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Intra-Articular Hyaluronan Injections For Osteoarthritis of the Knee: Issues for Coverage Policy and Utilization

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INTRA-ARTICULAR HYALURONAN INJECTIONS FOR OSTEOARTHRITIS OF THE KNEE: ISSUES FOR COVERAGE POLICY AND UTILIZATION

Summary

Though intra-articular hyaluronan (IAHA) injections are widely used to treat osteoarthritis (OA) of the knee, coverage policies vary among managed care organizations, and utilization criteria differ widely among individual clinicians. The objectives of this advisory board were to review the evidence supporting the IAHA class; compare the available IAHA products with respect to their composition, cost, and clinical profile; and attempt to reach consensus regarding appropriate utilization policies. Clinical trial data were presented on the safety, efficacy, and cost-effectiveness of IAHA. Laboratory data were presented describing the chemical, physical, and biological differences between the available IAHA products. Randomized clinical trials (RCTs) comparing different IAHA products were reviewed. Consensus was reached on many points, and open questions requiring additional data were identified. IAHA was acknowledged as a valuable new treatment option indicated for knee OA patients who fail conservative treatment and simple analgesics. Discussions focused around the types of patients that are most likely to respond favorably to IAHA. There was considerable debate regarding whether IAHA should be used before or after high-dose nonsteroidal anti-inflammatory drug (NSAID) therapy and intra-articular corticosteroids; however, there was agreement as to the value of IAHA in patients at risk for NSAID or corticosteroid associated iatrogenic morbidities. IAHA was assessed as being most effective in patients with moderate OA, who present without a large effusion or other clinical signs of acute synovitis. Though success rates are somewhat lower for patients with advanced disease, the probability of response was considered sufficiently high for IAHA utilization in select patients to defer or obviate surgery. Major malalignment and mechanical instability were identified as negative predictors of success for all patient categories. Radiologic grade was accepted as relevant, but remains a rather poor predictor of either patient symptomology or successful IAHA treatment outcome. Managed care plans can optimize IAHA utilization by adapting coverage policies to the growing body of available information and the evolving understanding of how these agents work. Head-to-head RCT data suggest that there is no detectable difference in effectiveness among current IAHA products. Moreover, hylan products are associated with an increased incidence of acute reactions in the injected knee during repeat treatment. Product acquisition costs vary widely between suppliers, and can be relevant to product preference decisions. IAHA coverage policies should be adapted to reflect current treatment algorithms, emphasizing conservative measures, minimizing the iatrogenic morbidities associated with OA disease management, and ensuring that surgical approaches are appropriately utilized. All agreed that IAHA could contribute to a cost-effective strategy for managing knee OA.

Intra-Articular Hyaluronan Injections For Osteoarthritis of the Knee: Issues for Coverage Policy and Utilization

OA Epidemiology and Costs:

The Problem for Health Care Systems

OA is a chronic degenerative disease associated with aging. As population distributions shift toward older ages, OA has moved to the forefront of public health issues, and will increasingly impact health care budgets.¹ OA also can occur in younger patients, where it is generally secondary to a prior injury, family genetics, or high-risk factors such as malalignment and obesity. The prevalence of clinically defined OA was reported to be 27 million Americans in 2005, up from 21 million in 1995.² Arthritis and other rheumatic diseases are a leading cause of disability in the United States, with direct and indirect medical costs estimated to be \$116 billion in 1997, approximately 1.4 percent of the U.S. gross domestic product.^{3,4} Major cost factors include OA-related prescription medication, surgery, and physician visits.⁵ OA and related conditions account for more ambulatory care visits than cardiovascular disease or essential hypertension.⁶ In 2003, \$11.3 billion was spent in the United States for primary knee replacements, with an additional \$1.5 billion for revision surgeries.⁷ Moreover, the number of knee replacements performed in the United States has been steadily climbing, and this trend is predicted to continue (Figure 1).⁸ This exponential increase in the number of joint replacements and revisions highlights a looming health and economic problem for public and private payers. Considering the aging of the U.S. population and the importance of an active lifestyle to overall health, all participants recognized the need for both cost containment and improved patient outcomes.

OA Pathology and Progression

OA can affect almost any joint, but is most common in the knee, hip, and hand.² Symptomatic OA of the knee is both common and costly, and because new treatments specifically indicated for knee OA

are available, the advisory group focused its discussion on knee OA.

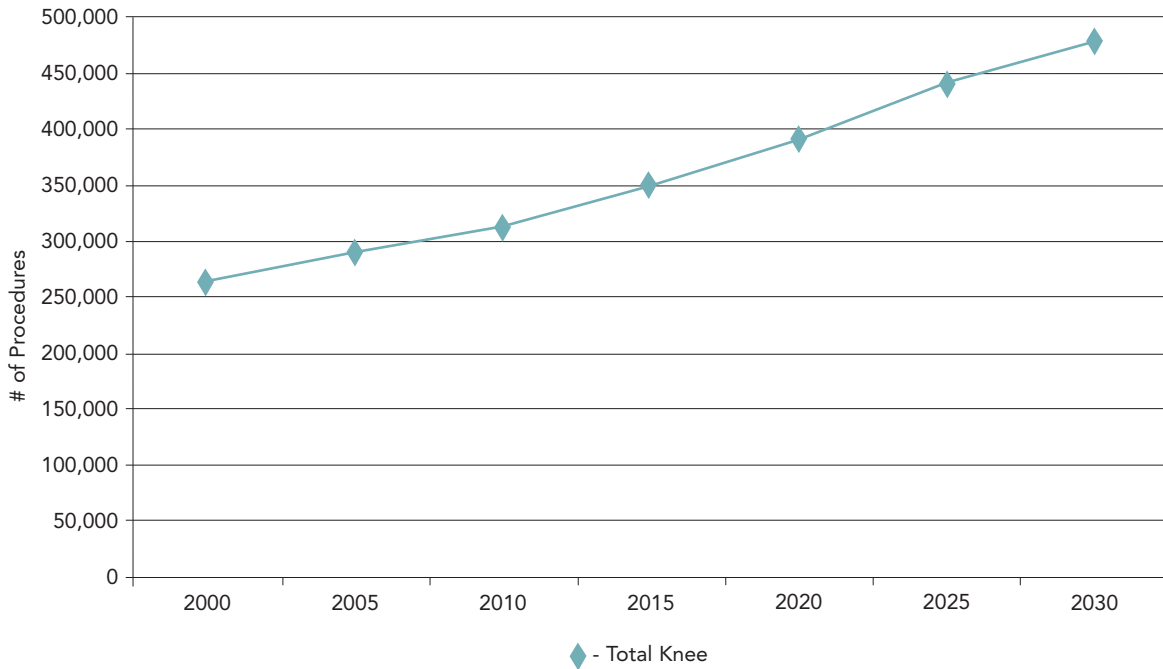
The diagnosis of OA is typically based on clinical symptoms, exclusion of other causes of joint pain, and confirmation by radiologic changes in the affected joint. The severity of radiologic abnormality can be scored based on the presence of osteophytes and subchondral sclerosis, and the degree of joint space narrowing on weight-bearing X-rays. However, it is important to note that radiologic scores correlate poorly with patient symptomatology.⁹ Physicians commonly encounter elderly patients who exhibit radiologic changes indicative of late-stage OA, yet remain functional and relatively symptom-free for years. The ability of such patients to successfully manage their symptoms is encouraging, because it highlights the potential for patients with radiologically advanced OA to function normally. Longitudinal studies of OA progression likewise indicate that many patients can remain stable for extended time periods; some even can improve.^{10,11}

Cartilage deterioration and breakdown has long been considered the pathologic hallmark of OA, as reflected in radiologic joint space narrowing. However, cartilage tissue cannot be a primary source of OA pain because it is aneural. More recently, it has become clear that synovium, periarticular soft tissue, and subchondral bone all contribute to OA pathology and symptomatology.¹² The joint capsule is richly innervated with nociceptors that sense noxious stimuli and have nonmyelinated termini in direct contact with the fluid intercellular matrix of joint tissues. Neurogenic mechanisms are recognized as important factors underlying the pathophysiology of chronic joint pain.¹³

OA symptomatology is typically characterized by periods of quiescence and flare, which are often not associated with clinical signs of synovitis and inflammation. Only about half of patients presenting with knee OA pain have clinical signs of synovitis and/or effusions.^{14,15} Thus, many patients experiencing a flare of knee OA can be characterized as having a “dry” painful joint. Appropriate clinical management of OA flares is important because pain causes patients to reduce the mobility necessary for normal joint metabolism, and can increase the risk for disability, disease progression, and the need for joint replacement.

