Synvisc-One™ for the treatment of knee osteoarthritis

Knee osteoarthritis is a chronic, progressive, degenerative disease that most commonly presents in individuals over the age of 50 years with symptoms of pain, swelling, stiffness, crepitus and functional limitations. It is characterized by the progressive loss of hyaline cartilage resulting in joint space narrowing and bony changes. Furthermore, the synovial fluid contained within osteoarthritic joints, of which hyaluronan is a major protective constituent, undergoes a degenerative process. This has led to a treatment modality to replace hyaluronan, which is known as viscosupplementation. Viscosupplementation use has been supported by numerous studies and several meta-analyses to be safe and effective in ameliorating the pain and functional limitations associated with knee osteoarthritis. However, up until fairly recently, viscosupplementation was provided through weekly intra-articular injections over a course of 3–5 weeks. Synvisc-One™ (Genzyme Biosurgery Corporation, MA, USA) is one example of a newly released and promising group of single-dose intra-articular injections that is proving to be effective, safe and convenient for the treatment of knee osteoarthritis.

KEYWORDS: hyaluronan ■ hyaluronic acid ■ hylan G-F 20 ■ osteoarthritis ■ Synvisc-One™ ■ viscosupplementation

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Osteoarthritis (OA) is a chronic, progressive, degenerative disease that affects many joints and is the most common type of arthritis. OA is classified as idiopathic, or as secondary, owing to traumatic, congenital or medical causes. It is characterized by the progressive loss of hyaline cartilage leading to joint space narrowing, osteophyte formation and bony changes. Patients with OA typically present in their later years with pain, swelling, stiffness and varying functional limitations [201].

Osteoarthritis affects approximately 27 million Americans with nearly a third of individuals over the age of 65 years having some form of OA [1]. The knee is considered one of the more common sites of developing OA, with a symptomatic prevalence ranging between 10–16% of individuals over the age of 45 years [2–4]. The overall radiographic incidence of knee OA is 2% per year, with a symptomatic incidence of 1% per year [5]. This incidence rate increases with age until the age of 80 years at which time the incidence rate plateaus. In addition, there seems to be an increased prevalence of knee OA in females, especially after the age of 50 years [6,7].

The diagnostic criteria set forward by the American College of Rheumatology (GA, USA) for knee OA are based on individuals over the age of 50 years and permutations of clinical, radiographic and laboratory evaluations, which include knee pain for most days over the previous month and osteophyte formation at the joint margin [8]. The pain associated with knee OA has profound effects on quality of life and general functional ability. In fact, knee OA is one of the top five leading causes of disability in noninstitutionalized adults [9]. Therefore, it is easy to see how the treatment of knee OA affects the general well-being of a large number of individuals as well as the associated medical costs inherent in such a debilitating disease.

The exact mechanism by which certain individuals develop OA while others do not is poorly understood. However, there are modifiable and non-modifiable risk factors associated with the development of knee OA (Table 1).

Treatment options for knee OA focus on addressing modifiable risk factors. Medical therapies are not considered curative for knee OA; they are adjuncts in the treatment of the symptoms associated with the disease. The goals for treatment include controlling pain, improving function and return to normal life activities. These are accomplished by a combination of pharmacological and nonpharmacological means. For example, treatments include exercise, weight control, physical modalities, alternative treatments and medications. Medication treatment for OA typically begins with acetaminophen and/or NSAIDS. NSAIDs are widely accepted as a treatment option; however, they are associated with an increased risk of gastrointestinal and cardiovascular side effects [10,11]. Estimates

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Table 1. Risk factors for knee osteoarthritis.

Modifiable	Non-modifiable
Excess body mass	Gender (higher risk in women)
Previous joint injury	Age (increases with age until ~80 years)
Excessive mechanical stresses due to repetitive motion, hard labor, heavy lifting and so on	Race (lower risk in some Asian populations)
	Genetic predisposition
Structural misalignment	
Muscle weakness	

Data from [2,97–99].

of NSAID-induced bleeding resulting in death range as high as 16,500 patients per year in the USA [12]. The use of all types of NSAIDs potentially increases the risk of cardiovascular events such as hypertension, congestive heart failure and thrombotic events (i.e., myocardial infarction) [11].

