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REVIEW

Managing joint pain in osteoarthritis: safety and efficacy of hylan G-F 20

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Abstract: The use of intra-articular viscosupplementation in the nonoperative management of patients with osteoarthritis has become quite popular. Recent clinical data have demonstrated that the anti-inflammatory and chondroprotective actions of hyaluronic acid viscosupplementation reduce pain while improving patient function. We review the basic science and development of viscosupplementation and discuss the mounting evidence in support of the efficacy and safety profile of hylan G-F 20. Recent evidence suggesting a disease-modifying effect of hylan G-F 20 is also assessed. Furthermore, although the primary focus of this article is on treatment of osteoarthritis of the knee, we also discuss the use of viscosupplementation in other joints, such as the hip, ankle, and shoulder.

Keywords: viscosupplementation, osteoarthritis, knee, hyaluronic acid, hylan G-F 20

Introduction

Osteoarthritis is the most common joint disorder in the aging population.[1] In the United States alone, recent projections report that by the year 2030 the disease will affect almost 63 million Americans. The Centers for Disease Control and Prevention has estimated that the annual direct and indirect costs associated with osteoarthritis and other rheumatologic conditions total approximately US$86.2 billion.[2] Osteoarthritis is also a clinically significant cause of disability. In a recent survey of all causes of lost productive time in the US workforce, Stewart et al[3] discovered that arthritis was second only to low back pain as a specific cause of lost work and reduced performance at work.

Although surgical treatment of osteoarthritis can reduce pain and improve joint mobility and function, the operative management of osteoarthritis is associated with significant cost and potential morbidity. Furthermore, not all patients are candidates for surgical intervention, and they may wish to delay or avoid it if possible. There are several nonsurgical treatment options for symptomatic osteoarthritis including weight loss, exercise, activity modification, physical therapy, bracing, wedged shoe insoles, walking aids, nonsteroidal anti-inflammatory drugs (NSAIDS), and intra-articular injections of corticosteroids.[4,5] In September 2000, the American College of Rheumatology guidelines for the treatment of osteoarthritis of the knee recommended that one treatment option to be considered is the use of intra-articular injections of hyaluronic acid for the relief of osteoarthritic pain.[5] Since then, hyaluronic acid viscosupplementation has become one of the more popular nonoperative treatment options for symptomatic osteoarthritis.[6–8] More recently, in 2008, the Osteoarthritis

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Research Society International (OARSI) cited intra-articular hyaluronic acid as a useful therapeutic modality, that has delayed onset, but prolonged duration of symptomatic benefit, in treating patients with osteoarthritis of the knee or hip.[4] In addition, although marketed as analgesics, viscosupplements have been postulated to have potential chondroprotective effects as well.[9]

We reviewed the development, indications, clinical efficacy, and safety profile of hylan G-F 20 (Synvisc®; Genzyme Biosurgery, Cambridge, MA, USA) primarily in the management of osteoarthritis of the knee; however, we will also briefly discuss recent evidence that suggests the efficacy of hylan G-F 20 in other joints, such as the hip and ankle.

Basic science of hyaluronic acid

Hyaluronic acid (HA), also known as hyaluronan or hyaluronate, is a high-molecular-weight glycosaminoglycan made up of repeating disaccharide units of N-acetyl-glucosamine and glucoronic acid.[10] The average molecular weight of synovial fluid HA is 5 to 7×10^6 Da. Type B synoviocytes and fibroblasts synthesize HA and secrete it into the joint space. HA molecules occupy a large spheroidal space while in their fully hydrated state. Therefore, the viscoelasticity and flow characteristics of synovial fluid are intimately tied to its HA content.

Synovial fluid viscoelasticity is essential for normal joint function. Hyaluronic acid has both viscous and elastic properties, and the degree to which either predominates depends on distinct loading conditions. This allows synovial fluid the unique capacity to function differently depending on the amount of shear force applied.[11] For example, in the presence of low shear forces, typically with slow joint mechanics, HA molecules exhibit high viscosity with reduced elasticity. With increased rates of joint motion (high shear), this reverses as the synovial fluid becomes more elastic and absorbs energy more efficiently.[121] Therefore, synovial fluid acts as a lubricant during slow movements and as a shock absorber during rapid movements. Because of this energy dependent viscoelasticity, HA has been termed "pseudoplastic."[10]

The normal adult knee contains approximately 2 mL of synovial fluid, with a HA concentration of 2.5 to 4.0 mg/mL.[13] In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50% because of dilution from inflammatory effusion, abnormal synoviocytes, and molecular fragmentation.[14,15] These alterations lead to dramatically poorer viscous and elastic properties and, thus, distorted joint mechanics. Decreased lubrication leads to increased stress on the already diseased cartilage, which further disrupts the collagen network and the integrity of the chondral surface. The loss of barrier integrity also adversely affects cartilage nutrition and waste removal. Finally, fragmented low-molecular-weight HA may actually have a proinflammatory effect.[16]