It is important to note that radiologic scores correlate poorly with patient symptomatology.⁹

Figure 1: Total Knee Replacement Projections



Reference: 8

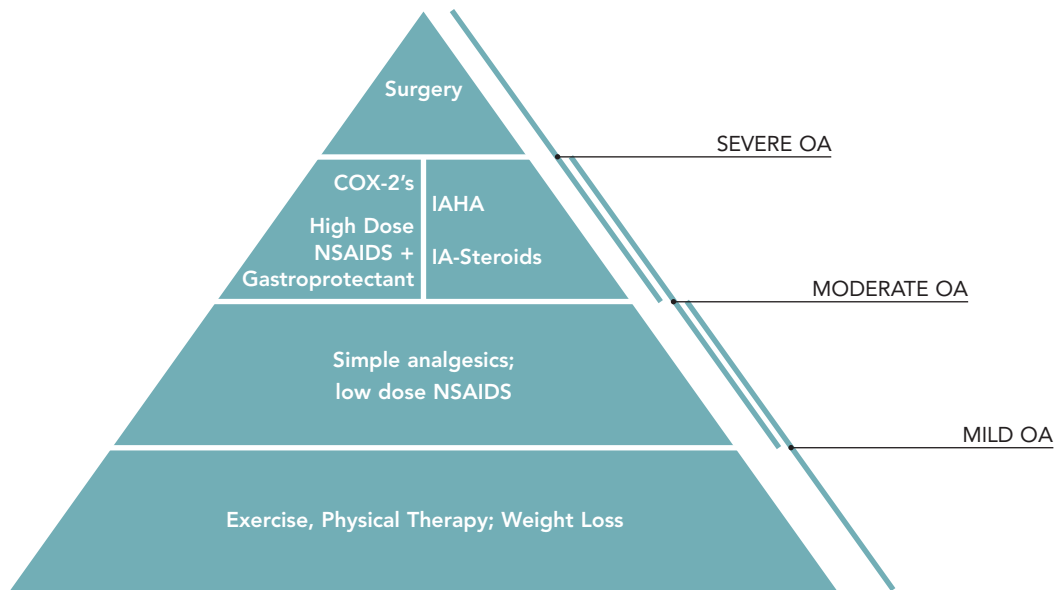
OA Treatment Options

Current treatments for OA focus on symptom management, and demand a multifaceted clinical approach. Invasive interventions should not be utilized until more conservative pain management strategies have been exhausted. Surgery should never be indicated based on radiologic findings alone. To

quote Dr. Norton Hadler, the well-known rheumatologist: “Pain is the malady. Not osteoarthritis.”¹⁶

Figure 2 illustrates an algorithm for knee OA treatment, based on the Guidelines published by the American College of Rheumatology (ACR).¹⁷ The pyramid is intended to reflect the relative numbers of patients with mild, moderate, and severe OA, with

Figure 2: Guidelines for Managing Knee OA



Reference: 17

Only about half of patients presenting with knee OA pain have clinical signs of synovitis and/or effusions.^{14,15}

the majority of OA patients having mild or moderate disease. Treatment options are placed within the pyramid to indicate how their utilization relates to disease severity, and how different treatments might be sequentially considered for patients with advancing disease.

Conservative treatment: Patients with mild disease can often be managed with oral analgesics (acetaminophen, up to 4 grams daily), topical analgesics, and counseling with respect to simple lifestyle changes, weight loss, moderate exercise, and possibly physical therapy. This conservative strategy is considered the safest approach to OA treatment, with the caveat that acetaminophen overdose must be carefully avoided. Even at recommended doses, acetaminophen has some toxicity for patients who consume moderate amounts of alcohol.

NSAIDs: NSAIDs are the most commonly used agents to treat OA-related pain. Patients frequently self-medicate with over-the-counter NSAIDs, with serious and costly iatrogenic morbidities, so it is important that patients be instructed to limit utilization of NSAIDs to the lowest effective dose for the shortest duration possible.¹⁸ Patients also should be counseled regarding the symptoms of NSAID toxicity, and the use of proton pump inhibitors to minimize GI toxicity. Despite precautions, NSAID asso-

ciated GI toxicity accounts for approximately 16,500 deaths annually in the United States and greater than 100,000 hospitalizations.¹⁹ Unfortunately, only 1 in 5 people who have a serious GI problem from NSAIDs have warning symptoms.²⁰ In North America, the economic consequences of NSAID use results in \$0.66 to \$1.25 spent on upper gastrointestinal toxicities for each dollar spent on NSAIDs.²¹

More recently, attention has focused on potential cardiovascular toxicities associated with NSAID usage. In 2005, FDA added a black box warning to all NSAID labels, OTC and prescription, both nonselective and cox-2 selective, stating that “NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.” The Agency for Healthcare Research and Quality (AHRQ) estimates that for every 10,000 patients taking NSAIDs, 30 patients will have a heart attack that they wouldn’t have had if they were not taking NSAIDs.²² Significant additional risk for adverse reactions arise from potential drug interactions, liver toxicity, kidney problems, and hypertension—further urging that a good dose of caution accompany every NSAID prescription.

Many patients with long-standing OA can function very well until they experience a painful flare of symptoms. When conservative measures and intermittent low-dose NSAID therapy are no longer effective for pain management, patients can be considered as progressing beyond mild or moderate disease, and more invasive therapies are considered (third level in the Figure 2 pyramid). The major non-surgical options for patients with advancing disease are high-dose nonselective NSAIDs plus proton pump inhibitors, cox-2 selective NSAIDs, and intra-articular injections. The appropriate treatment choice should be based on multiple factors, including the patients’ symptomology (e.g., mono- vs. polyarticular disease, presence of synovitis), risk factors for iatrogenic morbidity, and multiple patient-specific factors (e.g., existing comorbidities, risk for drug interactions). Oral medication is often considered first, unless patients are at high risk for iatrogenic morbidities. Sometimes non-NSAID prescription analgesics are considered, such as opiates or tramadol. The primary objective of therapy is to safely treat the painful flare, returning the patient to a symptom level that can be effectively managed with conservative treatments. Most therapeutic options for patients at this stage of disease have increasingly serious risk for iatrogenic complications, and treatment becomes more costly to the health care system. Moreover,

For people age 45 to 64:

- 15 out of 10,000 people taking NSAIDs will have a serious bleed
- 2 out of 10,000 people taking NSAIDs will die from a bleed

For people age 65 to 74:

- 17 out of 10,000 people taking NSAIDs will have a serious bleed
- 3 out of 10,000 people taking NSAIDs will die from a bleed

For people age 75 or older:

- 91 out of 10,000 people taking NSAIDs will have a serious bleed
- 15 out of 10,000 people taking NSAIDs will die from a bleed

Adapted from reference 22.

treatment failure at this stage of disease leaves only surgical options remaining, so OA disease management strategies become especially important from both an economic and risk standpoint.

