Medical Policy

BlueCross BlueShield of Kansas
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Title: Intra-articular Hyaluronan Injections for Osteoarthritis

Professional
Original Effective Date: January 2001
Revision Date(s): April 11, 2001; May 1, 2002; June 12, 2002; April 7, 2006; May 19, 2006; January 9, 2007; April 19, 2007; July 1, 2007; December 31, 2007; January 1, 2008; January 1, 2010; January 1, 2012; September 24, 2012; October 26, 2012; October 1, 2013; May 1, 2014
Current Effective Date: May 1, 2014

Institutional
Original Effective Date: July 1, 2007
Revision Date(s): December 31, 2007; January 1, 2008; January 1, 2010; January 1, 2012; September 24, 2012; October 26, 2012; October 1, 2013; May 1, 2014
Current Effective Date: May 1, 2014

DESCRIPTION

Intra-articular injection of hyaluronan (HA) into osteoarthritic joints is thought to replace HA, restore the viscoelastic properties of the synovial fluid, and improve pain and function. The majority of studies to date have assessed HA injections for knee osteoarthritis, and this is the U.S. Food and Drug Administration (FDA)-approved indication. Other joints, such as the hip and shoulder, are currently being investigated for intra-articular HA treatment of osteoarthritis (OA).

Background

Hyaluronan (HA) is a naturally occurring macromolecule that is a major component of synovial fluid and is thought to contribute to its viscoelastic properties. Chemical crosslinking of hyaluronan increases its molecular weight; cross-linked hyaluronans are referred to as hylans. In osteoarthritis (OA), the overall length of HA chains present in cartilage and the HA concentration in the synovial fluid are decreased. Intra-articular injection of HA (IAHA) has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in patients with OA. This treatment has been called viscosupplementation. Currently, no curative therapy is available for OA, and thus the overall goals of management are to reduce pain and prevent disability.

Regulatory Status

Six preparations of intra-articular (IA) hyaluronan have been approved by the FDA as an alternative to nonsteroidal anti-inflammatory drug therapy in the treatment of OA of the knee (Synvisc® and Synvisc-One®, Genzyme; Hyalgan®, Fidia; Supartz®, Smith and Nephew; OrthoVisc®, Anika; and Euflexxa®, previously named Nuflexxa, Savient). All products are manufactured from rooster combs except for Euflexxa and Orthovisc, which are produced from bacterial fermentation. Also, Synvisc undergoes additional chemical crosslinking to create hylans with increased molecular weight (6,000 kDa) compared to Hyalgan (500-730 kDa) and Supartz (620-1,170 kDa). The differing molecular weights of the products lead to different half-lives; the half-life of Hyalgan or Supartz is estimated at 24 hours, while the half-life of Synvisc may range up to several days.

Intra-articular hyaluronic acid is “indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen.” The product inserts further indicate that Synvisc® and Euflexxa® should be injected intra-articularly into the knee joint once per week for a total of 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hyalgan® and Supartz® products, and 3–4 weekly injections are recommended for OrthoVisc®. In February 2009, the FDA approved the use of single-dose hylan G-F 20 (Synvisc-One™) for the treatment of OA of the knee. In 2011, the FDA approved the use of the single-dose cross-linked hyaluronate Gel-One® (also known as Gel-200) for the treatment of OA of the knee. In 2000, the FDA approved removal of a precautionary statement from the package inserts for Hyalgan and Synvisc that stated that the safety and efficacy of repeat courses have not been established. The FDA has not approved intra-articular hyaluronan for joints other than the knee.

POLICY

Intra-articular hyaluronan injections are considered **not medically necessary.**

RATIONALE

Knee

Systematic Reviews

This policy was originally based on a TEC Assessment on intra-articular hyaluronan (IAHA) for osteoarthritis (OA), (1) and in 2004, TEC published a Special Report on IAHA for OA of the knee.