Intra-articular kinetic studies argue against improved biomechanics as the major explanation for viscosupplementation efficacy. Fraser et al[17] developed a HA assay in a sheep model. They reported the mean half-life of [^{3}H] acetyl-labeled hyaluronic acid in normal joints was 20.8 hours, compared with 11.5 hours in acutely inflamed joints. Extrapolating these figures and using them as a rough guide to the kinetics of the human osteoarthritic joint, the mechanism of action of viscosupplementation must be more than the simple replenishment of degraded HA. This has led to further research into other significant functions of HA within the joint. Recent studies have suggested that HA exerts anti-inflammatory, analgesic, and possibly chondroprotective effects in the articular cartilage and joint synovium.[8,12,18]

Hyaluronic acid exerts its anti-inflammatory effect within the joint space by influencing a variety of leukocyte functions both in vivo and in vitro. These include inhibition of migration, chemotaxis, phagocytosis, adherence, and proliferation.[12,19–21] Tamoto et al[21] demonstrated in an animal model that HA affects leukocyte signal transduction via cell-surface receptors, which are dependent on the size of the HA molecule. Furthermore, intra-articular injection of HA reduces the concentration of inflammatory mediators, such as prostaglandins, fibronectin, and cyclic AMP in the synovial fluid of patients with arthritis.[22,23] Tobetto et al[24] used in vitro assays to demonstrate that HA can affect the release of arachidonic acid from human synovial fibroblasts.

Although the anti-inflammatory properties of HA may explain some of its analgesic properties, direct analgesic activity of intra-articular HA injection has been demonstrated in recent animal models. This seems to be mediated both directly through inhibition of nociceptors and indirectly via decreasing the synthesis of or binding to bradykinin, substance P, and other hyperalgesic compounds.[25–28]

Of even greater significance are the results of basic science studies demonstrating various positive effects of HA on both synoviocyte and chondrocyte metabolism.[29] Ghosh[25] demonstrated *de novo* HA biosynthesis by fibroblasts upon *in vitro* exposure to exogenous HA. This effect was dependent on both concentration and molecular weight of exogenous HA. In this same study, the authors also demonstrated that high molecular

weight, cross-linked derivatives of HA actually provided a protective effect on chondrocytes exposed to leukocyte proteinases, IL-1, or oxygen-derived free radicals. Again, this effect was viscosity dependent, with higher molecular weight HA providing superior protection compared with lower viscosity formulations.

Development of viscosupplements

Balazs and associates[10] pioneered the concept of visco-supplementation in the 1960s. This concept was based on extensive research into joint fluid flow and HA itself. They believed an ideal viscosupplement should meet 4 specific criteria: 1) permeability to metabolites and macromolecules, 2) non-immunogenic, 3) similar molecular weight to native synovial fluid, and 4) a long half-life.

The first clinical use of viscosupplementation did not occur until the late 1980s when Hyalgan® (Fidia, Italy) and Artz® (Seikagaku, Japan) were placed on the foreign market for use in human arthritic knees. Viscosupplementation with intra-articular (knee) HA was approved by the Food and Drug Administration (FDA) in 1997. The FDA currently does not approve viscosupplementation therapy for use in joints other than the knee. However, several trials, to be discussed later, have shown that it may be useful in treating osteoarthritis pain in other joints such as the hip, ankle, and shoulder.

The aforementioned HA formulations required multiple injections because they were relatively lower in molecular weight. To address this issue of shortened half-life, cross-linked hyaluronans, called hylans, were developed. Hylans have been reported to have improved viscoelastic properties and an increased duration within the joint, as a function of cross-linking.[30] Hylan G-F 20 was the first, and remains the only, cross-linked HA available in the United States.[2] Hylan G-F 20 consists of a combination of the fluid and gel forms at a 4:1 ratio. Its molecular weight is 6×10^6 Da, similar to that of HA in a healthy joint. There are four other HA formulations approved for use in the United States: Hyalgan® (Sanofi-Sythelabo Inc, New York, NY, USA), Supartz® (Seikagaku Corp, Tokyo, Japan), Orthovisc® (Anika Therapeutics Inc, Woburn, MA, USA), and Euflexxa® (Ferring Pharmaceuticals Inc, Suffern, NY, USA) (Table 1). The few published head-to-head clinical trials in humans have not demonstrated a clear efficacy advantage of one product over another.[31] However, some published studies suggest that higher-molecular-weight HA is more efficacious.[6,32]