Another widely accepted pharmacologic treatment regimen, which is classified as a device and not a drug, is hyaluronic acid supplementation. The US FDA classifies all viscosupplementation under a medical device category rather than a drug category because its effects are believed to be due to its physical action in providing analgesia by increasing elastoviscosity within the joint rather than a direct drug effect. Synovial fluid within the knee joint of an individual with OA undergoes fundamental changes in its viscosity and elasticity that contributes to degradation and destruction of the articular cartilage and bony surfaces. The viscosity and elasticity of the synovial fluid, collectively known as rheological properties, are altered as the native hyaluronan within the arthritic joint is degraded. The decrease in the average molecular weight and concentration of hyaluronan further reduces the elastoviscosity of the synovial fluid. In normal individuals without knee OA, the knee contains less than 2 ml of synovial fluid, with hyaluronic acid making up between 4 and 8 mg [13,14]. In arthritic joints, the disruption on the relationship between molecular weight and elastoviscosity diminishes the rheological properties of the synovial fluid [14,15].

Hyaluronic acid serves two main physical functions within a joint: it acts as a lubricant to the joint during low-impact activity, and as a cushion during high-impact activity. In patients with knee OA, there may be joint swelling or effusions that reduce the concentration and alter the distribution of hyaluronic acid. Hyaluronan is the only component in synovial fluid that provides elastoviscosity. The cells that produce hyaluronic acid – type A synoviocytes – may also be damaged in knee OA [16]. These changes in the rheological properties of synovial fluid are listed in Table 2 and are based on previous studies comparing differences in the elasticity and viscosity of normal and aged patients with OA. These fundamental changes within the physical properties of the synovial fluid are thought to be partially responsible for the progression of wear and destruction of the articular cartilage.

Viscosupplementation, or intra-articular injection of exogenous hyaluronic acid, addresses the degraded form of hyaluronic acid within the arthritic joint by supplanting it with a form that retains the rheological properties of normal synovial fluid [14]. This treatment modality was first introduced in the 1970s with the introduction of a high molecular weight preparation called by its acronym 'NIFNaHA', or noninflammatory fraction of sodium hyaluronan [17]. This preparation retained the elastoviscous properties of normal hyaluronic acid and was a sterile, noninflammatory substance that allowed for its medical use. Viscosupplementation, as a therapeutic option for knee OA, has been scrutinized and evaluated for the treatment of knee OA since its introduction [18–22]. This pharmaceutical class has been widely studied, evaluated and proven safe and effective for knee OA through several controlled clinical studies and meta-analyses [23–37]. Currently, viscosupplementation is a widely utilized and accepted practice by many professional societies for the treatment of knee OA [38–43].

The advent of a new single-dose viscosupplementation product, Synvisc-One™ (Genzyme Biosurgery Corporation, MA, USA), is the focus of this article. The benefits of a single-dose injectable viscosupplementation product are numerous. Given the small but potential risk of infection and other local adverse reactions that can be seen with any intra-articular injection, decreasing the need to repeatedly violate the sterile intra-articular environment is a great benefit, decreasing the risk of septic arthritis and other local comorbidities. Furthermore, decreasing the number of visits allows for better patient compliance, improved convenience and decreased medical expenses [44].

Overview of the market

The number of viscosupplementation formulations has grown over the years with more than 20 formulations currently available worldwide. The products mainly vary with molecular weight, residence time in the joint and recommended dosing regimens ranging from one–five injections at weekly intervals [33]. TABLE 3 summarizes several viscosupplementation compounds currently approved in the USA with their associated characteristics.

