IA-Hylan G-F 20 ($P < 0.05$), but not IA-Hyalgan. Statistically significant between-group differences confirmed that IA-Hylan G-F 20 was superior to IA-Hyalgan in reducing VAS pain score at 6-month follow-up ($P = 0.02$). There was no difference in the rate of treatment-related AEs between the

**Table 3.** High- versus Low-Molecular-Weight IAHA Preparations.

| | Synvisc | | | Durolane | | |
|---|---|---|---|---|---|---|
| | Superior | Noninferior/No Difference | Inferior | Superior | Noninferior/No Difference | Inferior |
| Hyalgan | $N = 392$[128]<br>*Superiority design*<br>• ITT (LOCF): Synvisc superior to Hyalgan in the primary endpoint, VAS pain, at 6-month follow-up | $N = 32$[129]<br>*Superiority design*<br>• No statistically significant differences between IA-Synvisc and IA-Hyalgan for VAS pain, WOMAC index scores, and SF-36 at 26-week follow-up | | | | |
| Supartz | $N = 70$[130]<br>*Superiority design*<br>• ITT and PP: Synvisc superior to Supartz in VAS (100 mm) weight-bearing pain, most painful knee movement, and overall treatment response, up to 12 weeks<br>$N = 41$[131]<br>*Superiority design*<br>• Synvisc superior to Artz in VAS pain up to 20-week follow-up, but not by 26-week follow-up | $N = 246$[132]<br>*Superiority design*<br>• ITT and PP: No statistically significant difference between Artzal, Synvisc, and placebo for VAS weight-bearing pain at 26-week follow-up, or duration of clinical benefit (0-52 weeks) | | | $N = 349$[133]<br>*Noninferiority design*<br>• ITT and PP: Durolane was non-inferior to ARTZ in WOMAC pain up to 26-week follow-up | |

IAHA = intraarticular hyaluronic acid; ITT = intention-to-treat; PP = per protocol; VAS = visual analogue scale; IA = intraarticular; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36.

treatment groups (Hyalgan, 30 patients vs. Hylan G-F 20, 39 patients). In a small level II randomized study,[129] 32 patients treated with either IA-Hyalgan or IA-Hylan G-F 20 exhibited statistically significant improvements relative to baseline for VAS pain on walking ($P < 0.01$), WOMAC index scores ($P < 0.01$), and SF-36 ($P < 0.05$). However, no statistically significant differences were observed between the treatment groups. No AEs related to treatment were reported.

*Supartz/Supartz FX versus Hylan G-F 20.* One level I double-blind multicenter randomized study (70 patients [73 knees], lost to follow-up)[130] compared IA-Supartz and IA-Hylan G-F 20 in VAS weight-bearing pain, improvement in most painful knee movement, and improvement in overall pain, at 12-week follow-up. Analysis of the ITT population showed that IA-Hylan G-F 20 was superior to IA-Supartz in all primary outcome measures examined ($P < 0.05$). The rates of local AEs were not statistically different between groups (0.9% with IA-Supartz and 1.8% with IA-hylan G-F 20). Similar results were reported in a prospective comparative study[131] of 41 patients who received treatment with IA-Hylan G-F 20 in one knee (3 weekly injections) and IA-Artz in the other (5 weekly injections). Low rates of local adverse reactions were reported, which were not significantly different between groups. Treatment with IAHA improved all clinical outcomes examined up to 26-week follow-up, relative to baseline ($P < 0.05$). IA-Hylan G-F 20 was superior to IA-Artz for degree of improvement in VAS pain in the first 20 weeks ($P < 0.05$), but this difference was not sustained at 26 weeks. Consistent with this time frame, a study comparing the efficacy of IA-Artzal and IA-Hylan G-F 20 at longer follow-up times of 26 and 52 weeks did not find statistically significant differences between the 2 IAHA preparations. In this double-blind multicenter trial,[132] 246 patients were randomized to treatment with either IA-Artzal (2.5 mL), IA-Hylan G-F 20 (2.0 mL), or IA-placebo (3 mL). The primary outcome measure was VAS weight-bearing pain during the first 26 weeks of the study, and duration of clinical benefit (time to clinical failure) in a Kaplan–Meier survival analysis (0-52 weeks). A PP analysis ($N = 210$ patients) showed a statistically significant reduction in VAS weight-bearing pain relative to baseline in all 3 treatment groups ($P < 0.001$). However, there were no