(2) Overall, the 2004 review found that the evidence was still consistent with that presented in the 1998 TEC Assessment, showing a statistically significant effect in almost all studies, although the magnitude and clinical significance of the effect may be small. Similar results were obtained in Cochrane reviews in 2005 and 2006. (3, 4) In 2007, the TEC Evidence-based Practice Center published a technology assessment for the Agency for Healthcare Research and Quality (AHRQ) on the treatment of primary and secondary OA of the knee. (5) The report concluded that results from 42 trials (n=5,843) generally showed positive effects of viscosupplementation on pain and function scores compared to placebo for patients with primary OA of the knee. However, the evidence on viscosupplementation was accompanied by considerable uncertainty due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported. Trials of hylan G-F 20 (Synvisc, 6,000 kDa), the highest molecular weight cross-linked product, generally reported better results than other trials. Similar concerns were noted in a 2012 meta-analysis of 89 trials (12,667 patients) on viscosupplementation for OA of the knee. (6)

In 2013, the American Academy of Orthopaedic Surgeons (AAOS) conducted a systematic review of treatments for osteoarthritis (OA) of the knee. (7) Included was a meta-analysis of 3 high-strength and 11 moderate-strength studies of IAHA for OA of the knee. Pain outcomes were significantly lower in the treatment group compared to placebo, but the difference was found to be not clinically important, since the lower bound of the confidence interval was higher than the minimal clinically important difference. This indicated a low likelihood that an appreciable number of patients achieved clinically important benefits. Similar results were obtained for functional outcomes. This meta-analysis found evidence that high molecular-weight preparations were more effective than those with low weights, indicating a possible clinically important difference for the higher molecular-weight preparations.

Section Summary

There are a large number of RCTs completed on treatment of OA of the knee with hyaluronan (HA) and numerous systematic reviews of these trials. The majority of systematic reviews concluded that there is a modest beneficial effect of treatment, but that the clinical significance of the magnitude of difference is uncertain. A 2013 meta-analysis by the AAOS that included 14 moderate- to high-strength studies concluded that the improvements in health outcomes with IAHA were statistically but not clinically significant.

Joints Except the Knee

Colen et al. conducted a 2012 systematic review of prospective trials of IAHA for joints other than the knee. (8) In addition to nonrandomized prospective studies, the search identified 5 randomized controlled trials (RCTs) for the hip, 1 for the shoulder, 4 for the ankle, 5 for the carpometacarpal-1 joint, 1 for the lumbar facet joint, and 1 for the first metatarsophalangeal joint. Examination of the literature for each joint found evidence for a positive effect of IAHA when compared to baseline, with limited evidence that IAHA is superior to placebo, and no evidence that IAHA is better than corticosteroids or other conservative therapies. Following is a summary of systematic reviews and primary evidence by joint.

Ankle

Migliore and colleagues conducted a review of 7 studies on IAHA for ankle OA, identified from the period of 2006-2009, that included 3 small RCTs with a total of 75 patients, and 4 case series. (9) For 2 of the RCTs, IAHA was compared to saline injection, and the results showed benefit on some outcome measures but not others. The third RCT compared IAHA to exercise

therapy and reported no differences in outcomes. The authors were unable to do a meta-analysis due to the limited number of studies and study heterogeneity.

In 2012, DeGroot et al. reported on an RCT of 64 patients with ankle OA that compared a single IAHA to a single intra-articular (IA) saline injection. (10) At 6 weeks and 12 weeks, there were no significant differences in improvement between treatment groups on the American Orthopaedic Foot & Ankle Society clinical rating score, the Ankle Osteoarthritis Scale score, and the patient-reported visual analog pain scale (VAS).

Foot

There is a very limited amount of evidence on IAHA injections in the foot. Munteanu and colleagues reported on an RCT of a single IAHA injection in 151 patients with first metatarsophalangeal joint OA. (11) At 1, 3, and 6 months' follow-up, there were no significant differences between the IAHA and placebo groups on the Foot Health Status Questionnaire.