There are two main subtypes of viscosupplementation – hyaluronan and hylans (cross-linked derivatives of hyaluronan). There has been considerable debate as to the competing efficacy of the differing subtypes in treatment of knee OA. In general, the two types of viscosupplementation are accepted as equal in terms of their efficacies [26,35,45–47]. However, others consider that efficacy may be dependent on the viscoelastic properties of the hyaluronic acid injected [14], with some suggestions that hyaluronic acids with a higher molecular weight may provide improved clinical benefits [34,48–50]. Of note, the molecular weight of hyaluronan in healthy synovial fluid is approximately $3–4 \times 10^3$ kDa.

Introduction to the compound

Hyaluronan is a polysaccharide consisting of repeated linear dimers of *N*-acetylglucosamine and glucuronic acid. It is physiologically ubiquitous in the animal kingdom where it functions as a lubricant, cushion and transport medium for nutrients, proteins and degradation products related to joint tissue metabolism [51].

Hylan G-F 20 (Synvisc [Genzyme Corporation, MA, USA]) is a high molecular weight, cross-linked derivative of hyaluronan. It was first approved by the FDA in 1997 for the treatment of knee OA in symptomatic patients. Based on an initial treatment schedule clinical trial [52], it has been used as a 2 ml intra-articular injection administered weekly for 3 weeks in total. In OA of the knee, hylan G-F 20 has demonstrated a strong safety and efficacy profile over the years, which is supported by prospective clinical trials [30,52,54] and large retrospective studies [55,56].

In clinical controlled studies, hylan G-F 20 versus placebo has been demonstrated to decrease pain and improve joint mobility [30,52–54,57,58]. After a full 3-week course of hylan G-F 20 intra-articular injections, peak efficacy is observed between weeks 8 and 12 after the first injection, and can last for up to 12 months [54]. The use of hylan G-F 20 has also been experimented with in patients with hip [59,60], shoulder [61] and ankle [62] OA on off-label use, which has demonstrated significant sustained and symptomatic effects for up to 6 months.

The introduction of a single injection of hylan G-F 20 product was approved by the FDA in February 2009. It is administered via a single 6 ml intra-articular injection treatment regimen, which is equal to the total of the three weekly dose injections of 2 ml hylan G-F 20 that is currently utilized [202].

Chemistry

Synvisc-One™ is a combination of three doses of hylan G-F 20, which consists of a highly purified, viscoelastic fluid with properties similar to the synovial fluid found in young healthy knee joints. The compound is a cross-linked molecule consisting of two polymers, hylan A and hylan B. Hylan A is a soluble, high molecular weight molecule with an average molecular weight of 6000 kDa and makes up 80% by volume of the compound. Hylan B is an insoluble gel-like continuous molecular network of infinite molecular weight that makes up the remaining 20% by volume. Cross-linked hylan solutions possess considerably greater viscoelastic properties than solutions of natural hyaluronan [63]. Each 10 ml glass syringe contains sterile and nonpyrogenic hylan polymers in a buffered physiological sodium chloride solution (TABLE 4) [64].

Pharmacodynamics

Hylan G-F 20 is administered via single intra-articular injection into the knee utilizing sterile precautions. It is nonimmunogenic, non-inflammatory, and does not cause a foreign-body reaction. The compound is permeable to metabolites [65] and has a substantially longer residence

Table 2. Rheological properties of synovial fluid in varying patient populations.

Synovial fluid analysis	Average molecular weight of hyaluronic acid (million Da)	Elasticity (Pa at 2.5 Hz)	Viscosity (Pa at 2.5 Hz)	Volume of hyaluronic acid (mg/ml)	Ref.
Normal synovial fluid	6	117	45	2.50–3.65	[64,100,101]
Osteoarthritic synovial fluid	1.9	1.9	1.4	1.07–2.60	[102,103]

Table 3. Hyaluronic acid products available in the USA ranked in order of molecular weight.