**Table 4.** High- versus Medium-Molecular-Weight IAHA Preparations.

| | Synvisc | | |
|---|---|---|---|
| | Superior | Noninferior/No Difference | Inferior |
| Euflexxa | | $N = 321$[139]<br>*Noninferiority design*<br>• ITT (LOCF): Euflexxa noninferior to Synvisc up to 12 weeks<br>• A later post hoc analysis[140] performed with OMERACT-OARSI response criteria: Euflexxa noninferior to Synvisc | |
| Orthovisc | $N = 82$[138]<br>*Superiority design*<br>Synvisc superior to Orthovisc for VAS pain, WOMAC-function, SF-36 pain and social functioning, at 6-month follow-up | $N = 40$[136]<br>*Superiority design*<br>• No statistically significant differences in WOMAC scores between Synvisc and Orthovisc (pain, function, stiffness) up to 1-week after last injection (4 weeks)<br>$N = 660$ patients[134]<br>*Superiority design*<br>• No statistically significant differences between the Synvisc and Orthovisc in WOMAC scores up to 6 months<br>$N = 78$ patients[135]<br>*Superiority design*<br>• No statistically significant differences between the Synvisc and Orthovisc up to 6 months<br>$N = 92$ patients (184 knees)[137]<br>*Superiority design*<br>• No statistically significant differences in KSS scores between Synvisc and Orthovisc up to 12-month follow-up | |
| Gelsyn | | $N = 381$[141]<br>*Noninferiority design*<br>• ITT and PP: noninferior to Synvisc in WOMAC pain up to 26-weeks | |

IAHA = intraarticular hyaluronic acid; ITT = intention-to-treat; PP = per protocol; VAS = visual analogue scale; IA = intraarticular; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36.

**Table 5.** Medium- Versus Low-Molecular-Weight IAHA Preparations.

| | Monovisc | | |
|---|---|---|---|
| | Superior | Noninferior | Inferior |
| Adant | | $N = 41$[127]<br>*Superiority design*<br>• No statistically significant differences between Monovisc and Adant in VAS pain (activity and at rest), WOMAC pain, function, and stiffness at 1-, 3-, or 6-month follow-up<br>• One exception: VAS pain at rest at 6-month follow-up was superior with Adant | |

IAHA = intraarticular hyaluronic acid; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

statistically significant differences between the treatment groups.

*Supartz/Supartz FX versus NASHA.* One level I multicenter, double-blind, noninferiority study (349 patients)[133] compared the efficacy and safety of 5 weekly injections of IA-Artz (2.5 mL) versus one single injection of IA-NASHA (3 mL). The primary outcome measure was WOMAC pain up to 26 weeks (noninferiority margin: 8%). IA-NASHA was found to be noninferior to IA-Artz in the PP (319

patients) and ITT (349 patients) populations at 18- and 26-week follow-up. There were no differences in rate of AEs between the treatment groups.

### *Medium- versus High-Molecular-Weight IAHA Preparations*

*Hylan G-F 20 versus Orthovisc.* One level I study comparing Orthovisc to Hylan G-F 20 was identified. In this multicenter single-blind trial,[134] 660 patients were randomized to receive 3 weekly injections of either (1) IA-Hylan G-F 20, (2) IA-Orthovisc, or (3) IA-Ostenil, which is not approved in the United States. Analysis of the ITT population indicated that improvement in the primary outcome measure (WOMAC pain at 6 months) was similar across IAHA treatment groups. The were no statistically significant differences in AEs with the different IAHA preparations.

One level II study (78 patients, 15 lost to follow-up)[135] compared treatment with (1) IA-Hylan G-F 20, (2) IA-Orthovisc, and (3) IA-saline placebo. Improvement in WOMAC physical function ($P < 0.01$) and stiffness ($P < 0.01$) scores were significantly better in both IAHA groups compared to placebo from 1-month follow-up onward. WOMAC pain scores with both IAHAs were significantly improved from baseline ($P < 0.05$) but not different from placebo. By 6-month follow-up, the IAHA groups also reported significantly better patient and physician global assessments (PGA) scores compared to placebo ($P < 0.05$). No statistically significant differences between the IAHA groups were reported in any of the outcome measures, at any follow-up.