Clinical efficacy

The efficacy of hyaluronic preparations has been published in numerous clinical outcome studies.[6,33–42] The first human clinical trial of intra-articular HA in the treatment of arthritis was published by Peyron and Balazs[33] in 1974. In this study, 14 patients were randomly assigned to either treatment or placebo groups. At 4-month follow up, the treatment group reported some improvement in joint symptoms. Since then, numerous large, multicenter, randomized, blinded, placebo-controlled studies have been performed.[38,40,42–45] The reported benefits, however, have been variable. Wang et al[6] performed a meta-analysis to determine the effects of intra-articular injection of HA on knee osteoarthritis and to elucidate the therapeutic efficacy and safety of the procedure. They evaluated 20 randomized controlled trials that compared both cross-linked (hylan G-F 20) and noncross-linked hyaluronates with placebo. All trials used validated outcome measures and safety was assessed by the relative risk of an adverse event. The authors reported that both cross-linked (hylan G-F 20) and noncross-linked hyaluronates do indeed have a therapeutic effect in patients with osteoarthritis of the knee when compared with placebo. They found significant improvements in pain on activity, pain at rest, and function. Furthermore, trials that involved hylan G-F 20 showed much greater pooled estimates of efficacy than did the trials involving non-cross-linked hyaluronates. The most recent

Table 1 Commercially available viscosupplements

Product	Molecular weight (× 105 d)	Hyaluronic acid concentration (mg/mL)	Proven duration of action (weeks)	Dosing regimen	Approximate cost (1 course)
Synvisc	60 (cross-linked)	8	26	3-weekly injections	$589
Euflexxa	24–36	10	12	3-weekly injections	$437
Hyalgan	5.0–7.3	10	8.5 (3 injections) 26 (5 injections)	3- to 5-weekly injections	$524
Supartz	6.2–11.7	10	14 (3 injections) 26 (5 injections)	3- to 5-weekly injections	$533
Orthovisc	>10	15	22	3-weekly injections	$543

meta-analysis from the Cochrane database also confirmed the overall efficacy of all HA products.[35] Bellamy and colleagues identified 76 randomized placebo-controlled trials that fulfilled strict methodology and study design criteria. Based on their careful analysis of the literature, the authors concluded that viscosupplementation is an effective treatment for osteoarthritis of the knee with favorable effects on pain, function, and patient global assessment, especially during the 5- to 13-week postinjection period.

In the specific case of hylan G-F 20, most studies report significant improvements in pain and physical functioning in patients followed for up to 3 months to a year (Table 2). However, a few trials demonstrate similar outcomes between hylan G-F 20 and intra-articular controls. Overall, clinically meaningful improvements with hylan G-F 20 have been demonstrated by pain improvements from baseline of 33% to 80% compared with 21% to 26% with placebo.[46] We have identified 4 randomized, placebo-controlled trials investigating the use of 3 weekly intra-articular injections of hylan G-F 20 for the treatment of knee osteoarthritis.[38,40,44,45] In a 26-week study, Wobig et al[38] reported significant improvements on visual analog testing versus placebo for pain during weight-bearing, pain at rest, pain during most painful knee movement, and treatment success. At the end of the 26 weeks, significantly more hylan G-F 20-treated patients versus placebo-treated patients were symptom free and required less use of NSAIDS or steroid as rescue therapy. Scale et al[44] published similar significant improvements in activity, weight-bearing pain, most painful knee movement, and investigator and patient global evaluations in their 12-week study of 80 patients treated with two and three injections of hylan G-F 20. Another 12-week study (n = 165) indicated significant improvements with hylan G-F 20 versus placebo on the WOMAC A (pain walking on flat surface, pain while sitting or lying) and WOMAC C total scores of the Western Ontario McMasters University Osteoarthritis Index.[45] Finally, Karlsson et al[40] did not find any difference in clinical efficacy between patients treated with hylan G-F 20 or placebo group at 26 or 52 weeks. However, pooled data for all HA treatment arms revealed significantly longer duration of improvement when compared with placebo.

Open-labeled, prospective, comparative, and retrospective studies have also shown improvement of symptoms of knee osteoarthritis after treatment with hylan G-F 20.[30,32,39,41,47–50] For example, Waddell et al[41] published treatment results in 1047 patients treated with intra-articular hylan G-F 20 (3 weekly injections) for osteoarthritis knee pain. They reported decreased pain, improved mobility, and decreased need for rescue pain medication in most of the treated knees (89%). Raman et al[51] evaluated the functional outcome of almost 200 patients treated with hylan G-F 20 at pre-injection, 6 weeks, 3, 6, and 12 months. The authors noted an improvement in WOMAC, Oxford knee and EuroQol EQ-5D scores at each time point. In addition, a 2008 multi-center study conducted by Huskin and colleagues[47] demonstrated that hylan G-F 20 provided effective pain relief and improved stiffness and physical function in patients will mild to moderate osteoarthritis presenting with persistent osteoarthritic pain 4 to 12 weeks after arthroscopic meniscectomy.