Intra-articular injections: Physicians frequently consider an intra-articular injection for patients in whom a painful flare in one or two joints has prompted the office visit. Two types of intra-articular agents are approved for patients with knee OA: corticosteroids or hyaluronan. Intra-articular corticosteroid (IA-CS) injections are specifically indicated in product labeling for the treatment of synovitis associated with OA. IAHA injections are specifically labeled as intra-articular analgesics, indicated for pain relief when conservative therapy and simple analgesics fail. Despite the fact that only about 50 percent of patients presenting with knee OA pain exhibit clinical signs of synovitis and/or effusion, the first intra-articular treatment tried on most patients is IA-CS, largely because of low cost and familiarity.^{14,15}

Corticosteroids have systemic actions, and many potential adverse effects are listed in product labeling. Importantly, corticosteroid injections should be limited to no more than three to four injections per year, because corticosteroids are catabolic agents that can lead to serious joint atrophy (e.g., thinning of cartilage, weakening of ligaments, tendon rupture, and nerve damage).²³ Though the short-term benefit of IA-CS over placebo injections is well established, differences from placebo only extend out to two to four weeks, and long-term benefits have not been documented.²⁴

Recently published guidelines for the management of knee OA considered both IAHA and IACS to have level 1a evidence supporting their use in knee OA.²⁵ These guidelines provide clear evidence-based statements regarding the proper utilization of IAHA and IACS. IACS is recommended for patients who fail oral medication and for those with effusion or other physical signs of inflammation. IAHA is recommended for symptomatic OA patients, but the guidelines note that IAHA has a delayed onset of action and a longer duration of benefit compared to IACS. The value of IAHA as an alternative to IA-CS will be discussed below.

Surgery: When high-dose NSAIDs and intra-articular injections fail, patients move into the top level of the pyramid, and surgical options can be considered. Surgical approaches include arthroscopic lavage and debridement, tibial osteotomy, and joint arthroplasty. For knee OA, arthroplasty can be unicompartmental or total knee replacement (TKR). It must be emphasized that joint replacement is an option of last resort, and many patients with persistent OA pain do not require immediate joint replacement. Surgery always

Figure 3: Dissatisfaction with Drug Therapy Worsens with OA Disease Stage

	Mild	Moderate	Severe
OA population (US)	7.6 mil	10.3 mil	6.1 mil
Drug-treated population	5.5 mil (73%)	9.2 mil (89%)	6.1 mil (100%)
IA steroid-treated population	0.6 mil (11%)	2 mil (23%)	2 mil (32%)
Patient satisfaction	85%	69%	51%

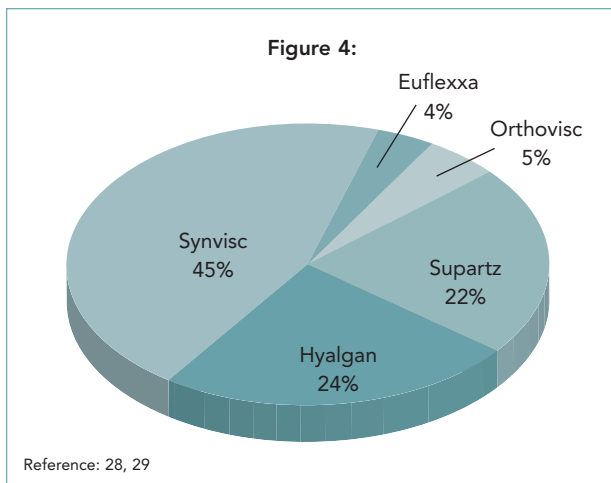
Reference: Adapted from 27

carries the risk of infection (approximately 1 percent for knee replacement), which requires surgical management in almost all instances. Because joint replacements have a finite lifespan, typically 15 to 25 years, it is especially important to medically manage OA symptoms in patients under 60 for as long as possible. TKR in younger patients is a growing concern because of the need for, and complications associated with, revision surgeries. In one case series of TKR patients 55 years old and under, 13 percent of patients required some form of surgical revision within 18 years.²⁶ TKR revisions yield inferior patient outcomes, have a higher complication rate (including fracture and malalignment of components), and are extremely costly. This pressure on health care budgets can be expected to worsen over time. New cost-effective approaches to advanced OA are a critical societal and medical objective.

The Gap in OA Treatment

There is a gap in the treatment armamentarium between early and end-stage disease. Datamonitor conducted a survey in 2002 that found low rates of patient satisfaction with oral medications and IACS in patients with moderate to severe disease (Figure 3).²⁷ Approximately 6 million patients with moderate or severe disease are dissatisfied with their current medical treatment. All participants recognized this level of patient dissatisfaction as unacceptable. Moreover, current dissatisfaction among OA patients is probably higher than it was in 2002, because of the

IAHA injections are specifically labeled as intra-articular analgesics.



increased publicity about NSAID-associated side effects since Vioxx[®] and Bextra[®] were removed from the market and all NSAIDs were given a black box warning. Note also that the figure illustrates the increased utilization of IACS injections as patients develop more advanced disease. Clinicians increasingly recognize advancing OA as a local disease because generally only one or two joints are driving the patient's disability. There is a pressing need for safer and more effective local therapies for patients with advancing OA because it would lighten the strain on health care budgets from the anticipated increase in OA-related joint replacement.

Intra-articular Hyaluronan

Background: Intra-articular hyaluronan (IAHA) injections were first approved by the FDA for the treatment of knee OA in 1997, and have been approved in Europe and Japan since 1987. The FDA approved IAHA as a Class III medical device, meaning that approval required randomized controlled trials (RCTs) demonstrating evidence of safety and effectiveness. Despite its device status, IAHA is currently reimbursed as a drug under four J codes (7321 for Supartz and Hyalgan, 7322 for Synvisc, 7323 for Euflexxa, and 7324 for Orthovisc), specifically as "incident to" arthrocentesis. In the United States, IAHA has become the third largest-selling prescription medication for the treatment of OA, second only to celecoxib and meloxicam. The U.S. market was estimated at \$433 million in 2007, of which Medicare pays approximately 60 percent. From the private insurer perspective, the market is less than \$200 million. In 2006, Synvisc, Supartz, and Hyalgan accounted for 91 percent of the market (Figure 4).^{28,29} Orthopedic surgeons administer IAHA most often (76 percent), with some utilization by rheumatologists (12 percent) and family practitioners (12 percent).

The IAHA class has become so widely accepted

because it safely fills the gap in treatment options between early and end-stage OA. Because IAHA exerts its therapeutic actions by physical (synovial fluid replacement) rather than pharmacologic means, it is not associated with the iatrogenic morbidities common to systemic medications for knee OA. IAHA has no known effects on the GI tract, cardiovascular system, or liver, and has no problems associated with drug interactions or common comorbidities. The major adverse event related to IAHA is a local reaction in the injected knee, which can vary in incidence and severity between products (see below), plus some rare occurrences (e.g., allergy) listed in labeling.

Hyaluronan in synovial joints: Hyaluronan (also called hyaluronic acid or sodium hyaluronate) is a nonsulfated glycosaminoglycan distributed widely throughout connective tissue, and identical in its chemical composition across all vertebrate species. Hyaluronan, present at high concentration in synovial fluid, is a principle component of the extracellular matrix in cartilage, synovium, capsular, and other peri-articular soft tissues. Hyaluronan is solely responsible for the viscoelastic properties of synovial fluid, and serves many important functions essential to normal joint physiology and homeostasis.³⁰ Healthy synovium produces large amounts of hyaluronan continuously, which is pumped through soft tissues by natural movement, and drains into lymphatics with tissue fluid. It is then quickly eliminated from the circulation, mostly by the liver and kidneys. Because of its concentration and molecular weight in synovial fluid, hyaluronan forms an entangled polymer network that helps trap metabolites, debris, and inflammatory mediators, and clears them from the joint. Normal joint movement drives this flow of hyaluronan, one of the reasons that mobility is so important to maintaining synovial joint homeostasis.