Three additional studies directly comparing 3 weekly injections of IA-Hylan G-F 20 (2 mL, 16 mg) to IA-Orthovisc (2 mL, 30 mg) were identified. One level II randomized study (40 patients)[136] investigating the effects of different preparations of IAHA on inflammatory markers in synovial fluid also reported on clinical outcomes. WOMAC pain and physical function scores were significantly improved from baseline at 1-week follow-up onward ($P < 0.05$ to 0.001), and WOMAC stiffness was significantly improved by the last follow-up at 4 weeks ($P < 0.05$ to 0.01). There were no statistically significant between-group differences. A second level II randomized study (92 patients [184 knees]; 30 patients lost to follow-up)[137] used Hospital for Special Surgery (HSS) knee score up to 12 months as the primary outcome measure. By the end of the trial, the total HSS score was significantly improved compared to baseline in both groups ($P < 0.01$), but there were no statistically significant differences between the treatment groups in any of the outcomes. No AEs were reported. In the third study, Hylan G-F 20 and Orthovisc were also compared to physical therapy. In the third level II study,[138] 82 (2 lost to follow-up) patients were randomized to 3 weekly injections of IA-Hylan G-F 20 (20 patients) or IA-Orthovisc (20 patients), followed by a fourth injection at 6-month follow-up. Patients in the physical therapy group received treatment 5 times per week for 3 weeks (42 patients). Direct comparisons of the IAHA treatment groups indicated that statistically significant improvements in VAS night pain, pain at rest, pain on touch, WOMAC-function, SF-36 pain, and social functioning were superior with IA-Hylan G-F 20 ($P < 0.05$), but not VAS pain on movement, WOMAC-pain, and WOMAC-total. The rate of local adverse events was not significantly different between the IAHA groups (3 patients (IA-orthovisc) versus 1 patient (IA-hylan G-F 20 group).

*Hylan G-F 20 versus BioHA.* One level I noninferiority trial[139] (321 patients, 7 lost to follow-up) compared IA-Hylan G-F 20 and IA-BioHA. An ITT (LOCF) analysis indicated that both groups experienced statistically significant improvements in the primary outcome measure WOMAC (100 mm) pain up to 12-week follow-up, compared to baseline ($P < 0.0001$). Mean improvement in the WOMAC pain met the criteria for noninferiority. Overall, the rate of TEAEs was similar between the treatment groups (BioHA [54/160, 33.8%] vs. Hylan G-F 20 [65/161, 40.4%]). In the BioHA group, 84.6% of TEAEs were coded as mild or moderate, compared to 90.5% in the IA-Hylan G-F 20 group. However, a statistically more effusions were reported with IA-Hylan G-F 20 (8.1%) compared with IA-BioHA (0.6%, $P = 0.0015$). A post hoc analysis[140] of these data was later performed with OMERACT-OARSI response criteria. In the IA-Hylan G-F 20 group, 99 of the 158 patients (63%) were considered responders compared to 112 of the 157 patients (71%) in the IA-BioHA group ($P = 0.10$), confirming that IA-BioHA is noninferior to IA-Hylan G-F 20.

*Hylan G-F 20 versus Sinovial/Gelsyn-3.* One double-blind noninferiority study[141] randomized 381 patients to 3 weekly injections of IA-Hylan G-F 20 (2 mL, 16 mg) or IA-Sinovial (2 mL, 16 mg). The primary efficacy measure was improvement in mean WOMAC pain score from baseline to the final 26-week visit (margin for noninferiority: 8 mm). The mean change in WOMAC pain score with IA-Sinovial met the prespecified criteria for noninferiority in both the ITT and PP populations. No statistically significant differences in AEs rates were reported.