Table 2 Prospective, randomized, placebo-controlled trials of hylan G-F 20 for treatment of osteoarthritis of the knee

Study	N	Intervention	Duration of study	Outcome measures	Outcomes
Scale et al[44]	80	Study 1: hylan G-F 20, 2 injections vs placebo Study 2: hylan G-F 20, 3 injections vs placebo	12 weeks	VAS, activity level, physician global assessment	Significant improvement in VAS, activity level, most painful knee improvement, physician global assessment in the treatment group compared with placebo at 12 weeks
Wobig et al[38]	110	Hylan G-F 20, 3 injections vs placebo	26 weeks	VAS pain scale, VAS functional scale	Significant improvement in all parameters in treatment group; less use of "rescue therapy" in treatment group
Dickson et al[45]	165	Hylan G-F 20 vs diclofenac vs arthrocentesis plus oral placebo	12 weeks	WOMAC A pain	Significant improvement in WOMAC A pain categories
Karlsson et al[40]		Hylan G-F 20, 3 injections vs placebo	52 weeks	VAS, Kaplan-Meier Survival, SF-36, WOMAC, Lequesne algofunctional index	No difference in outcome between treatment group and placebo at 52 weeks

Abbreviations: VAS, visual analog scale; WOMAC, Western Ontario McMasters University Osteoarthritis Index.

Increasing attention has shifted toward comparing hylan G-F 20 with other nonoperative knee osteoarthritis treatment strategies. These include NSAIDs and intra-articular steroid injections. Several randomized controlled trials comparing hylan G-F 20 viscosupplementation with NSAIDs have reported that the benefit obtained with intra-articular hylan G-F 20 was similar to or greater than that observed with NSAIDs, with fewer gastrointestinal side effects.[37,46,52] In a multicenter Canadian trial, Adams and colleagues[37] compared three treatment groups: oral NSAIDs alone, hylan G-F 20 treatment (3 weekly injections), and a combination of oral NSAIDs and hylan G-F 20 treatment. At 6 months, both the hylan G-F 20 only and the combined NSAID and hylan G-F 20 groups were statistically superior to the NSAID only group. These findings are further supported by the previously mentioned Cochrane review, which reported that when hylan G-F 20 was added to pre-existing NSAID therapy, combination therapy was associated with greater improvement in pain and joint function than use of NSAIDs alone.[35]

Studies comparing intra-articular therapy with corticosteroids and hylan G-F 20 have demonstrated that both treatments are effective in reducing knee osteoarthritis symptoms; however, viscosupplementation has a longer duration of action while corticosteroids have a more rapid onset of action.[53] Two recent prospective trials have compared intra-articular hylan G-F 20 to intra-articular corticosteroids. Leopold et al[54] prospectively compared 2 treatment arms. The first groups received 3-weekly injections of hylan G-F 20, and the second group received 1 injection of intra-articular betamethasone. At the 6-month follow-up, both groups improved. However, there was no statistically significant difference between the two groups for VAS and WOMAC scores, or the Knee Society Scoring System. Caborn and associates[53] also studied similar cohorts. In their comparison of intra-articular hylan G-F 20 (3 weekly injections) and intra-articular triamcinolone (1 isolated injection) they found that although the maximal benefit of corticosteroids appeared more rapidly (week 2), pain reduction and functional improvement were significantly superior ($P < 0.01$ and $P < 0.001$, respectively) with hylan G-F 20 viscosupplementation at the 3- to 6-month follow up periods.

Juni et al[55] and others also explored the effect of the increased molecular weight of hylan G-F 20. In a randomized, controlled, blinded study, Karlsson et al[40] evaluated 3 parallel cohorts of patients with knee osteoarthritis. The patients in each group received 1 of 3 treatments: 3-weekly injections of sodium hyaluronate (Artzal®), 3-weekly injections of hylan G-F 20 (Synvisc®), or placebo. No significant differences were noted between those treated with low or high molecular weight preparations. Kotevoglu et al[31] also examined the efficacy of different molecular weight hyaluronan solutions. Their 6-month follow-up data revealed no statistically significant difference in clinical efficacy between hylan G-F 20 and sodium hyaluronate. Wobig et al[32] treated patients with 3 weekly injections of either hylan G-F 20 or sodium hyaluronate. However, in their group of 70 patients, the authors observed that patients treated with hylan G-F 20 had superior outcomes to those treated with the low molecular weight viscosupplement with regards to pain and physician assessment at 3-month follow-up. Finally, in a 2005 review, Goldberg and Buckwalter[56] affirmed that, to date, no substantive clinical evidence has been put forth to suggest that differences in the molecular weight of currently available viscosupplements have any impact on clinical efficacy.