Hyaluronic acid type	Brand name	Hyaluronic acid source	Manufacturer/US distributor	Dosing schedule (ml × no. of weeks)	Average molecular weight (kDa)
Sodium hyaluronate	Hyalgan®	Rooster combs	Fidia Farmaceutici SpA/Sanofi-Aventis	2 × 3[-5]	500–730
Sodium hyaluronate	Supartz®	Chicken combs	Seikagaku Corporation/Smith & Nephew, Inc.	2 × 3[-5]	630–1170
Sodium hyaluronate	Orthovisc®	Chicken combs	Anika Therapeutics, Inc./DePuy Mitek	2 × 3	1100–2900
Sodium hyaluronate	Euflexxa™	Bacterial fermentation	Bio-Technology General (Israel)/ Ferring Pharmaceuticals, Inc.	2 × 3	2400–3600
Hylan G-F 20 (80% hylan A and 20% hylan B)	Synvisc® Synvisc-One™	Chicken combs	Genzyme Biosurgery	2 × 3 6 × 1	6000

Data from [68,85].

time in joints than hyaluronan [66]. An animal model study investigating the intra-articular joint residence time of hylan A and hylan B found that both were still present at 2 and 7 days, respectively. Residence time in the rabbit animal model is approximately 23 h for a 1% solution of hyaluronan and approximately 20–30 days for a 0.4% solution of hylan B [67]. Hylan B contributes greatly to the viscoelasticity of hylan G-F 20 as well as the augmenting of the residence time in the joint [68].

Because of initial studies demonstrating relatively short residence times in the joint for hyaluronans (half-life: 1–2 days), injections were recommended to be repeated at weekly intervals [69]. However, current research suggests that the long-term symptomatic effect of the therapy, in some cases up to 12 months, which exceeds the residence time of the product in the joint, may be due to the restoration of normal, endogenous synthesis of high-quality hyaluronic acid within the joint [14,70–72]. In addition, some of the analgesic effects of high viscosity solutions such as hylan G-F 20 may be mediated through free radical scavenging [73], effects on inflammatory cells, [79,74–78] and antinoceptive properties [79,80].

Clinical efficacy

The clinical efficacy of hylan G-F 20 in the treatment of knee OA has been previously and elegantly reviewed in a similar drug review involving the 'weekly injections over 3 weeks' form of delivery [81]. Briefly, the use of hyaluronic acid injections is accepted as providing a more durable analgesic effect than injection of a corticosteroid [82]. In examining the efficacy of various types of viscosupplementation products available on the market, there is a general consensus regarding its effectiveness, regardless of whether the supplemented hyaluronans are of low and high molecular weights [83]. However, there is a well-controlled clinical study that found hylan G-F 20 to be associated with better clinical effectiveness and general patient satisfaction than a traditional low molecular weight sodium hyaluronan product [84]. Arguments also arise in favor of straight-chain hyaluronic acid due to a better risk–benefit profile as they are not associated with flare effusions, which may be seen with hylan G-F 20 [85]. Some evidence also suggests that knee lavage prior to viscosupplementation may further the benefit of hylan G-F 20 in the efficacy of pain relief [86]. In summary, hylan G-F 20, as it has been studied extensively in its original three injection form, is a proven treatment option for knee OA in patients with low- to medium-grade radiographic changes [87].

The clinical efficacy in treating knee OA extends beyond its analgesic properties. There is growing evidence that intra-articular hylan G-F 20 injections have the potential to alter the natural history of the disease by decreasing excessive loads on the knees, modifying the structure of the diseased joint and slowing the rate of OA disease progression [88,89].

Table 4. Chemical composition of Synvisc-One™ (hylan G-F 20).

