Synvisc® in knee osteoarthritis

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Osteoarthritis (OA) is a chronic degenerative disease of synovial joints that is characterized by the deterioration of hyaluronan and other constituents of hyaline cartilage, resulting in intermittent pain, swelling, inflammation and varying degrees of functional loss. Viscosupplementation is one of the treatment options for OA-related pain and has been used successfully for several years. Hylan GF-20 (Synvisc®) is a viscosupplement composed of two cross-linked hylan polymers that form a high-molecular-weight hyaluronan compound. Numerous systemic reviews, clinical trials and meta-analyses have established the efficacy of Synvisc for OA knee pain. In comparison with multiple control groups, multiple active comparators and other hyaluronic acid treatments, it has provided equal or better pain relief. Synvisc is effective in repeat treatment cycles and in delaying total knee replacement. Overall, Synvisc has proved efficacious in the treatment of knee OA and has a well-established track record of safety, efficacy and tolerability.

Osteoarthritis (OA) is a chronic deteriorating condition of synovial joints. All tissues within the joint are affected, including the synovial fluid, bone, cartilage, synovium, joint capsule and periarticular muscles. The disease process generally includes synovial fluid biochemical changes, cartilage loss, the development of osteophytes, and sustained or sporadic inflammation, with resultant pain and/or disability. It particularly affects large weight-bearing joints, such as the hips and knees, the cervical and lumbar spine regions and the small joints of the hands and feet. Although it potentially affects all joint components as described above, perhaps most relevant to the subject of this paper is the reduction in concentration and molecular weight of hyaluronan, the fundamental element of the synovial fluid [1]. OA is the most common form of arthritis, affecting over 20 million Americans. The incidence rate of knee OA is 1% annually, with a 2% annual radiographic incidence [2,3]. The clinical progression of OA is often phasic and can be rather disparate. Use of the affected joint during activities of daily living often leads to discomfort and, sometimes, intermittent swelling.

Although all tissues that comprise the synovial joint are adversely affected by OA, the effects upon hyaline cartilage and synovial fluid have been most thoroughly studied. Proteoglycans comprise the major backbone of cartilage. A decrease in proteoglycan concentration results in exposure of the type II collagen fibers, another major component of cartilage, to mechanical forces acting on the joint. The production of hyaluronate within cartilage is also impaired in OA [4]. This decrease in proteoglycan, collagen and hyaluronate results in an overall loss of cartilage integrity and thickness [5]. Cartilage-forming cells known as chondrocytes then proliferate in an attempt to compensate for the loss in cartilage. However, cartilage is an avascular tissue and is eventually unable to reconstitute itself at a rate equal to that of its loss. Therefore, OA can be depicted as an imbalance of the catabolic and anabolic processes that act upon cartilage [5]. As the hyaline cartilage progressively deteriorates, the adjacent subchondral bony surfaces come into contact. In addition to causing inflammation, this bony contact can prompt the growth of osteophytes (bony spurs), particularly at the joint margins. Since cartilage is an aneural tissue, bony contact rather than cartilage loss *per se* is more likely responsible for some of the pain associated with OA.

In addition to cartilage, synovial fluid is also adversely affected in OA. Hyaluronate, the major component of the synovial fluid (3–4 mg present for every ml of synovial fluid), is the conjugate base of hyaluronic acid. It is also referred to as hyaluronan because of the molecule's form in the human body as a polyanion. Hyaluronan is a glycosaminoglycan with a molecular weight ranging from 4,000,000 to 6,000,000 Da in synovial joints [6]. It is composed of repeating units of the disaccharides glucuronic acid and *N*-acetyl glucosamine [7]. Hyaluronan allows synovial fluid to function as a 'shock absorber' under high-joint-load conditions, such as when landing after stepping off of a curb, and a 'lubricant' under

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low-load conditions, such as with range of motion of the joint. In OA, there is a decrease in normal, high-molecular-weight synovial hyaluronan and a subsequent increase in the concentration of lower-molecular-weight hyaluronan and fragments [4]. The conversion from higher- to lower-molecular-weight synovial hyaluronan and dilution due to increased water content and inflammatory-cell mediators in osteoarthritic joints impairs the function of hyaluronan [4].