Multiple studies of intra-articular HA have confirmed the benefit of treatment with more than one course of hylan G-F 20. In a prospective open-label study, Waddell et al[57] evaluated the efficacy and tolerability of a second course of hylan G-F 20 for the treatment of osteoarthritic knee pain over a 12-month period in patients who previously experienced a beneficial initial course of therapy. Most patients experienced continued pain relief as all efficacy parameters significantly improved ($P < 0.001$) from baseline at weeks 1, 2, 4, 8, 12, 26, and 52. Furthermore, Raynauld and colleagues,[58] in a randomized controlled trial, reported that a second course of therapy with hylan G-F 20 was just as effective as the first course in a study comparing intra-articular HA with appropriate care. They also demonstrated the safety of repeat treatment in that the incidence of local mild adverse events with hylan G-F 20 was not significantly higher than with a first course of therapy. This safety profile is also supported in a recent meta-analysis by Pagnano et al[59] However, as we discuss later, the incidence of a rare severe acute inflammatory reaction after repeated treatment may be slightly higher with the use of hylans.[60]

Clinical safety

The safety profile HA viscosupplementation has been well established over its 20 years of clinical use. In fact, no viscosupplement product has been withdrawn because of safety concerns.[61] Intra-articular HA and hylan products are generally well tolerated with low incidence of local adverse events.[44] The overall incidence of adverse events has been reported to be approximately 1% to 4% per injection.[13,30,41,62] In the specific case of hylan G-F 20, the incidence is closer

to 0% to 1%.[38,45] However, in one small retrospective series, clinically significant local inflammatory reactions were noted in 27% of the 22 patients (11% of injections) that received hylan G-F 20.[63]

Postmarketing surveillance for hylan G-F 20 (Synvisc®) has indicated that the most common adverse event is local reaction at the injection site, consisting of mild pain, swelling, or effusion, and warmth or redness, or both.[38,64] Such injection site reactions are usually mild and self-limited, resolving with 1 to 3 days and generally respond to NSAIDs and local modalities. Other mild adverse effects that have been reported include postinjection itching, headaches, and calf pain.[65,66] Furthermore, the incidence of adverse events with viscosupplementation is similar to that observed with other intra-articular procedures used to evaluate the efficacy of treatment for knee osteoarthritis. In controlled comparisons of Synvisc® and arthrocentesis or intra-articular saline injections involving 122 patients, there were no significant differences in the numbers or types of adverse events between treatment groups.[53,61,67] Moreover, self-limited synovitis with corticosteroids has been reported in about 2% of cases.[68]

A number of US and international trials have established the safety of hylan G-F 20. The combined results of 7 clinical trials consisting of 511 subjects and 1711 injections revealed no serious adverse events.[61] Furthermore, only 7% of subjects (2.3% injections) reported swelling and/or knee pain after injections. In a large, retrospective review of viscosupplementation with hylan G-F 20, local reactions occurred after 42 (2.7%) of 1537 injections and occurred in 28 (8.3%) of 336 patients overall.[30] Seventy-nine percent of these reactions resolved without sequelae. Five patients had a total of nine reactions with sequelae, including residual swelling and intermittent pain. The incidence of adverse events was significantly related to the injection technique used: a medial approach to a partially bent knee was associated with 5.2% adverse events by injection, compared with1.5% with straight lateral injections. Interestingly, injection laterally has also been shown to have a higher incidence of intra-articular injection accuracy when compared with injection into the flexed knee using conventional arthroscopic portal approaches.[69] Brockmeir and Schaffer[12] postulated that adverse reactions are related more closely to the accuracy of intra-articular injection than to the substance itself.

Rare cases of crystalline induced arthropathy related to hylan G-F 20 have also have also been reported.[70,71] The mechanisms underlying the development of pseudogout after HA injection remain unclear. What is clear is that this synovitis tends to occur after the second or third injection suggesting an immune mediated response. Furthermore, recurrence of the reaction has been noted in some particular patients, also suggesting that some individuals may be predisposed to these reactions. Therefore, clinicians should consider pseudogout as a possible, although rare, adverse effect when administering Synvisc®, especially in patients with radiographic evidence of calcium pycophosphate dihydrate (CPPD) crystals.[70]

Overall, hylan G-F 20 has a very good tolerability profile in clinical trials and practice. However, there is growing evidence to suggest that hylan G-F 20 in particular may be associated with a specific adverse event termed pseudosepsis or severe acute inflammatory reaction (SAIR).[64] Pseudosepsis appears to be a distinct clinical reaction unrelated to the previously discussed minor adverse events. Its clinical presentation may be difficult to differentiate from a true septic knee or even pseudogout episode without joint fluid aspirate studies. The syndrome itself is characterized by the following: 1) severe pain occurring 1 to 3 days after an injection; 2) usually occurring after the first injection or treatment course (prior exposure); 3) highly cellular joint effusion without crystals or bacteria by culture; 4) usually requires clinical intervention (NSAIDs, arthrocentesis, or intra-articular steroid injection).[61] Although severe, pseudosepsis seems to be a relatively rare occurrence after Synvisc® injection. In several case reports and retrospective studies pseudosepsis has been identified in a total of 22 patients, and, in 2 prospective studies, pseudosepsis occurred once in 213 injections in patients who received a second treatment of Synvisc® and once in 171 injections in patients who received an initial Synvisc® treatment.[41,60,72,73]