Contents of each 10 ml syringe	Weight
Hylan polymers (hylan A & hylan B)	48 mg
Sodium chloride	51 mg
Disodium hydrogen phosphate	0.95 mg
Sodium dihydrogen phosphate monohydrate	0.24 mg
Water for injection	Up to 6 ml

It is difficult to make a direct correlation between the clinical efficacy of the single dosing 6 ml injection regimen based on the numerous studies that have shown benefit with hylan G-F 20 weekly dosing injections. Although the composition of the viscosupplementation is the same, the varying dosage regimens do not share a similar safety profile. There is only a single pilot study that directly examined varying dosing regimens of hylan G-F 20 and clinical improvements [44]. In that study, 100 patients with mild-to-moderate unilateral, symptomatic knee OA were randomized to receive varying doses of hylan G-F 20. The regimens consisted of one 6 ml, one 4 ml, two 4 ml 2 weeks apart, three 4 ml 1 week apart, or three 2 ml 1 week apart injections. The greatest mean improvements were observed in the one 6 ml, three 4 ml and three 2 ml groups. However, the highest percentage (30%) of device-related local adverse events (AEs) was seen in the three 4 ml group, compared with only 10% of AEs in the one 6 ml and three 2 ml groups. Therefore, considering a risk–benefit scenario and excluding this highest risk regimen, the results were promising that a single 6 ml injection might be just as efficacious as three 2 ml injections administered 1 week apart without any decrement in the safety profile.

The confirmatory randomized, double-blind, placebo-controlled study soon followed, with patients randomized to receive either a single 6 ml injection of hylan G-F 20 or placebo [90]. A total of 253 patients were randomized and treated. Statistically significant improvements in walking pain, as recorded by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index A (WOMAC A1), were found between placebo and treatment groups. Findings of this study support that a single 6 ml injection of hylan G-F 20 provides statistically significant improvements in pain relief over 26 weeks.

Safety & tolerability

Overall, the entire spectrum of viscosupplementation products have proven to demonstrate a favorable safety profile [33]. Adverse reactions may occur in individuals who have a hypersensitivity (allergy) to hyaluronan preparations, especially those of avian derivation, and these should thus not be administered in those individuals. Because the vast majority of viscosupplementation products are avian derived (chicken/rooster combs), the products should also not be administered to individuals with avian protein, feather, or egg product hypersensitivity or allergy. In addition, as with any intra-articular injection, sterile precautions are of utmost importance to decrease the risk of septic arthritis, which may be seen in any intra-articular injection that penetrates through the skin into a sterile environment.

Hylan G-F 20 has demonstrated a strong safety profile over more than a decade of use within the USA. The three-injection form has demonstrated a comparable tolerability profile to intra-articular corticosteroid injections with an improved duration of effect [51]. The overall tolerability has been favorable with a low incidence of local AEs [56,91]. Based on these large clinical studies, the overall local treatment-related and procedure-related AEs were reported in 4.2% of patients and 2.4% of injections. The most frequently reported AEs were joint effusion (reported in 2.4% of patients), joint swelling (1.3%), arthralgia (1.2%), joint warmth (0.6%) and injection site erythema (0.3%). Most AEs were mild-to-moderate in nature and resolved either spontaneously or with only symptomatic treatment.

Based on population data of over 4000 patients receiving intra-articular hylan G-F 20, predictors of favorable short-term effectiveness included patients who were underweight, of male gender, with a shorter term since diagnosis and with severe baseline pain. On the other hand, those who were more likely to experience a local AE included patients under the age of 70 years, with a longer duration since diagnosis of OA and who were previously treated with viscosupplementation [91]. There is some concern that hylan G-F 20 may possess some inherent predisposition to the development of local inflammatory reactions, which is attributable to its physiochemical characteristics that are not seen in other hyaluronan products [92,93]. These local inflammatory flares are defined as hot, painful, swollen knees that occur within 48 h of injection [94,95]. Although there is some concern that the incidence of this inflammatory reaction increases with repeat administration of the three-injection form, the types of AEs seen with repeat courses of hylan G-F 20 are not qualitatively different to those in the current published literature [96].