Hand

Two small RCTs that enrolled a total of 100 patients evaluated HA injections compared to steroid injections for arthritis of the thumb. (12, 13) Fuchs et al. (13) reported that steroid injections were superior at 2-3 weeks posttreatment but that IAHA was superior at 6 months' follow-up. Stahl et al. (12) reported essentially equivalent outcomes between steroid injections and IAHA, although IAHA was superior to steroids for some aspects of fine motor function. The results of these trials are not sufficient to determine the efficacy of IAHA for thumb arthritis and are not sufficient for determining comparative efficacy to steroids.

Hip

A 2008 systematic review of 2 RCTs and 9 cohort studies concluded that viscosupplementation therapy with HA appears to be "a safe and effective method in the treatment of hip OA resistant to conventional treatment modalities."(14) In their 2012 systematic review, Colen et al. identified 3 RCTs that compared IAHA with placebo, 1 that compared IAHA with IA anesthetic, and 1 that compared hyaluronans of different molecular weights. (8) These 3 trials showed a statistical effect favoring IAHA treatment. However, the effect size was small compared to saline injections, and there were not significant differences between IAHA and other conservative treatments such as steroid injections.

The largest RCT randomized 101 patients to receive either HA injections or saline. (15) There was a small reduction in pain with walking in patients treated with HA injections over the 3-month evaluation period. An industry-sponsored RCT compared a single 2.5 mL IAHA (Adant, 900 kDa, unavailable in the U.S.) to saline injection for treatment of hip OA in 85 patients. (16) At 3 months, there were no significant differences between groups in any outcome measure. The number of patients who experienced mild to moderate treatment-related adverse events (injection-site pain, pain flare, hematoma, pruritus) did not differ between groups. Atchia and colleagues reported on a randomized, controlled trial (RCT) of 77 patients with hip OA who were potential candidates for total hip replacement. (17) In this study, patients were randomized to receive standard care or an injection of saline, hyaluronan or methylprednisolone and followed for 8 weeks. Significant improvement was only seen in the steroid group in the numerical rating scale for worst pain, and the Western Ontario and McMaster Osteoarthritis Index for pain and function. No improvements were reported in the IAHA group.

In an industry-sponsored, single-center, randomized, double-blind, active-controlled trial, published in 2009, 42 patients with OA of the hip were randomly assigned to receive 2 monthly injections of high-molecular weight IAHA (Hyalubrix® - unavailable in the U.S.) or IA mepivacaine, a local anesthetic. (18) At 3 and 6 months, there was a significant decrease in the Lequesne algofunctional index (LFI) in the IAHA group compared to the mepivacaine group (5.15 vs. 6.53 at 3 months; 3.94 vs. 6.41 at 6 months, both respectively). The only reported adverse event was injection-site pain occurring in 1 patient in each group.

Shoulder

A 2010 meta-analysis of 19 blinded RCTs examined the use of viscosupplementation for chronic painful shoulder in a total of 2,120 patients. (19) A variety of shoulder disorders were included, e.g., adhesive capsulitis, rotator cuff tear, shoulder impingement syndrome, and frozen shoulder. Sample size ranged from 20 to 660 patients, mean trial duration was 3.5 weeks, and mean Jadad score was 3.5 ± 1.5. Ten trials (1,435 patients) reported pain outcomes. The combined effect size (standardized mean difference) for categorical and continuous pain ratings favored IAHA (0.39). There was no heterogeneity and no evidence of publication bias. Because the studies included in the meta-analysis were of short duration and included a variety of shoulder diseases, they do not provide conclusive evidence of the effectiveness of IAHA in OA of the shoulder.