The concentration and molecular weight of hyaluronan decrease in patients with osteoarthritis, and the resulting decrease in synovial fluid's viscoelastic properties is believed to contribute to the pain and pathology of OA.³¹ IAHA injections, often referred to as viscosupplementation or joint fluid therapy, are intended to replace the pathologic synovial fluid with a viscoelastic hyaluronan solution, thereby temporarily restoring the natural protective properties of synovial hyaluronan. Treatment is generally administered as a course of three to five weekly injections. Arthrocentesis with an empty syringe should be carefully performed before each injection, to remove pathologic fluid and ensure proper needle placement.

IAHA is not an anti-inflammatory drug, and is not intended for the treatment of acute synovitis. IAHA is indicated as an intra-articular analgesic, to reduce pain and restore function. It has been most studied in

patients with significant knee pain and moderate radiologic disease (Kellgren and Lawrence radiologic grades 2 and 3). The goal of therapy is to help patients though a painful flare not accompanied by acute synovitis, get them moving again, and return them to a symptom state that can be managed with conservative therapy.

Because IAHA is not a drug, it has no known systemic adverse reactions other than rare allergic reactions. Local reactions in the injected knee do occur, but are generally mild and self-limiting, with some notable differences between the available products, particularly with repeat courses (see below).

Evidence for IAHA efficacy: Numerous RCTs and meta-analyses have been published, comparing IAHA to saline injection or arthrocentesis with respect to pain relief and physical function improvement.^{24,32,33} The meta-analyses all find that IAHA is statistically superior to control injections, but they differ in their calculated effect size, and in their interpretation of its clinical importance. The meta-analysis published in the *Journal of the American Medical Association* evaluated 22 RCTs and reported a pooled class effect size of 0.32, comparable to the benefit of NSAIDs over acetaminophen.³³ The largest number of trials was analyzed in the Cochrane Review of IAHA (37 placebo-controlled RCTs), which concluded that the IAHA class was significantly superior to placebo, the effect was clinically important, and the evidence supported utilization of IAHA in the

treatment of knee OA. In the context of interpreting these meta-analyses, it should be noted that the effect size being considered in all cases is that of HA over a saline placebo, which should not be considered in the same category as a placebo pill. Removal of effusion by arthrocentesis is an acknowledged therapeutic procedure, and injection of a variety of salt solutions into the joint has been known to provide clinical benefits for more than 50 years.^{34,35} Though there may be some ongoing academic debate regarding the magnitude of the effect size relative to saline injections, from the clinical practice perspective all the IAHA trials uniformly demonstrate impressive improvements from baseline compared to other treatments for OA of the knee.³⁶

IAHA Products Available in the United States: Similarities and Differences

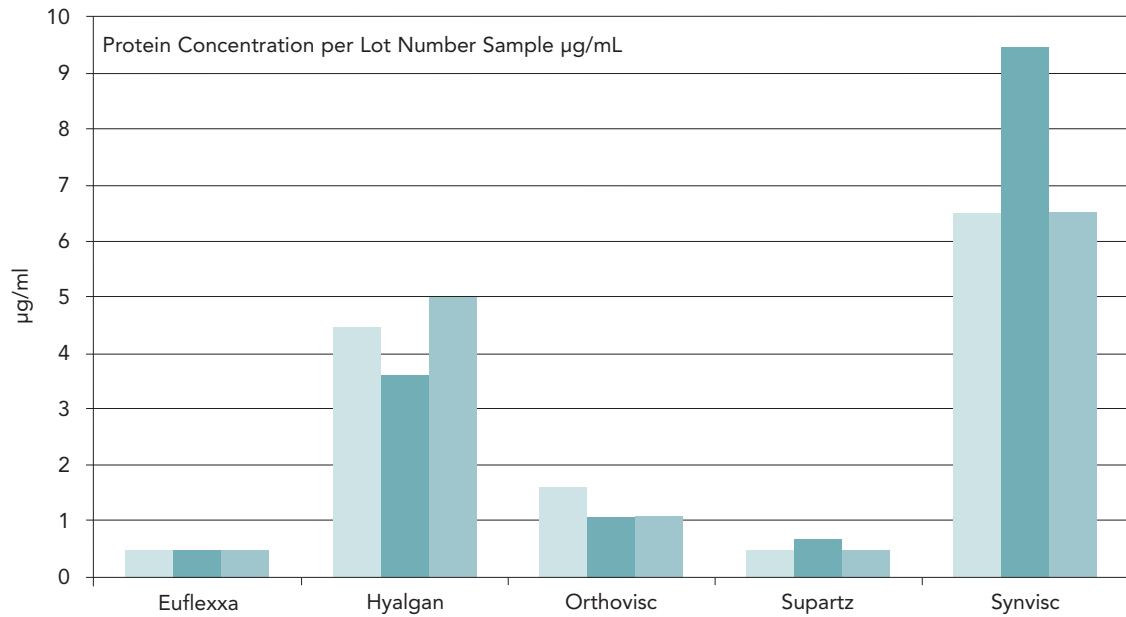
Five brands of IAHA are commercially available in the United States: Euflexxa[®], Hyalgan[®], Orthovisc[®], Supartz[®], and Synvisc[®] (Figure 5).³⁷⁻⁴¹ Four of the products are derived from unmodified hyaluronan. One product (Synvisc) is based on hyaluronan derivatives (hylan), and contains both soluble hylan and water-insoluble hylan gel particles. Four of the products are derived from avian tissue (chicken comb), and one (Euflexxa) is derived from fermentation of gram-positive bacteria. The FDA has reported that avian- and fermentation-derived hyaluronan can be similar enough to allow their interchange without additional

Figure 5: IAHA Products Available in the U.S.

Trade Name US Introduction US Marketer	Composition	Volume Injected	Labeled Treatment Schedule	Source	mg/Injection
Euflexxa 2005 Ferring Pharmaceutical	1% hyaluronan	2 mL	3 weekly injections	Fermented	20 mg
Hyalgan 1997 Sanofi-Aventis	1% hyaluronan	2 mL	3-5 weekly injections	Avian	20 mg
Orthovisc 2004 DePuy Mitek, Inc.	1.5% hyaluronan	2 mL	3-4 weekly injections	Avian	30 mg
Supartz 2001 S&N Orthopedics	1% hyaluronan	2.5 mL	3-5 weekly injections	Avian	25 mg
Synvisc 1997 Genzyme	0.8% hylan G-F 20	2 mL	3 weekly injections	Avian	16 mg

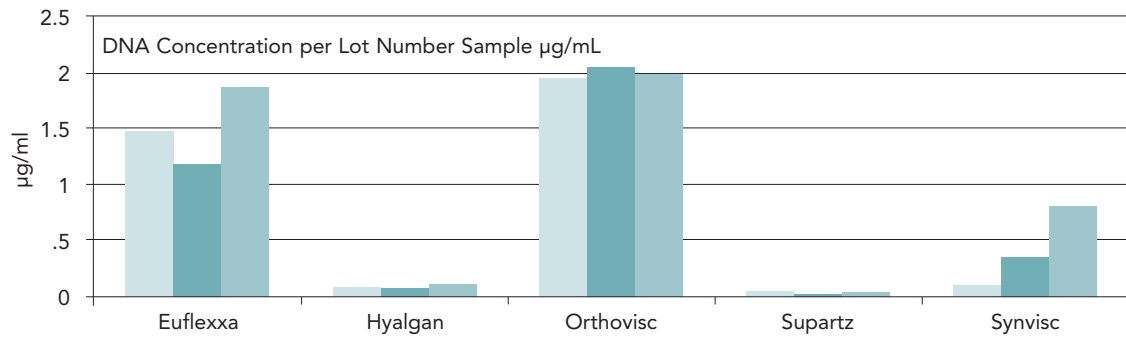
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Figure 6: Protein Contaminants in HA Products