Because Synvisc-One is a recently approved product, there are fewer data supporting the safety and tolerability profile of a single 6 ml dose of hylan G-F 20 compared with the three-injection version. There have only been two published studies [44,90] of the single injection regimen with an overall tendency to support the safe use of this treatment. In an original pilot study, the risk of AEs from a single dose of 6 ml was comparable to the widely accepted regimen of

three doses of 2 ml each, performed weekly [44]. This was further supported by a randomized, saline-controlled trial that found a slightly higher incidence, but was statistically nonsignificant, of related local AEs in the 6 ml hylan G-F 20 group (5.7%) compared with the saline control group (3.1%) [90]. Furthermore, in individuals with AEs following the first administration of the device, repeat administrations of the 6 ml hylan G-F 20 did not reproduce AEs in subsequent administrations, which supports the safety and tolerability profile of repeat administrations.

Regulatory affairs

In 1987, hyaluronan solutions were approved for the treatment of arthritic pain in Japan and Italy [30]. Since the original form of hylan G-F 20 for viscosupplementation in OA of the knee was introduced, it was since approved for marketing in Canada in 1992, in Sweden in 1995, in the European Economic Area in 1995 and in the USA in 1997 [14]. The development of the single 6 ml dose of hylan G-F 20 has followed accordingly and is now approved in the European Union and a number of Asian and Latin American countries.

The approval of Synvisc-One by the FDA in 2009 is indicated for patients with knee pain owing to OA and who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen). The relief of pain associated with knee OA has been demonstrated to last up to 6 months with the treatment.

Conclusion

Knee OA is a very common and, in some cases, debilitating disease. The disease affects both the articular cartilage within the joint, as well as the synovial fluid. Viscosupplementation provides an exogenous source of hyaluronan, the main protective factor contained within synovial fluid, which provides lubrication and cushioning to the joint. Currently, Synvisc-One is the only single-dose, high molecular weight, viscosupplement product available in the USA for the treatment of knee OA.

Future perspective

Although Synvisc-One is the only FDA-approved single-dose viscosupplement product available on the US market, others may soon follow. Monovisc™ (Anika Therapeutics, Inc., MA, USA), a single-dose, lightly cross-linked sodium hyaluronan is currently only approved in the European Economic area and Turkey. A current US and Canadian clinical trial is underway with anticipated FDA approval and commercialization of the device in 2010. Durolane® (Smith&Nephew, Warwick, UK) is a single-dose injectable that is currently approved in 32 countries including Canada. It is not FDA approved in the USA. Another product currently under evaluation by the FDA is Gel-200 (Seikagaku Corporation, Tokyo, Japan). It remains to be seen whether competing single-dose viscosupplement therapies in the future will clarify the ongoing debate regarding the optimal molecular weight of supplemental hyaluronan needed for optimal clinical outcomes.

The future treatment of knee OA will likely not end with viscosupplementation. New areas of research into disease-modifying agents, gene therapy, growth factors and cartilage transplant may pioneer a new era of treatment for knee OA. These new therapies will be more likely to treat the structural basis of disease, rather than solely the symptoms associated with it.

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Executive summary

- Osteoarthritis (OA) is a chronic, progressive, degenerative disease of synovial joints, which leads to destruction and deterioration of hyaline cartilage and synovial fluid.
- Knee OA is a leading cause of disability with excessive costs associated with treatment.
- Hyaluronan, a constituent of normal synovial fluid that functions physically as a lubricant and protective cushion, undergoes dilution and deterioration in patients with OA.
- Viscosupplementation is a means of providing exogenous hyaluronan into the joint via an injection to restore some of the natural elastoviscous properties of the joint and improve symptoms.
- Synvisc-One™ (Genzyme Biosurgery Corporation, MA, USA) is a single-dose viscosupplement product that allows for better patient compliance, improved convenience and decreased medical costs.
- Synvisc-One has demonstrated clinically meaningful symptomatic improvements in knee OA patients that were statistically superior to saline control, and has a favorable safety profile showing no increase in local adverse events with repeat administration.

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