Naturally derived sodium hyaluronates, such as Hyalgan®, have not yet been linked with pseudosepsis, suggesting a possible connection between pseudosepsis and the chemical modification (covalent cross-linking) of the hyaluronan molecule used to manufacture Synvisc®. When it does occur, pseudosepsis characteristically is seen after previous exposure, prompting some investigators to postulate that the cause of pseudosepsis may be immune-based and possibly reflective of immunologic sensitization.[64,74,75] In a recent prospective study comparing joint aspirates from 16 patients who presented with pseudosepsis after Synvisc® treatment with 20 joint aspirates from control patients with osteoarthritis, analysis was notably more consistent with a type 4(cell-mediated) hypersensitivity reaction than with an antibody-mediated reaction.[71] Additional studies are required to elucidate the cause of pseudosepsis. Understanding the

cause will enable the treating physician to identify patients at risk for this injection-related complication and to determine whether patients with a history of pseudosepsis can safely receive further viscosupplementation therapy.

Although the cause of local adverse events associated with Synvisc® injection is not clear, these events are typically mild-to-moderate in nature, resolve spontaneously or after treatment of symptoms, and do not result in any long-term sequelae. Therefore, it is often difficult to clinically distinguish the symptoms of a reaction from the symptoms of osteoarthritis. Additionally, the types of usual local adverse events observed after viscosupplementation are not as potentially serious as the systemic adverse effects that may occur with NSAIDs or COX-2 inhibitors.[76]

Indications

The ideal candidate for intra-articular viscosupplementation is has yet to be clearly defined. Previous guidelines for the treatment of knee osteoarthritis recommend the use of HA only in patients who have not responded to nonpharmacologic therapies and simple analgesics, and after the unsuccessful trial of NSAIDs and selective COX-2 inhibitors.[74,77] However, given the cardiovascular, gastrointestinal, and renal side effects of selective and nonselective NSAIDs, the use of HA products earlier in the osteoarthritis treatment paradigm should be considered.[79,80] Again, despite failure to identify the optimal cohort, there is evidence suggesting that the greatest potential benefit of HA would likely be among younger patients and those in the earlier stages of osteoarthritis. In the meta-analysis by Wang et al[6] patients older than 65 and those with the most advanced stages of osteoarthritis were less likely to benefit from hylan G-F 20 therapy. Evanich et al[49] also reported greater improvements in pain scores for patients with less severe radiographic disease compared with those having more severe disease with hylan G-F 20. Last, a short-term safety study of 4253 patients given hylan G-F 20 revealed that those patients who were most recently diagnosed with knee osteoarthritis were more likely to have an early benefit of therapy compared with those who had been diagnosed at a later time point in the disease course.[50] As a whole, these studies support the use of HA earlier in the osteoarthritis treatment regimen.

The most recent OARSI guidelines state that optimal management of patients with knee osteoarthritis requires a combination of nonpharmacological and pharmacological modalities of therapy.[4] Physicians should therefore consider incorporating the use of HA or hylan G-F 20 into a comprehensive treatment program for knee osteoarthritis. The best evidence to support this idea are the studies conducted by Kahan et al[81] and Raynauld et al[39] demonstrating significant improvements in knee osteoarthritis symptoms when hylan G-F 20 was added to usual therapy for managing knee osteoarthritis. Hylan G-F 20 may also decrease the use of concomitant corticosteroids and NSAIDs when added to standard care for knee osteoarthritis.[50] A few studies also indicate that the use of hylan G-F 20 may even delay the need for total knee replacement. For example, Waddell and colleagues[82] demonstrated the ability of hylan G-F 20 to delay the need for total knee replacement by approximately 2 years in patients with grade IV osteoarthritis. Bell and associates[83] also showed that over a 30-month period, almost 60% of treated patients were able to delay knee replacement surgery after up to four courses of hylan G-F 20.

Finally, the dosing regimen can be as important as the timing of HA injections. Different dosing regimens of hylan G-F 20 can limit the availability of treatment and affect patient compliance. Yet the appropriate number, dose, and timing of hylan G-F 20 injections have yet to be determined. In a recent prospective, multi-center, randomized trial, Conrozier et al[36] evaluated the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic knee osteoarthritis: 1) a single injection of 6 mL, 2) a single injection of 4 mL, 3) two injections of 4 mL 2 weeks apart, 4) 3 injections of 4 mL 1 week a part, or 5) 3 injections of 2 mL 1 week apart. The treatment was well-tolerated overall, and there were no serious device-related adverse events. There was a statistically significant improvement from baseline at week 24 in all efficacy endpoints for all treatment regimens. However, the 1×6 mL, 3×4 mL, and 3×2 mL treatment groups showed the greater mean improvements in the patient-rated knee osteoarthritis pain assessment VAS than the other groups. Another more recent randomized, placebo-controlled trial specifically compared a single, 6 mL, injection of hylan G-F 20 with placebo. A 2009 study by Chevalier and associates[84] demonstrated that, in patients with knee osteoarthritis, a single 6 mL intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks, with a modest difference versus placebo. These findings suggest that a single-dose preparation (6 mL) may be as efficacious and as well-tolerated as the more commonly used 3×2 mL dosing.