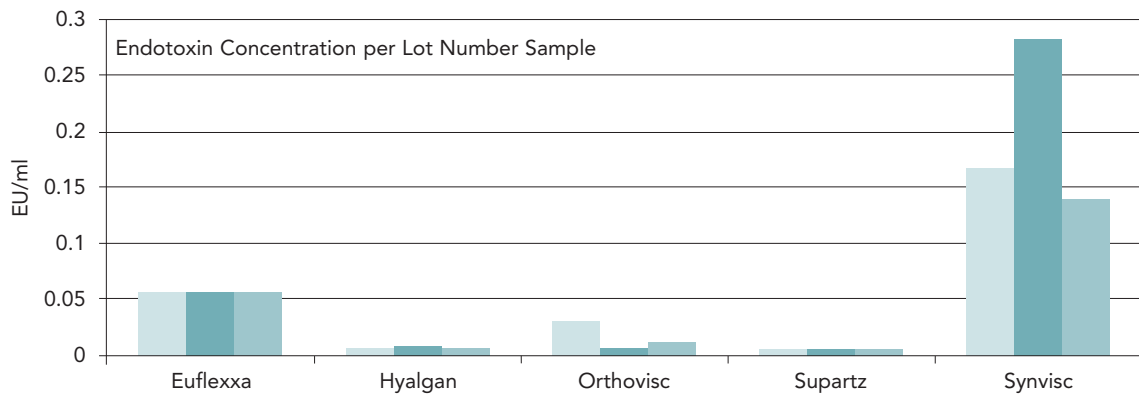
Reference: 44-46

Figure 7: DNA/RNA Contaminants in HA Products



Reference: 44-46

Figure 8: Endotoxin Contaminants in HA Products



EU, endotoxin unit
Reference: 44-46

clinical trials.⁴² Because these products are derived from natural hyaluronan sources using diverse manufacturing technologies, the clinical response to specific products can vary in significant ways (see below).

Dosage and treatment schedule: The products listed in Figure 5 differ in hyaluronan concentration and the volume and quantity of hyaluronan injected. There also are differences between the products in treatment schedule, which is the number of weekly injections constituting a complete course of treatment. Synvisc and Euflexxa were approved based on trial data that evaluated a course of three weekly injections. Orthovisc is labeled for three or four weekly injections, because its approval was based on combining the data from trials that evaluated three or four injections. Supartz and Hyalgan were approved in the United States based on trials of five weekly injections, but their labels were subsequently modified to allow three, four, or five weekly injections based on supplementary data submitted to the FDA after approval. The original treatment schedule for Supartz and Hyalgan was based on the treatment schedule used where they were first approved (1987) in Japan and Italy, respectively. These differences in the labeled treatment schedule are often confusing to clinicians, as there is evidence of similar efficacy between the products from head-to-head RCTs comparing three-injection treatment schedules (see below). Though most physicians and patients prefer a three-injection course, Orthovisc allows the use of a fourth injection, and Supartz and Hyalgan allow the use of a fourth or fifth injection for selective patients. In this context, both physicians and patients should be reminded that improvement continues after the injection series is completed, and that many patients do not reach their maximal benefit until eight to twelve weeks after the onset of treatment.^{24,27}

Some publications describe differences in the duration of benefit after treatment with different IAHA products, which would influence cost-effectiveness if true. For example, a recent publication in *JMCP* presented a figure indicating that a three-injection regimen of Synvisc provides six months of clinical benefit, whereas for Supartz, a five-injection regimen is required for six months' benefit, and a three-injection regimen only provides three months of benefit.⁴³ The implication is that patients treated with three Supartz injections will require a second course of treatment after three months, whereas Synvisc-treated patients would not require a second course until six months. This suggested difference between Synvisc and Supartz is not borne out by multiple head-to-head RCTs (see below), some of which followed patients out to one year. Moreover, the duration of a clinical trial does not define the

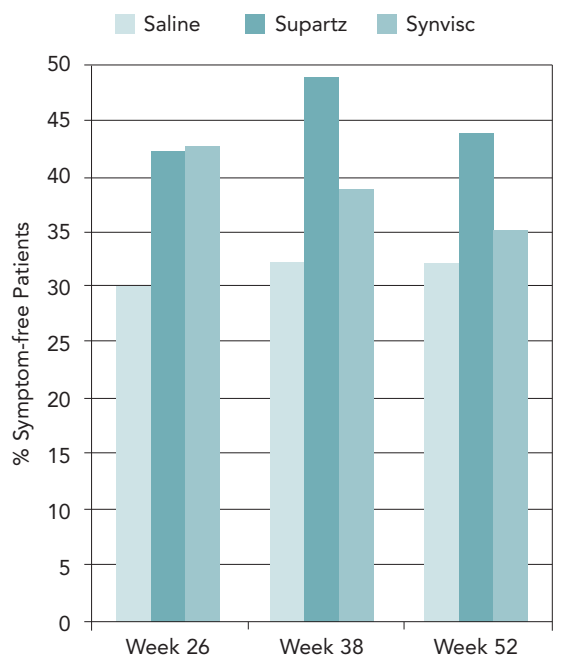
When asked about differences between currently available brands, medical directors differentiated IAHA products by the number of injections per series: "There is a perception right now that Supartz is strictly a five-injection product, but it actually has a label that says it is a three- to five-product, as opposed to strictly five."

duration of clinical benefit. It is therefore incorrect to imply that patients require repeat treatment at either six or three months, as most do not. Repeat treatment should only be considered when the patient experiences a new flare in OA pain, and only if the patient benefited from the first course of treatment.

Compositional and biological comparisons: IAHA products are not chemically manufactured. They are purified from natural sources (tissue extracts or bacterial fermentation), and in the case of hyaluronan derivatives like Synvisc, subjected to a secondary chemical modification. As such, each IAHA product has different physical characteristics, a different molecular weight distribution, and a different impurity profile. There also can be significant batch-to-batch variation, with the extent of this variation determined by the specifications for impurities established by each manufacturer. The major impurities occurring in IAHA products are protein, nucleic acid (DNA, RNA), and endotoxin. Figures 6, 7, and 8 compare the level of these impurities in the five available IAHA products, as measured from several commercially acquired lots.⁴⁴⁻⁴⁶ Supartz had the highest overall purity when all three major impurities are considered, and had the lowest lot-to-lot variability. Levels of protein and endotoxin impurity were highest in Synvisc. Levels of DNA/RNA were highest in Euflexxa and Orthovisc. The clinical significance of these impurity levels has not been specifically documented, as there is a paucity of data available on long-term use for many of the available products. Because IAHA products are intended to manage knee OA for

**Figure 9: Supartz vs Synvisc vs Saline
3-Injection Regimen**

Efficacy Results: ITT Analysis



Saline is the "placebo" treatment involving arthrocentesis

Reference: Adapted from 52

extended time periods, which will require repeated courses of treatment, impurities need to be considered based on their known biological actions.