Although there is no nonsurgical cure for OA, treatment can relieve pain, reduce inflammation, restore range of motion and, potentially, improve joint function. Well-recognized nonpharmacologic therapies include patient education, therapeutic exercises, including aerobic conditioning, weight loss, range-of-motion exercises, strength training and proprioceptive training, joint-protection techniques and orthotic devices [8]. Simple analgesics such as acetaminophen, medications such as tramadol and opioid analgesics, NSAIDs such as COX-2 inhibitors, and injectable corticosteroids are often used to treat osteoarthritic pain. Topical analgesics, such as capsaicin, and topical anti-inflammatories, such as aspirin-based creams and topical NSAIDs, are additional adjuvant treatment options that are most applicable to joints close to the skin surface, such as the knees and the small joints of the hands and feet. Viscosupplementation, the administration of sodium hyaluronate into the synovial fluid (usually weekly, for a time period ranging from 3 to 5 weeks), represents another treatment option. Synvisc® (hylan GF-20), a viscosupplement, is the subject of this article.

Introduction to the compound

Synvisc has been US FDA approved since 1997 for the treatment of patients with symptomatic knee OA. It has a well-established track record with respect to efficacy and has a well-characterized tolerability and safety record. According to current labeling, it can provide pain relief for up to 6 months, but has been shown in some studies to be effective beyond that, delaying total knee replacement (TKR) for an average of 2.1 years [7,9]. As is true in general of the viscosupplements, as local therapy it lacks many of the systemic safety concerns inherent in the oral analgesic and oral anti-inflammatory medications. Like all viscosupplements, Synvisc is technically classified by the FDA as a medical device rather than a medication because it provides analgesia, in part, through physical action (elastic and viscous properties) (Table 1). Initially used in ophthalmic surgery in humans since 1972, sodium hyaluronate has been employed since 1987 for the treatment of knee OA pain. It is currently available globally, as discussed in detail in the Regulatory affairs section. Synvisc is one of the five currently available viscosupplements in the USA (shown in Table 2).

Chemistry

Synvisc is an elastoviscous liquid composed of two hylan polymers within a buffered, physiological NaCl solution (Table 3) [7]. The phenomenon of crosslinking creates two variations of hylan polymers. Hylan A, a soluble, high-molecular-weight molecule, is formed by the pairing of two to four hydrated hyaluronan molecules. Hylan B is an insoluble gel consisting of a highly uninterrupted, crosslinked network [6,10]. In contrast to Synvisc, the remaining four viscosupplements are ultrapurified, high-molecular-weight hyaluronan solution dissolved in saline. Hylan GF-20 has a greater average molecular weight than the other four viscosupplements owing to the crosslinkage by hydroxyl groups (Table 2).

Pharmacokinetics

Synvisc is administered into a synovial joint by intra-articular injection. Owing to its crosslinked structure, it has a significantly longer joint-residence time compared with hyaluronan [10]. The device is cleared from the joint space in humans via the lymphatic system, where it is then processed by the liver and kidneys. In a study on the intra-articular residence time of hylan in the goat knee, hylan A and B were still present at 2 and 7 days, respectively [5]. Fluorophores (molecular components that cause a molecule to be fluorescent)

Table 1. Physical properties of Synvisc® and synovial fluid.

Substance	Elasticity (storage modulus G')	Viscosity (loss modulus G")
Synvisc	2.5 Hz of 111 ± 13 Pa	25 ± 2 Pa
Knee synovial fluid (normal 18–27-year old)	2.5 Hz of 117 ± 13 Pa	45 ± 8 Pa
Osteoarthritis	2.5 Hz of 8.5 ± 0.5 Pa	4.8 ± 0.3 Pa

Data taken from [6,7].

Table 2. US FDA-approved hyaluronates (listed in order of date of approval).