## Conclusion

The high MW *versus* low MW head-to-head trials suggest that Hylan G-F 20 is superior to the low MW preparations. Two studies compared Hylan G-F 20 to Hyalgan.[128,129] The level I study[128] reported superior outcomes with IA-Hylan G-F 20 compared to IA-Hyalgan in VAS pain scores at 6-month follow-up in an ITT (LOCF) analysis. Three studies compared IA-Hylan G-F 20 to IA-Supartz (2 level I[130,132]

and 1 level II[131]). Overall, these studies reported superior pain outcomes with IA-Hylan G-F 20 than IA-Supartz for up to 3- or 5-month follow-up, but not thereafter. One level I study[133] reported that NASHA is noninferior to Supartz at 26-week follow-up. Together, these studies suggest that the high MW preparation IA-Hylan G-F 20, specifically, is superior to the low MW IAHA preparations of IA-Hyalgan and IA-Supartz. Compared to these other IAHA preparations, IA-Hylan G-F 20 has been consistently superior to IA-Saline in 3 randomized placebo-controlled studies,[105-107] including a level I study[107] with a 26-week follow-up, using the single-injection preparation Hylan G-F 20 (Synvisc-One, 6 mL). In addition, 4 level I studies[115,116,119,120] have reported superior pain and functional outcomes with IA-Hylan G-F 20 as an adjunct to standard care at 12- to 52-week follow-up. Placebo-controlled studies with IA-Hyalgan have yielded inconsistent results,[49-52] while outcomes with IA-Supartz have been consistently superior to IA-saline,[77-80] but both low MW preparations have not consistently improved outcomes when used as adjuncts to standard care in level I or level II studies.[54-58,82] Also, IA-NASHA failed to meet primary efficacy endpoints in ITT analyses in 2 level I randomized placebo-controlled studies with 6- to 26-week follow-ups.[100,101] In addition, the safety profile reported for IA-NASHA has varied across studies, with some studies reporting rates of treatment-related AEs that are higher than IA-Saline[100] or IA-corticosteroids.[104]

Seven studies comparing medium versus high MW IAHA were identified, all of which used IA-Hylan G-F 20 as the high MW preparation. None of these studies reported statistically significant differences in outcomes. Five studies[134-138] compared IA-Orthovisc to IA-Hylan G-F 20 in a range of outcomes measures (ie, WOMAC index, VAS pain, HSS knee score, SF-36) with follow-ups that ranged from 4 weeks to 1 year, and did not find any difference in efficacy between the IAHA preparations. However, one of the level II studies[138] which assessed multiple clinical outcomes reported superior results with IA-Hylan G-F 20 for VAS pain, WOMAC-function, SF-36 pain, and social functioning. Notably, of the 5 studies comparing Orthovisc to Hylan G-F 20, 4 studies were poor-quality randomized trials with small sample sizes.[135-138] While placebo-controlled studies have reported superior outcomes with IA-Hylan G-F 20, this has not been the case with IA-Orthovisc in level I studies.[89,91] In the one level I placebo-controlled study comparing IA-Orthovisc to IA-saline, treatment with IA-Orthovisc failed to meet the primary efficacy.[89] A second level I study that compared IA-Orthovisc to an arthrocentesis control procedure also failed to meet the primary efficacy endpoint.[91]

One level I study[139] reported that medium MW IA-BioHA is noninferior to Hylan G-F 20 in WOMAC pain up to 12-week follow-up. BioHA has shown superiority over IA-saline in one level I study, the Flexx trial,[96] and an extension study.[97] Medium MW IA-Synovial was also reported to be noninferior to Hylan G-F 20 in WOMAC pain at 26 weeks in one single level I head-to-head trial.[141] However, there are no published placebo-controlled studies to support the efficacy of IA-Synovial.

## Future Recommendations

Based on our review of the current literature, we recommend BioHA and Hylan G-F 20 as the IAHA preparations with the best efficacy and safety profiles. Of these 2 preparations, only Hylan G-F 20 is available in a single-injection preparation (Synvisc-One), which has been shown to reduce pain up to 26-week follow-up in a level I placebo-controlled trial.[107] More high-quality level I randomized head-to-head trials are needed to compared the safety and efficacy of the different FDA-approved IAHA preparations. Level I studies comparing efficacy for IAHA preparations stratified by molecular weight would also provide valuable insights.

Concomitant use of IA corticosteroids with IAHA is becoming an increasingly frequent practice, with the aim of reducing AEs, particularly pseudosepsis, and improving short- and long-term outcomes. Level I studies comparing the incidence of pseudoseptic reactions with IAHA preparations of high and low molecular weight, injected with and without concomitant IA corticosteroid, are needed to evaluate the potential therapeutic benefits of this practice.

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