Protein impurities are relevant because proteins can induce a clinical immune response that tends to amplify with repeat administration. Laboratory studies comparing the immune response to Supartz and Synvisc in guinea pigs reported delayed type hypersensitivity, passive cutaneous anaphylaxis, and the induction of Synvisc-specific antibodies in Synvisc-treated animals.^{47,48} In this context, it should be noted that a recent study demonstrated that Synvisc also elicited a greater short-term inflammatory response than either Supartz and Hyalgan.⁴⁹ The latter study also reported detecting antibodies that were specific to a non-hyaluronan component of Synvisc, which did not cross-react with either Supartz or Hyalgan.

Endotoxin impurities are relevant because of their well-known adjuvant activity, and their utilization in vaccines to stimulate immune response. Synovium is an immunologically active tissue, through which immune cells and antigen-presenting cells extensively migrate. Thus the presence of high levels of endotoxin and foreign protein may be particularly problematic for products requiring repeat intra-articular administration. In addition, endotoxin itself is potentially problematic, because when injected directly

into animal joints it will induce arthritis, with persistent synovial inflammation, cartilage destruction, and impaired mobility.⁵⁰ Though all of the available products contain less than 0.5 endotoxin units per ml, and thus meet the FDA's general requirements for parenteral products (< 0.5 EU/mg), the specific limits on endotoxin for intra-articular administration have never been specifically addressed in public communications. Hyaluronan preparations produced for intra-ocular injection are required to have tenfold lower levels of endotoxin (<0.05 EU/mg) to meet current standards (ASTM standard F 2346-03).

The clinical relevance of DNA/RNA impurities is less well understood, and relatively little is known about the biological consequences of nucleic acid impurities in parenteral products. Standards for DNA impurities in parenteral products have not yet been established in meaningful ways. One publication reported that two of six approved HA products stimulated the release of inflammatory cytokines (tumor necrosis factor and interleukin-12) in human monocyte cultures, and that the inflammatory activity was associated with an impurity that could be eliminated by enzymatic digestion of DNA.⁵¹

Head-to-head RCTs comparing IAHA products: Several RCTs evaluate safety and effectiveness of different IAHA products in head-to-head trials for the treatment of knee OA. Three blinded RCTs that directly compared lower molecular weight products to Synvisc are particularly interesting to review.⁵²⁻⁵⁴ These three trials evaluated a three-injection regimen for both products, studied different types of patients with knee OA, and were funded by the competing manufacturers. The first publication, funded by the manufacturer of Synvisc, studied patients with mild to moderate OA, and reported that Synvisc was significantly better than Supartz.⁵⁴ Subsequent journal correspondence clarified that the authors published selective data from the trial, and that the FDA had specifically stated that no definitive conclusions could be drawn from this trial.^{55,56} The second publication, funded by the distributor of Supartz, reported that there was no difference in safety or effectiveness between Supartz and Synvisc.⁵³ Interestingly, this study enrolled a patient population with more advanced OA in which 40 percent of the patients had complete obliteration of the joint space. Though a high number of study dropouts limited data analysis (approximately 30 percent by six months and 60 percent by one year), it is noteworthy that all study groups improved by 30 percent to 40 percent despite their advanced radiologic disease. Moreover, despite the patients' advanced disease, the combined Supartz and Synvisc group was superior to saline injections with respect to the duration of benefit

as measured by survival analysis. The third publication, funded by the manufacturer of Synvisc, found no superiority for Synvisc over Supartz in patients having OA symptoms and arthroscopically confirmed cartilage lesions.⁵² This study followed patients for one year, after a single three-injection regimen of Supartz, Synvisc, or placebo. It reports the percentage of symptom-free patients at 26 weeks to be 43 percent, 44 percent, and 30 percent in the Supartz, Synvisc, and placebo groups, respectively. At one year, the percentage of symptom-free patients was 44 percent, 36 percent, and 32 percent in the Supartz, Synvisc, and placebo groups respectively (Figure 9).⁵² Based on these three trials, non-crosslinked hyaluronans such as Supartz appear equally effective to chemically modified hyaluronans, such as the hylan in Synvisc.

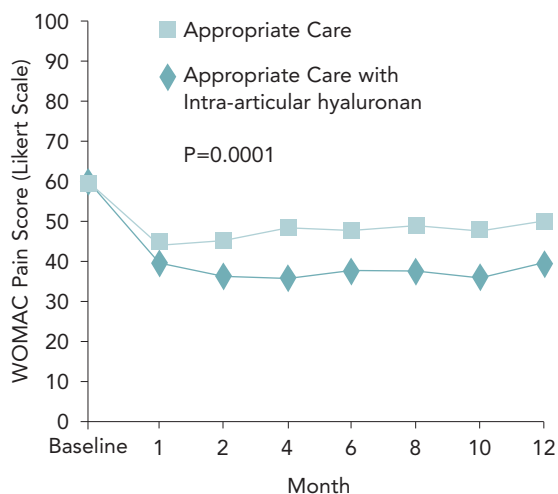
Another blinded RCT comparing Synvisc to non-crosslinked hyaluronan is important to mention because of its safety findings. This trial, comparing three-injection regimens of Synvisc and Euflexxa, was specifically powered to determine noninferiority of effectiveness.⁵⁷ The trial met its noninferiority endpoint, but more importantly, reported a significant difference in the incidence of post-injection effusions. Fourteen of 160 patients (9 percent) in the Synvisc group compared to 1 of 161 patients (0.6 percent) in the Euflexxa group developed effusions.

This similar effectiveness of hyaluronan and hylan products, and their differences in local reaction incidence, was confirmed by a recent head-to-head RCT funded by the Swiss Health Insurance Authority.⁵⁸ This trial randomized 660 patients to receive hylan (Synvisc), or one of two brands of non-

modified hyaluronan (Orthovisc or Ostenil, the latter not available in the United States). Though powered as a superiority trial to detect any clinically meaningful differences between the products, no difference in effectiveness was observed at any time point during the one-year trial duration. With respect to safety endpoints, there was a trend toward a higher rate of local reactions in the hylan group compared to the hyaluronan group during the first course of treatment (2.2 percent higher), which became statistically significant during the second course of treatment (6.4 percent higher in the hylan group).

This increase in the incidence of local reaction during repeat treatment with hylan (Synvisc) has not been found for any noncrosslinked hyaluronan product studied. Several publications have reported a granulomatous reaction to hylan gel particles in biopsies taken from patients in whom a local reaction to Synvisc required arthroscopic treatment.^{59,60} It remains unclear whether these local reactions are a reaction to hylan gel particles, or related to the higher level of protein and endotoxin impurities in Synvisc. Nonetheless, this risk is specifically noted in current Synvisc labeling, which states that the incidence may increase from 7.2 percent of patients during the first course to 22.3 percent of patients during repeat courses.⁴¹ Hyalgan labeling includes data from trials that demonstrate the safety and effectiveness of up to six courses of Hyalgan during a two-year period.³⁸ Supartz labeling references a post-market study that evaluated Supartz safety in more than 9,023 patients receiving treatment during a six-year period (7,404 injected in knee; 1,619 in shoulder).⁴⁰ The safety of Supartz remained consistent over time, with 1,674 patients receiving more than 10 Supartz injections, 443 patients receiving more than 20 injections, and some patients receiving more than 50 Supartz injections. Conversely, a recently published post-market study of 4,253 Synvisc-treated patients