Trade name	Date of FDA approval	Weekly injections	Molecular weight (million Da)
Hyalgan® (sodium hyaluronate)	28 May 1997	Three or five	0.5–0.73
Synvisc® (hylan GF-20)	8 August 1997	Three	6.0
Supartz® (sodium hyaluronate)	24 January 2001	Three or five	0.62–1.17
Orthovisc® (high-molecular-weight hyaluronan)	5 February 2004	Three or four	1.0–2.9
Euflexxa® (1% sodium hyaluronate)	3 December 2004	Three	2.4–3.6

were detected in the cartilage and synovium for up to 28 days [5]. Most hyaluronate injections do not remain in the joint for longer than 48 h, and in animal models are shown to clear quickly (20 h) [11,12]. Furthermore, Hyalgan® (sodium hyaluronate) has a residence time of 17 h [13].

Clinical efficacy

There is a large body of literature supporting the efficacy of Synvisc. The Academy of Managed Care Pharmacy format-based Synvisc dossier lists 79 clinical publications as of 2006 [14]. Various issues pertaining to efficacy for knee OA have been studied, including comparison with multiple control groups, multiple active comparators and other hyaluronic acid preparations, repeat treatment cycles, patient-selection criteria and its effect in those patients who were being considered for TKR.

Comparison with control groups

Synvisc has been compared with various control groups, including, but not limited to, intra-articular saline, intra-articular steroid, NSAIDs and appropriate care. Two randomized, placebo-controlled trials comparing Synvisc with intra-articular saline both found a statistically significant improvement from Synvisc in two key outcomes, weight-bearing pain and activity-related pain, at both 12 and 26 weeks [10,15]. A randomized, evaluator-blinded, multicenter trial found that Synvisc had a significantly longer efficacy (pain and overall condition) and continuation rate compared with intra-articular steroid at 26 weeks [1]. Synvisc has been compared with continuous NSAID use in two randomized, multicenter trials [9,10]. One study concluded that there was equal efficacy, whereas the other concluded that Synvisc had greater efficacy [16,17]. A 1-year randomized, open-label study compared appropriate care for knee OA with or without Synvisc [18]. While appropriate care was moderately effective, the addition of Synvisc improved all study outcome measures, in relation to appropriate care alone, including significant improvement in patient assessment of overall health and study knee, fewer corticosteroid injections received by patients, and a 25% WOMAC™ pain score improvement [18].

A Cochrane systematic review regarding efficacy study data in general concluded that Synvisc was significantly better than placebo for weight-bearing pain, night pain, function and patient global assessment, significantly better than intra-articular steroid and appropriate care, and equally effective as NSAIDs [19]. The Cochrane review included 76 trials, 24 involving Synvisc, which compared viscosupplements with placebo, other viscosupplements, NSAIDs, intra-articular steroids, exercise, physical therapy, arthroscopy and conventional treatment. The analyses measured improvement in knee function, pain and patient valuation at various periods, including at 5- and 13-week intervals. Use of viscosupplementation for the treatment of knee OA is supported by the study results. Benefits versus placebo of some viscosupplements varied from modest to major. No major safety concerns arose in the analyses and adverse events were few. Owing to a limited sample size, no definitive conclusion could be made regarding the safety of viscosupplements. There have also been several other smaller published meta-analyses, which varied somewhat in their conclusion but overall supported the effectiveness of Synvisc and the other viscosupplements [20–23].

Table 3. Chemical composition of Synvisc® (hylan GF-20).

Contents of each Synvisc injection	Weight
Sodium chloride	17 mg
Hylan A and B	16 mg
Disodium hydrogen phosphate	0.32 mg
Sodium dihydrogen phosphate monohydrate	0.08 mg
Water	Up to 2 ml

Data taken from [7].

Efficacy versus other viscosupplements

Synvisc has been compared with other viscosupplements. The issue of whether there is a correlation between clinical efficacy and molecular weight has been controversial; no correlation has been established, despite individual studies and meta-analyses that noted significant interstudy heterogeneity in estimating efficacy [23–27].

Repeat treatment cycles

The question of efficacy of repeat treatment cycles of Synvisc has been studied prospectively, retrospectively and via an *a posteriori* analysis [28–31]. These studies examined up to three treatment cycles administered 6 months apart and concluded that there was a robust clinical response relative to that from the prior treatment cycle. The finding of ongoing efficacy from a viscosupplement given in repeat treatment cycles is consistent with the findings of the viscosupplement Hyalgan, which has been studied for up to five cycles administered over 30 months [32]. Retreatment data for the other viscosupplements are currently lacking.