The largest trial is an industry-sponsored RCT of 660 patients with persistent shoulder pain due to glenohumeral joint OA, rotator cuff tear, and/or adhesive capsulitis compared 3 weekly injections versus 5 weekly injections of sodium hyaluronate (Hyalgan) versus 5 weekly injections of saline. (20) Approximately 60% of patients had OA, although the majority of those with OA also had rotator cuff disorders or capsulitis. Sixty-nine percent (n=456) of the patients had a follow-up visit at 26 weeks. There was no significant difference among groups in the primary outcome measure, shoulder pain with movement at 13 weeks. Analysis of predefined, stratified subgroups revealed no significant differences in reported pain at 13 weeks but a statistically significant decrease of 7.5 and 7.8 mm (on a 100-mm VAS scale) in reported pain in both treatment groups at 26 weeks compared to placebo among patients with OA. In those without OA, there was no significant improvement with either regimen. Of note, this appears to be an as-treated analysis of the OA subgroup data, and the difference may not be clinically important.

In 2013, Kwon et al. reported a multicenter randomized double-blind placebo-controlled trial of IAHA in 300 patients with glenohumeral OA. (21) Intent-to-treat analysis found similar improvement in VAS for pain (19.88 mm for IAHA and 16.29 mm for placebo) and in the Outcome Measures in Rheumatoid Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) high responder rate (40.8% for IAHA and 34.9% for sham). In a subset of patients, there was a statistically significant difference in VAS of 4.0 mm on a 100-mm scale and 8.37% on the OMERACT-OARSI. However, the clinical significance of these differences is uncertain.

Other

Data from small pilot studies, and case series have been reported using hyaluronan for arthritis of the spine and for lateral condylitis of the elbow (tennis elbow).

Section Summary. The evidence on the efficacy of IAHA for joints other than the knee is less robust. While some studies show benefit, others do not, and systematic reviews have not concluded that there is a clinically significant benefit.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov in July 2013 identified a number of open trials with IAHA. These include Phase III and Phase IV trials evaluating IAHA for OA of the knee (NCT01372475, NCT01543737, NCT01557868, and NCT01335321), and a pivotal multicenter trial of Hylan G-F 20 for OA of the hip (NCT01618708).

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers (6 reviewers). Most reviewers agreed that IAHA of the knee was medically necessary. In addition, those providing input supported an interval of 6 months for repeat injections. In response to a question about total number of treatment courses, there was no consensus.

Summary

Intra-articular injection of hyaluronan into osteoarthritic joints is thought to replace hyaluronan, restore the viscoelastic properties of the synovial fluid, and improve pain and function. The largest amount of evidence is on treatment of osteoarthritis (OA) of the knee. Individual trials show inconsistent results in pain and functional outcomes for intra-articular injection of hyaluronan (IAHA) compared to placebo or active control. Meta-analyses of RCTs shows improvements in pain and function that are statistically but not clinically significant, and recent guidelines from the American Academy of Orthopaedic Surgeons give a strong recommendation against the use of IAHA.

IAHA continues to be investigated for off-label uses in other joints. Current evidence on these off-label uses is limited, consisting of small RCTs and case series. Some RCTs on IAHA injections for OA of the ankle, foot, hand and shoulder have shown treatment benefits; however, these studies are not consistent in reporting improvements that are significantly greater than placebo and/or control treatments. RCTs on IAHA injections for OA of the hip have also been inconsistent, with some RCTs reporting improvements in outcomes with IAHA hip injections and others reporting no improvement. Currently, given the limited and inconsistent available data, and the low likelihood that IAHA for joints other than the knee are more effective than IAHA for the knee, these uses are also considered not medically necessary.

Practice Guidelines and Position Statements

The American Academy of Orthopaedic Surgeons' (AAOS) 2013 guideline on treatment of osteoarthritis of the knee states that they cannot recommend using hyaluronic acid for patients with symptomatic knee OA. (7) This is a strong recommendation, meaning that the quality of the supporting evidence is high. This recommendation was based on a meta-analysis of 3 high-strength and 11 moderate-strength studies that showed that the overall effect was less than 0.5 minimally important different units, indicating a low likelihood that an appreciable number of patients achieved clinically important benefits. The AAOS states that practitioners should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is

present. This replaces a 2008 guideline in which a recommendation could not be made for IAHA due to inconclusive evidence.