**Figure 10: Is IAHA Effective in the Real World?
A Randomized, Pragmatic Outcomes Trial**



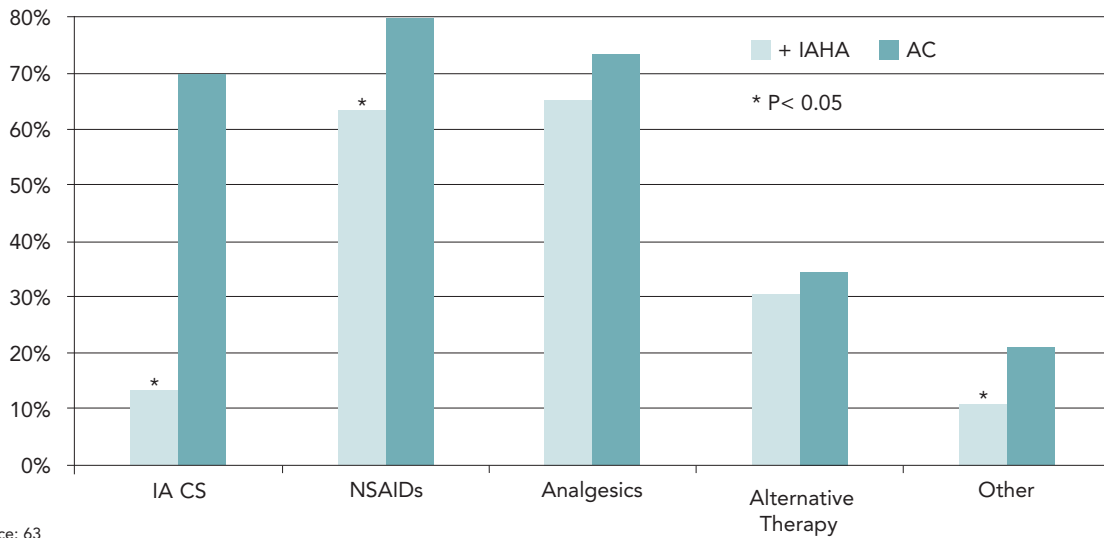
Likert score for WOMAC pain was normalized for a 0 to 100 scale. Reference: Adapted from 62

**Figure 11: Patient Global Assessments
of Improvement from Baseline**

% Improved Patient	UC+IAH	UC	Treatment p-value
OA in study knee	73%	27%	0.0001
OA in all joints	38%	17%	0.0006
Overall health	38%	16%	0.028

Reference: 62

Figure 12: Comparative Use of Medication for Knee OA
 Pragmatic RCT of IAHA vs. Appropriate Care:



Reference: 63

reported a local adverse reaction rate of 4.9 percent in patients that were naïve to IAHA treatment, increasing to 10.4 percent in patients that received a prior course of IAHA, a difference that was statistically significant.⁶¹

IAHA Economic Considerations

Data are available on the effectiveness, cost-effectiveness, and cost-utility of the IAHA class from a randomized, pragmatic trial designed and managed by an independent academic steering committee of international experts in rheumatology and health economics.^{62,63} The study was conducted in Canada, and randomized 255 patients to receive IAHA (Synvisc) plus Appropriate Care (AC+IAHA) or Appropriate Care alone (AC). Appropriate Care was defined by the protocol as following the guidelines published by the American College of Rheumatology, and encouraged the ongoing use of conservative measures in all patients. This trial measured costs and outcomes during a one-year period, in symptomatic patients who had been previously treated with acetaminophen and/or NSAIDs. The incremental clinical improvement in the group receiving IAHA was found to be statistically significant and clinically important for all primary and secondary outcome measures (WOMAC OA index, SF-36, Health Utilities Index—for calculating quality of life years, or QALYs—and global evaluations by patients and physicians). Figure 10 illustrates the change in WOMAC pain score over time, and Figure 11 shows the differences in patient global assessment.⁶² The trial also found a statistically significant

decrease in the utilization of NSAIDs, acetaminophen, and steroid injections in the IAHA group (Figure 12).⁶³ More importantly, there was a decrease in NSAID-related side effects and the use of medication to treat side effects in the IAHA group, which was statistically significant and clinically important. Though medication costs decreased in the IAHA group, this decrease did not fully balance the costs of acquiring and administering the IAHA. The incremental cost-utility ratio for adding IAHA to an Appropriate Care treatment regimen was calculated to be \$6,600 (1998 U.S. dollars) per quality-adjusted life year (QALY). The authors concluded that the results provided strong evidence for adoption of treatment with IAHA in the patients and settings studied in the trial.

As a general frame of reference for understanding “cost per QALY” data, new interventions that cost less than \$20,000 per QALY are considered good value, whereas those costing more than \$100,000 per QALY are considered to provide insufficient value to justify the expenditure.⁶⁴ For comparison, an analysis of the incremental cost of cyclooxygenase 2 (cox-2) selective NSAIDs over nonselective NSAIDs was found to be \$275,000 per QALY if they were prescribed for all patients, but only \$55,000 per QALY if prescriptions were limited to patients with a history of GI problems.⁶⁵ This justifies the limitation of cox-2 selective NSAIDs to patients at GI risk from nonselective NSAIDs. Moreover, the \$6,600/QALY (1998 U.S. dollars) cost-utility ratio of IAHA compares favorably to the cost-utility ratio of cox-2 selective NSAIDs.

In a second randomized study that evaluated the cost-effectiveness of IAHA (Synvisc) in France, the IAHA group was confirmed to provide superior outcomes over standard care, and the improvements were again statistically significant and clinically important. However, in France, the decrease in medication costs was sufficient to balance the costs of acquiring and administering the IAHA, leading to cost savings for the health care system.⁶⁶

Several studies have reported that IAHA can be effective in patients considered to be candidates for TKR, a major driver of OA-associated health care costs. A trial conducted in Thailand evaluated the usefulness of IAHA (Hyalgan) to delay TKR in patients considered to be candidates for surgery, and the associated costs to the health care system. Of the 208 patient-knees enrolled in the trial, 164 patient-knees were able to delay TKR during the two-year study period.⁶⁷ This corresponds to a success rate of 79 percent in these late-stage OA patients. Patients were permitted to receive repeat courses of IAHA as required, and approximately 40 percent of the patients got at least one additional course of IAHA treatment. The cost savings from delayed or canceled TKR procedures led the authors to conclude that IAHA should always be considered before surgical intervention.

In a retrospective case series review from an orthopedic specialty practice in the United States, the incidence and time to TKR was evaluated in TKR candidates with Grade IV OA treated with one or more courses of IAHA injections (Synvisc) during approximately six years.⁶⁸ The incidence of TKR in IAHA treated knees (1,187 knees; 863 patients) was 19 percent (n=225 knees). The median time to TKR in these patients was 638 days (1.8 years; minimum of 14 days, maximum of 2,147 days). For patients in whom a TKR had not yet occurred during the observation time, the median time of IAHA treatment and patient follow-up was 810 days (2.2 years).

Intra-articular hyaluronan injections can be effective in patients who are candidates for total knee replacement, and has been documented to delay the need for surgery.^{67,68}

During this study period, 1,978 courses of IAHA were administered, an average 1.67 courses of IAHA per patient. To evaluate cost-effectiveness, the authors calculated the total cost of the IAHA administered (\$852 for three Synvisc injections plus three arthrocenteses plus one office visit), divided by the total number of knees treated, and determined an average cost of \$1,419.76 per knee. This expenditure delayed TKR by a median of 2.1 years (772 days, minimum seven, maximum 2,222). Survival analysis showed that 75 percent of knees still had not had a TKR by 3.8 years. The authors again concluded that TKR could be delayed with IAHA treatment.

Though the incremental cost or savings associated with adding IAHA to a standard OA treatment regimen will depend on the practice setting and its ongoing costs of care, in all cases where the value of IAHA was rigorously determined in a prospective health economic trial, it was found to provide good value for the incremental improvements achieved in patient quality of life.