Patient selection

A retrospective chart review examined the important question of optimum patient selection [29]. The study concluded that better responses were found in patients with early and intermediate disease stages compared with those with advanced stages.

Patients being considered for total knee replacement

Three studies examined the effect of Synvisc treatment on the need for TKR in those patients who might go on to need surgical intervention [9,33,34]. While one study found that 75% of Synvisc-treated patients who met the criteria for TKR had not undergone TKR by 3.8 years after beginning treatment with Synvisc, the two others also concluded that Synvisc could delay the need for TKR in advanced OA patients. The cost–effectiveness of viscosupplementation is suggested by this potential delay in the need for TKR and subsequent revision procedures. A pharmacokinetic model-based analysis on the cost savings of Synvisc in the USA concluded that a total average saving of US$4706 per patient was realized over a 3-year period [35].

Safety & tolerability

The entire class of viscosupplements has an overall excellent safety profile. There have been no reports of product-associated deaths within the USA since their FDA approval in 1997 and there are no known oral medication interactions. In general, their use is contraindicated in patients with known hypersensitivity to hyaluronans. The hylan polymers that comprise Synvisc and the other viscosupplements, except the bacterially derived viscosupplement Euflexxa™, are extracted from chicken combs. Therefore, if the patient has a history of allergic reactions to avian proteins, such as feathers or egg products, the patient should not be administered Synvisc or any other viscosupplements that are avian derived.

Potential side effects associated with Synvisc administration include those that pertain to the entire viscosupplement class. Local injection-site pain with erythema has been described with the viscosupplements in general and all other intra-articular injections (corticosteroids), and can logically be explained by minor soft-tissue trauma from the needle and/or inadvertent delivery of the viscosupplement into the soft tissue of the joint rather than into the joint space. The incidence of this self-limited side effect specifically for Synvisc was found to be 0.31% by a prospective, multicenter observational trial of 12,699 injections in over 4000 patients [36]. Overall, the study concluded that Synvisc was generally well tolerated.

Iatrogenic infection from the joint-injection procedure itself is a rare but potential complication of viscosupplementation and other intra-articular joint injection, rather than a side effect of the product *per se*. Joint infection is usually due to *Staphylococcus aureus*, which gains entry from the skin surface into the joint space [37,38]. It is possible that the needle itself introduces the pathogen into the joint by carrying epithelial tissue along the path of needle excursion [39].

Infection can also occur by seeding from the bloodstream during the procedure if the needle causes bleeding into the joint from the synovial membrane. Fortunately, iatrogenic joint infection is very rare and has been best studied for corticosteroid injections. Rates in the range of 1/14,000–50,000 corticosteroid knee injections using sterile skin preparation have been reported [40–42]. Since there have been no specific estimates of the infection rate as a result of viscosupplements, at present it is only possible to extrapolate from the above data from corticosteroid injections, as the injection procedure is identical except for the injectate itself. As is true of injection procedures in general, viscosupplements should not be injected into patients

with an infection in the target joint, skin diseases, such as psoriatic plaques, at the injection site that would make it very difficult to sterilize the area, or soft-tissue infections in the area of the injection site.

Postinjection synovitis in patients with underlying calcium pyrophosphate dihydrate crystal deposition disease has been described for viscosupplements in general [43]. The exact mechanism for the inflammatory flare in these patients is not certain.

Most adverse events are of mild to moderate severity and either spontaneously resolve or resolve with symptomatic treatment that generally ranges from rest, ice and analgesics to these measures plus corticosteroid injections [44]. The incidence of these reactions in 511 patients (559 knees) who received 1771 injections in seven clinical trials was 2.2% of injections (7.2% of patients) for a single Synvisc course [7]. In three additional clinical trials of repeated Synvisc courses, the incidence was 6.3% of injections in 22.3% of patients [7]. A side effect that has been traditionally described with Synvisc and, more recently, in cases with a noncrosslinked, naturally derived hyaluronan is known as severe acute inflammatory reaction or severe acute reaction [45,46]. This has also been referred to as a pseudoseptic reaction or flare, as its clinical presentation can mimic that of a septic joint, displaying sudden pain and fluid accumulation within 48–72 h of injection [47]. Management of this includes an arthrocentesis to exclude joint infection. The synovial fluid cell count from arthrocentesis is often inflammatory and ranges from very few to over 50,000 [14]. The exact etiology of this flare reaction is unknown, but the increased incidence with repeated exposure during studies of repeat injection courses suggests that an immunologic mechanism may be responsible. A study on the mechanisms of the pseudoseptic reaction found an elevated $CD4^+$:$CD8^+$ lymphocyte ratio, sensitized $CD4^+$ T cells and symptom delay of 24 h or more, which are all consistent with a type 4 (cell-mediated) hypersensitivity reaction [48].