Alternative uses for viscosupplementation

As previously mentioned, evidence in the literature has demonstrated the disease-modifying properties of

viscosupplementation.[56,85] Several preclinical animal studies have supported the hypothesis that exogenous HA reduces cartilage breakdown and promotes tissue repair.[86–88] For example, Smith et al[88] assessed the pathological changes in the synovium of a sheep model of osteoarthritis and evaluated the effects of two HA preparations on this pathology. Increased fibrosis and vascularity are hallmarks of pathological changes in synovium in this meniscectomy model of osteoarthritis. The authors demonstrated that intra-articular treatment with Hyalgan® decreased aggregate score, vascularity and depth of fibrosis. HYADD 4-G (an amide derivative of HA) treatment also decreased vascularity, intimal hyperplasia and increased high-molecular weight HA synthesis by synovial fibroblasts. This provides a potential mechanism for improving joint mobility and function in osteoarthritis. Amiel et al[86] used a rabbit model of osteoarthritis, anterior cruciate ligament transection (ACLT), to investigate the long-term effects of single and sequential courses of HA therapy on osteoarthritis progression. One or two courses of 5 weekly intra-articular injections of sodium hyaluronate (Hyalgan®) or placebo were administered to rabbits (N = 10 per group). Gross morphological and histomorphometric evaluations were performed on harvested knee joints following sacrifice at 26 weeks after surgery. All the rabbits exhibited the characteristic pathologic changes of osteoarthritis. However, rabbits that received one or two courses of HA injections showed less disease progression than rabbits treated with ACLT alone or with 10 vehicle injections. Interestingly, rabbits that received 10 HA injections showed significantly less surface roughness of the femoral cartilage compared with rabbits treated with ACLT, 5 HA injections, or 10 vehicle injections, and showed significantly less surface roughness of the tibial plateau compared with all other treatment groups ($P < 0.05$).

Clinical studies have also provided evidence for the disease-modifying potential of HA. A large multicenter, blinded, randomized study performed by Jubb and associates[89] found that treatment with 3 cycles of HA significantly reduced joint space loss at 1 year in the subset of patients with less severe osteoarthritis. Bagga et al[90] examined the effect of intra-articular hylan GF-20 injections on synovial fluid HA concentration, viscosity, and elasticity over a 6-month period in patients with mild to moderate osteoarthritis of the knees. Sequential synovial fluid samples were available from 32 of 60 subjects injected at baseline (15 men, 17 women; mean age 65 years) at 3 months post injection. The mean HA concentration had increased by 13% ($P < 0.0008$), and the complex shear modulus had increased by 16% ($P < 0.03$). Furthermore, at 6 months the mean HA concentration increased by 10%. These results suggest that one possible mechanism of action of viscosupplementation is to promote endogenous HA production. However, whether or not this HA viscosupplementation is truly chondroprotective and will actually alter the natural history of osteoarthritis remains to be answered. Nonetheless, this potential benefit has increased the off-label use of intra-articular HA injections.

The use of intra-articular HA therapy after arthroscopy may have a positive effect on postoperative pain and improve the efficacy of treatment secondary to aiding in the rapid restoration of the lubricating and protective HA layer.[91] In a prospective, randomized, controlled study of 80 patients, Hempfling[8] evaluated the efficacy of HA injection immediately after knee arthroscopy for persistent knee pain. He found that compared with the control group, patients treated with HA injections after arthroscopy maintained significantly greater pain-relieving and functional benefits of this surgical procedure at 2-year follow-up.

A number of recent studies have also attempted to evaluate the efficacy of hylan G-F 20 in joints other than the knee. In those other joints, viscosupplementation has been studied more extensively in the hip in patients with osteoarthritis. In a single-center study, Vad et al[92] demonstrated statistically significant improvement in 22 patients with mild to moderate hip osteoarthritis pain 1 year after receiving 3 injections of hylan G-F 20. The overall success rate was 89% (90.5% among patients with mild to moderate osteoarthritis and 50% among patients with severe osteoarthritis). In a study conducted by Tikiz and colleagues,[93] 3 weekly injections of hylan G-F 20 were compared with the same regimen using a low molecular weight preparation in the treatment of patients with hip osteoarthritis. Both groups noted significant clinical improvement, with no difference noted between two compounds.[84] Recently, Migliore and associates[94] performed a prospective, observational, open study aimed to assess the efficacy and safety of hylan G-F 20 in a large cohort of patients with symptomatic hip osteoarthritis. Two hundred and fifty patients presenting with symptomatic hip osteoarthritis received one 2 mL intra-articular (IA) injection of hylan G-F 20 under ultrasound guidance. Patients were followed-up every 3 months for a total of 12 months. In addition to VAS, outcome measurements included Lequesne index scores, NSAID intake, and physician and patient global assessments scores. The authors observed statistically significant reductions in each of these outcome measures. No systemic, serious or severe side effects were observed.