Acquisition cost of these products can impact their cost-effectiveness. Pricing as of first quarter 2008 is shown in Figure 13. This figure includes Medicare reimbursement [average sale price (ASP) + 6 percent] and average wholesale price (AWP) per syringe and per milligram. Based on ASP and AWP, Supartz has

Figure 13: Competitive HA Pricing

	Per Syringe Q1 08 ASP	Per Milligram Q1 08 ASP	Per Syringe AWP	Per Milligram AWP
Euflexxa	\$110.87	\$5.54	\$145.81	\$7.29
Hyalgan	\$102.06	\$5.10	\$146.01	\$7.30
Orthovisc	\$171.37	\$5.71	\$261.36	\$8.71
Supartz	\$102.06	\$4.08	\$145.00	\$5.80
Synvisc	\$178.16	\$11.14	\$236.20	\$14.76

ASP, Average sales price + 6% (Medicare Reimbursement)

the lowest price per syringe and the lowest price per milligram of HA. Moreover, when comparing the total AWP cost for a three-injection regimen of the different products, Supartz (\$435), Euflexxa (\$437), and Hyalgan (\$438) have significantly lower costs than the two highest-priced products (\$708 and \$784 for Synvisc and Orthovisc, respectively) (Figure 14).

IAHA in a Managed Care Setting

The Advisory Board discussed OA disease management, where IAHA fits into the treatment algorithm for knee OA, and how the available IAHA products compared to each other.

The group agreed that OA and its associated comorbidities are an important factor in rising medical costs. Though OA isn't life threatening, they recognized its importance to overall health and quality of life. Patient dissatisfaction with current non-IAHA OA treatment options was widely acknowledged, and all considered it relevant to managed care decision-making. Much discussion centered on hidden costs associated with OA disease management, both arising from iatrogenic costs associated with OA treatment, and from comorbidities associated with reduced mobility and function. The discussion focused on the gap in the OA treatment paradigm between conservative therapies and joint replacement, and the relative roles of high-dose NSAID therapy, intra-articular corticosteroids, and IAHA in filling this gap in the OA treatment armamentarium.

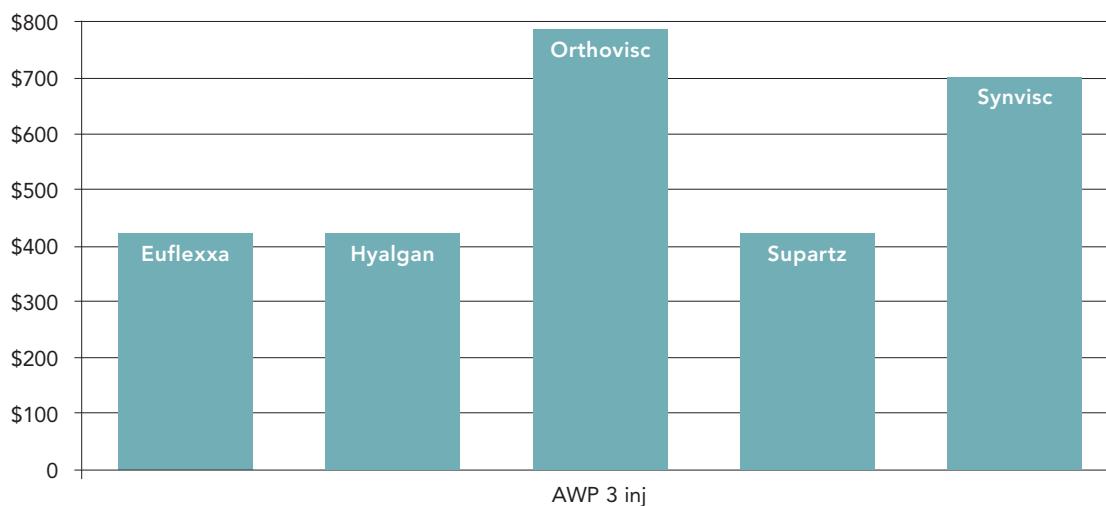
There was general consensus that IAHA added a valuable treatment option for many patients, primarily because of its safety and effectiveness profile relative to the other options. All considered it important

that IAHA had no known drug interactions, and was not problematic in patients with cardiovascular or GI risk factors. Most believed that oral NSAID therapy should be tried at maximal dosage before considering IAHA, unless the patient was specifically at risk for NSAID-associated adverse events. All acknowledged that patients should be informed about NSAID-associated side effects, and that physicians should be prepared to discuss IAHA if their patients bring it up as a treatment option.

There was some debate regarding the intra-articular treatment of choice for patients who fail high-dose NSAID therapy, or those for whom NSAID therapy is inappropriate. The low cost of corticosteroid injections and their apparent effectiveness was considered to provide good medical value, and there were different opinions regarding iatrogenic morbidities associated with corticosteroids. An orthopedic surgeon commented that corticosteroids have a catabolic action on tendon and ligament tissue, and that steroid overuse could result in serious damage to the joint, perhaps even accelerating the progression of OA. All agreed that patients should not get more than three to four IACS injections per year, but some felt that even this number might be too high.

There was discussion about the types of OA patients that should be treated with IAHA versus those that should be treated with IACS. Though it was pointed out that IACS is specifically indicated for treatment of synovitis associated with OA, not OA per se, all acknowledged the loose diagnostic criteria for synovitis and the potential role of subclinical synovitis in OA pathology. Some managed care plans require that patients fail IACS before they will

Figure 14: IAHA AWP Costs
3 injection series



“We think there should be a failure of three months’ conservative treatment [before allowing IAHA treatment].”

“The second course . . . should not occur prior to six months after the first injection of the first treatment course.”

“We think it is reasonable to limit coverage to two brands based on purity and cost.”

“Would we allow a repeat course of treatment? Yes, but we would want to see that there was a significantly good response.”

– Medical Directors’ Comments

reimburse IAHA injections. This may be problematic because IAHA has never been specifically studied in patients who fail IACS, so this type of limitation on utilization could actually be counterproductive. Most participants agreed that the choice between IAHA and IACS is appropriately made at the individual patient level.

Most participants agreed that a reasonable guideline for use of IAHA was failure of conservative treatment and failure of or contraindication to NSAID therapy. There was disagreement whether radiologic evidence of OA should be required. The participants agreed that a reasonable criterion for repeat treatment with IAHA is a favorable response to the previous course, defined as a minimum of six months benefit from the prior course of IAHA.

All participants were particularly interested in the discussion about using IAHA in TKR candidates. The medical directors were surprised that a high percentage of late-stage OA patients could benefit from IAHA, and that TKR could be delayed for years in many cases. Though the evidence that IAHA can delay TKR was based on single-arm observational studies, most agreed that IAHA was worth trying in appropriate TKR candidates because it might prevent unwarranted surgeries.

The medical directors were particularly interested in the discussion about differences between the available IAHA products. They were surprised that head-to-head RCTs comparing three injection regimens of Supartz and Synvisc did not find any difference in effectiveness between the two products, considering that Synvisc cost almost twice as much as Supartz. They also expressed some surprise when it was pointed out that Synvisc labeling notes an increased incidence of local reactions during repeat treatment.

Several additional issues were identified as requiring further research. All agreed that the available information was insufficient to predict which patients would respond to IAHA. Along the same lines, the medical directors also wanted guidance regarding the optimal number of injections for individual patients. More data on long-term outcomes, repeat treatment, and comparisons to other OA treatments also were considered important for cost-effective utilization of the IAHA class.

Overall, the medical directors were satisfied with the strength of the evidence supporting IAHA utilization for knee OA. All agreed that managed care plans already bear many hidden costs resulting from NSAID-associated side effects, and that IAHA could help reduce these iatrogenic cost factors. They considered it important to manage OA treatment costs, and acknowledged that appropriate IAHA utilization could add to the overall cost-effectiveness of OA disease management. **JMCM**

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