Adverse events reported both during clinical trials and as part of worldwide postmarketing surveillance have included rash, itching, nausea, muscle cramps and peripheral edema [7]. By contrast, a variety of other adverse events has been reported only during postmarketing surveillance but not during clinical trials, and includes hives, fever, headache, dizziness, chills, paresthesias, malaise, respiratory difficulties, flushing, facial swelling, and rare reports of thrombocytopenia [7]. The causal relationship of both of the above categories of adverse reactions to Synvisc is uncertain.

As is true for the other viscosupplements, the safety and effectiveness of Synvisc for use in nursing or pregnant women and in children have not been established.

Regulatory affairs

Synvisc is approved in more than 60 countries around the world. In the USA, the approved treatment regimen is for a three-injection cycle administered 1 week apart for patients with painful knee OA who have otherwise failed to respond to simple analgesic medications, such as acetaminophen and nonpharmacologic treament. This provides, on average, up to 6 months of relief. While not at present directly relevant to on-label use in the USA, Synvisc is approved to treat knee and hip pain in Canada. In Europe, Synvisc has been proven to provide up to 12 months of pain relief from knee OA and is approved for knee, hip, shoulder and ankle OA. The new, single-treatment Synvisc One™ has been approved in Europe for OA knee-pain relief.

Conclusion

OA is a very common synovial joint degenerative condition that particularly affects the cartilage and synovial fluid. Viscosupplementation is the exogenous weekly (3–5 weeks) intra-articular administration of hyaluronate, the major component of synovial fluid and a constituent of hyaline cartilage. Currently, there are five FDA-approved viscosupplements, including Synvisc, a structurally unique high-molecular-weight compound. Synvisc has proven efficacy and safety, but can cause a side effect known as severe acute inflammatory reaction.

Future perspective

Synvisc One is a new formulation that is administered as one 6-ml injection instead of three 2-ml injections given once every week for 3 weeks. Synvisc One is manufactured by Genzyme Biosurgery, NJ, USA; it has been approved in Europe, is under review by the FDA and is also seeking approval in Asia and Latin America.

It remains to be seen whether additional clinical studies can settle the debate as to whether the high-molecular-weight crosslinked viscosupplement Synvisc offers an advantage in terms of efficacy that offsets its potential to cause local inflammatory intra-articular reactions compared with the noncrosslinked viscosupplements.

Approval within the USA of intra-articular hyaluronic acids for use in joints affected by OA besides the knee joint is another potential area of future utility. The results of studies of Synvisc, as well as other viscosupplements, for painful OA of the hip, glenohumeral joint, ankle and other joints have been promising and could lead to future use of viscosupplements for these body regions by physicians who are capable of effectively injecting these areas [49–54].

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Executive summary

- OA is a disorder of synovial joints that adversely affects all tissues within a joint, especially the cartilage and synovial fluid.
- Hyaluronate, the major component of synovial fluid and a component of the hyaline cartilage, is adversely affected in OA.
- Viscosupplementation is the exogenous administration of hyaluronate.
- Synvisc® is a type of viscosupplement that is unique because it is chemically crosslinked in order to increase its molecular weight so that it approximates the weight of normal synovial fluid, which also allows for a prolonged intra-articular residence time.
- Synvisc has been shown to be efficacious when administered by a three-injection regimen and has a duration of efficacy per label of up to 6 months and longer in postmarketing studies.
- As is true for the viscosupplements in general, Synvisc is safe but can cause a side effect known as severe acute inflammatory reaction, especially with repeated administration.

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