The 2009 AAOS Clinical Practice Guideline on glenohumeral joint osteoarthritis (22) includes a weak grade C recommendation that "the use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis." Grade C recommendations are based on poor-quality evidence. In this instance, the recommendation is based on a single case series of 30 patients with OA of the glenohumeral joint who received 3 weekly IA injections of Synvisc. (23) At 1, 3, and 6 months, clinically significant improvements were seen in pain, function, and quality-of life-measures.

In 1995, the American College of Rheumatology (ACR) published guidelines for the treatment of osteoarthritis (OA) of the knee, which recommended acetaminophen as first-line therapy, followed by low-dose ibuprofen, and then full-dose nonsteroidal anti-inflammatory drugs (NSAIDs), when necessary. In 2000, the ACR published updated guidelines on the management of hip and knee OA. (24) These guidelines recommend nonpharmacologic approaches and drug therapy for management of hip and knee OA. Intra-articular hyaluronan (IAHA) or glucocorticoids are considered alternative approaches to oral agents for knee OA, based on studies demonstrating effectiveness in reducing knee pain. However, the guidelines noted the absence of studies demonstrating the efficacy of IAHA or glucocorticoids for hip OA. Updated guidelines from 2012 addressed OA of the hand, hip, and knee. (25) A conditional recommendation was given for IAHA to treat OA of the knee. The ACR recommends not using IAHA for OA of the hand. For OA of the hip, the ACR explicitly makes no recommendation regarding treatment with IAHA.

The Osteoarthritis Research Society International (OARSI) guidelines, (26) developed by consensus after review of existing guidelines and systematic reviews, recommend:

Injections of IA [intra-articular] hyaluronate may be useful in patients with knee or hip OA [osteoarthritis]. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids.

The recommendation is made with a strength of 64% (CI: 43-85%).

The 2009 Bannuru et al. meta-analysis, (27) noted above, was cited in a 2010 evidence update by OARSI. (28) In an accompanying editorial, OARSI authors note that IAHA "has a time-dependent trajectory of therapeutic effect. Thus, the time point at which its outcome is assessed will influence its apparent effectiveness." (29)

2008 Guidelines published by the National Institute for Health and Clinical Excellence (NICE) do not recommend IAHA injections for the treatment of OA because "the cost-effectiveness estimate is outside the realms of affordability" to the National Health Service. (30) However, guideline developers state, "Overall, the evidence suggests that hyaluronans and hylan derivatives seem to be superior to placebo in terms of efficacy and quality of life outcomes in patients with OA in the knee at different postinjection periods but especially at the 5- to 13-week postinjection period." Toxicity of IAHA was noted to be small.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg
J7326	Hyaluronan or derivative, Gel One, for intra-articular injection, per dose

REVISIONS

01-01-2007	Added HCPCS Codes: Q4083, Q4084, Q4085, Q4086
03-31-2007	Deleted HCPCS Code: J7319
12-31-2007	Deleted HCPCS Codes: Q4083, Q4084, Q4085, Q4086
01-01-2008	Added HCPCS Codes: J7321, J7322, J7323, J7324.
12-24-2008	In Description: ▪ Revised wording from "...intra-articular lubricants in patients with any musculoskeletal condition, including osteoarthritis." To "...intra-articular lubricants in patients with osteoarthritis of the knee." In Policy section: ▪ Added "The use of hyaluronan injections may be considered medically necessary when all of the following are met:" ahead of the three criteria.
01-01-2010	In Coding Section: ▪ Added HCPCS Code: J7325 ▪ Removed HPCS Code: J7322
	In Policy Section / Utilization: ▪ Added: "Synvisc-One is a single injection treatment regimen"
01-01-2012	In the Coding section: ▪ Added HCPCS code: J7326
09-24-2012	In the Policy Title, removed "of the Knee" to read "Intra-articular Hyaluronan Injections for Osteoarthritis"
	Description section updated.
	Added Medical Policy and Coding Disclaimers.
	In the Policy section: ▪ Revised the following policy language: The use of hyaluronan injections may be considered medically necessary when all of the following are met: 1. Diagnosis of Osteoarthritis (degenerative arthritis) for knee only. 2. Failed conservative treatment, i.e., anti-inflammatory agents, physical therapy, weight loss, activity modification, knee brace, and occasional corticosteroid injection. Reconstructive surgery where a knee is unstable and surgery is indicated. 3. The series of injections (one course) can be repeated every six months.