Fewer injections of high-molecular-weight HA may be required in hip osteoarthritis versus knee osteoarthritis.

Conrozier and associates[95] retrospectively applied the Outcome Measures in Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria to the results if a pilot study consisting of 56 patients with moderate to severe osteoarthritis of the hip who received 1 or 2 injections of high-molecular-weight HA. They discovered that, at 90 days after injection therapy, 58.9% of patients met the OMERACT-OARSI response criteria. This observation supports the potential benefit of fewer injections of high-molecular-weight HA in the setting of hip osteoarthritis.

The efficacy of HA viscosupplementation has also been demonstrated in the treatment of ankle, shoulder, and hand osteoarthritis.[96–100] In a prospective, multi-center study, Witteveen et al[99] evaluated the safety and efficacy of hylan G-F 20 in 55 patients with symptomatic ankle osteoarthritis. Patients received 1 mL × 2 ml intra-articular injection of hylan G-F 20, plus an optional, second injection if pain remained at baseline levels after 1, 2 or 3 months. The mean pain VAS score decreased from 68.0 mm (baseline) to 33.8 mm at 3 months ($P < 0.001$), which was maintained to 6 months (34.2 mm, $P < 0.001$). In a long-term prospective study, Luciani et al[100] treated 21 patients with painful ankle osteoarthritis with 3-weekly injections of hylan G-F 20. Significant improvement of the baseline ankle osteoarthritis score was seen after 6 months. This improvement was maintained over time with no further changes at 12- and 18-month follow-up examinations.

In general, HA injection into the shoulder is well tolerated and evidence suggests that it may be effective in shoulder pain of various etiologies, including bursitis, glenohumeral osteoarthritis and rotator cuff tears. Among the strongest evidence is that which comes from a large, double-blind, randomized, saline-controlled study of HA injection for persistent shoulder pain.[96] This study included 602 patients with shoulder pain of at least 6 months' duration, caused by glenohumeral osteoarthritis, rotator cuff tear, or adhesive capsulitis. Patients who received 3- or 5-weekly HA injections experienced significant pain reduction compared to controls ($P = 0.036$ and $P = 0.012$, respectively). Patients whose shoulder pain was secondary to glenohumeral osteoarthritis experienced the majority of benefit. Furthermore, at 6 months pain reduction remained significant in this group. Silverstein et al[101] reported encouraging results for hylan G-F 20 in the treatment of glenohumeral osteoarthritis. Their preliminary study of 20 patients, revealed significant improvements in VAS, University of California Los Angeles score, and Simple Shoulder Test scores ($P < 0.001$) at the 6-month follow-up.

Finally, viscosupplementation for hand pain associated with osteoarthritis is currently under investigation. A recent prospective, randomized, double-blinded clinical trial compared hylan versus corticosteroid versus placebo for the treatment of basal joint arthritis.[102] Sixty patients with basal joint arthritis were randomized to receive 2 intra-articular hylan injections 1 week apart, 1 placebo injection followed by 1 corticosteroid injection 1 week later, or 2 placebo injections 1 week apart. Patients were evaluated at 2, 4, 12 and 26 weeks and assessed with visual analog scale pain scores, strength measures, difference scores, Disabilities of the Arm, Shoulder, and Hand scores, and range of motion measurements. There were no statistically significant differences among hylan, steroid and placebo injections for most of the outcome measures at any of the follow-up time points. However, based on the durable relief of pain, improved grip strength, and the long-term improvement in symptoms compared with preinjection values, hylan injections should be considered in the management of basal joint arthritis of the thumb.

Conclusion

As a result of increased interest and scientific investigation of intra-articular viscosupplementation, its use in the nonoperative management of patients with osteoarthritis has become well accepted. In the case of hylan G-F 20, numerous prospective, randomized, placebo-controlled studies have proven its efficacy. Cumulative evidence also affirms it clinical safety. Furthermore, recent data suggest that multiple courses of hylan G-F 20 are effective in maintaining osteoarthritis pain relief, and that this benefit outweighs the associated risk of adverse events. In addition, a single, higher dose of hylan G-F 20 may be just as effective as the traditional 3 injection regimen. Further clinical studies are necessary to prove the potential disease-modifying effects of hylan G-F 20. Viscosupplementation as a whole must expand beyond pain relief and joint preservation and evolve to encompass therapies that restore normal cartilage and joint homeostasis, arrest the progression of osteoarthritis, interfere with cartilage-degrading mechanisms, and reverse existing damage.[96]

Disclosures

The authors disclose no conflicts of interest.

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