	▪ In the Utilization portion, added: • Euflexxa® is a 3-5 dose course of treatments. • Gel One ® is a 3-5 dose course of treatments. • Orthovisc ® is a 3-5 dose course of treatments.
	Added Rationale section.
	Updated Reference section.
10-26-2012	In the Policy section: ▪ In the Utilization section, removed the 4th bullet, "Gel One ® is a 3-5 dose course of treatments." ▪ In the Utilization section, last sentence, added "® and Gel-One ® are" and removed "is" to read "Synvisc-One ® and Gel-One ® are a single injection treatment regimen."
10-01-2013	Updated Description section.
	In Policy section: ▪ Revised the following medical policy language: "A. Intra-articular hyaluronan injections may be considered medically necessary for treatment of painful osteoarthritis of the knee in patients who have insufficient pain relief from conservative nonpharmacologic therapy and simple analgesics. B. Repeated courses of intra-articular hyaluronan injections of the knee may be considered medically necessary under the following conditions: • Significant pain relief achieved with the prior course of injections; and • At least 6 months have passed since completion of the prior course. C. The use of intra-articular hyaluronan injections in joints other than the knee is considered experimental / investigational." ▪ Removed "Utilization" section. ▪ Added "FDA Approved Indications and Dosage" table.
	In Coding section: ▪ Added ICD-10 Diagnosis codes. *(Effective October 1, 2014)*
	Updated Rationale section.
	Updated Reference section.
05-01-2014	Updated Description section.
	In Policy section: ▪ Changed the current medical policy language From: "A. *Preferred* Viscosupplements may be considered medically necessary when ALL the following are met: 1. The patient has a diagnosis of OA of the knee AND 2. The patient has tried and failed to respond adequately to conservative nonpharmacologic therapy AND to simple analgesics [acetaminophen or NSAIDs] AND 3. ONE of the following: a. The patient is receiving his/her first course of viscosupplement OR b. the patient's previous course of viscosupplement was at least 6 months previous OR c. the request is for the other knee joint not previously treated AND 4. The dose of the requested agent is within FDA labeled dosing guidelines. B. *Non-preferred* Viscosupplements may be considered medically necessary when all of the following are met:

	1. The patient has a diagnosis of OA of the knee AND 2. The patient has tried and failed to respond adequately to conservative nonpharmacologic therapy AND simple analgesics [acetaminophen or NSAIDs] AND 3. ONE of the following: a. The patient has evidence of use of the preferred agent in pharmacy claims or medical history at least 6 months prior to request of the non-preferred agent OR b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred viscosupplement agent. AND 4. It has been at least 6 months since the patient used the preferred agent OR any other viscosupplement for the same knee joint AND 5. The dose of the requested agent is within FDA labeled dosing guidelines C. Repeated courses of intra-articular hyaluronan injections of the knee may be considered medically necessary under the following conditions: 1. Significant pain relief achieved with the prior course of injections; AND 2. At least 6 months have passed since completion of the prior course. D. The use of intra-articular hyaluronan in the knee when the above criteria are not met, and injections in joints other than the knee is considered experimental / investigational." To: "Intra-articular hyaluronan injections are considered not medically necessary."
	Updated Rationale section.
	In Coding section: ▪ Removed Diagnoses codes
	Updated Reference section.

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