AJSM PreView, published on January 23, 2009 as doi:10.1177/0363546508326984

Hyaluronic Acid Viscosupplementation and Osteoarthritis

Current Uses and Future Directions

Eric J. Strauss,* MD, Jennifer A. Hart,† MPAS, PA-C, Mark D. Miller,† MD, Roy D. Altman,‡ MD, and Jeffrey E. Rosen,*§ MD

*From the *Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, New York, New York, the †Department of Orthopaedic Surgery, University of Virginia, Charlottesville, Virginia, and the ‡Division of Rheumatology and Immunology, University of California, Los Angeles, Los Angeles, California*

Intra-articular hyaluronic acid viscosupplementation is gaining popularity as a treatment option in the nonoperative management of patients with osteoarthritis. Recent clinical studies have demonstrated that the anti-inflammatory, anabolic, and chondroprotective actions of hyaluronic acid reduce pain and improve patient function. With evidence mounting in support of the efficacy of this treatment modality for patients with osteoarthritis, its potential use in additional patient populations and for other pathologies affecting the knee is being investigated. The current article reviews the use of intra-articular hyaluronic acid viscosupplementation in the management of knee osteoarthritis and presents the potential for expanding its indications for other joints and alternative patient subpopulations. Additionally, future directions for the use of hyaluronic acid and areas of active research are discussed.

Keywords: hyaluronic acid; viscosupplementation; osteoarthritis; knee

With the aging of the "baby boomers," the prevalence of osteoarthritis (OA) in the United States is increasing, with recent projections reporting that by the year 2030, almost 67 million Americans will be affected by the disease. The Centers for Disease Control and Prevention has estimated the annual direct costs associated with arthritis and other rheumatologic conditions to be approximately $51.1 billion and the indirect costs to be approximately $35.1 billion.[47] A recent survey of all causes of lost productive time in the US workforce found that arthritis was second only to back pain as a specific cause of lost work time and the primary cause of reduced performance at work.[74]

Although surgery can relieve the pain associated with OA and improve functional ability, not all patients are candidates for surgical intervention, and many want to avoid or delay it if possible. Nonoperative treatment options for symptomatic arthritis include lifestyle modifications, physical therapy, systemic anti-inflammatory medications, intra-articular injections of cortisone, and hyaluronic acid viscosupplementation. Intra-articular injection of hyaluronic acid, the viscoelastic mucopolysaccharide component of synovial fluid, has recently seen increased popularity in the nonoperative treatment of OA.[44,78]

Hyaluronic acid (HA), also known as hyaluronan or hyaluronate, is a high-molecular-weight glycosaminoglycan composed of continuously repeating molecular sequences of glucuronic acid and N-acetyl-glucosamine.[18,44,86] In addition to providing joint lubrication and shock absorbancy, HA acts as the backbone for the proteoglycans of the extracellular matrix, creating a hydrated pathway through which cells can migrate.[18,44,86] Recent studies have also suggested that HA promotes chondrocyte proliferation and differentiation, which has spurred interest in its use as a scaffold component in tissue-engineering techniques.[53,56,86]

In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50%, limiting its role in maintaining normal joint biomechanics.[83] The purpose of viscosupplementation is to replace the lost HA and potentially stimulate the production of endogenous HA

§Address correspondence to Jeffrey E. Rosen, MD, NYU Hospital For Joint Diseases, 301 East 17th Street, New York, NY 10003 (e-mail: Jeffrey.Rosen@nyumc.org).

One or more authors has declared a potential conflict of interest: Roy D. Altman is a consultant for Hyalgan and Euflexxa.

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546508326984

TABLE 1
Available Formulations of Intra-Articular Hyaluronic Acid Viscosupplementation

Brand	Year Approved	Type	Molecular Weight (kDa)	Number of Weekly Injections
Hyalgan	1997	Avian	500-720	3-5
Synvisc	1997	Avian	5000-6000	3
Supartz	2001	Avian	620-1200	5
Orthovisc	2004	Avian	1000-2900	3-4
Euflexxa	2004	Nonavian	2400-3600	3

within the joint.[11] Although at the present time the exact mechanism of action is not completely understood, recent research suggests that HA exerts anti-inflammatory, analgesic, and possibly chondroprotective effects on the articular cartilage and joint synovium.

Currently there are 5 injectable HA formulations approved for use in the United States. These include Synvisc (Genzyme Corp, Cambridge, Massachusetts), Hyalgan (Sanofi-Sythelabo Inc, New York, New York), Supartz (Seikagaku Corp, Tokyo, Japan), Orthovisc (Anika Therapeutics Inc, Woburn, Massachusetts), and Euflexxa (Ferring Pharmaceuticals Inc, Suffern, New York) (Table 1). These preparations differ with respect to origin, method of production, treatment schedule, molecular weight, half-life within the synovium, rheologic properties, pharmacodynamics, and cost.[6,8] Although intra-articular HA injection is currently indicated and FDA approved for treating pain associated with OA of the knee, recent studies demonstrating beneficial results with respect to pain reduction and functional improvement have led to increased off-label use for OA of the hip, shoulder, and ankle.[6,8] The current article reviews the use of intra-articular HA viscosupplementation in the management of knee OA and presents the potential for expanding its indications to other joints and alternative patient subpopulations. Additionally, future directions for the use of HA for other knee pathologies and areas of active research in orthopaedic surgery are discussed.

HA VISCOSUPPLEMENTATION IN KNEE OA

Within the normal adult knee, there is approximately 2 mL of synovial fluid with an HA concentration of 2.5 to 4.0 mg/mL. This endogenous HA, which is produced by type B synoviocytes and fibroblasts of the synovial membrane, has a molecular weight of 5 to 7 × 10^6 Da.[18,83] Studies have shown that during the progression of osteoarthritic degeneration, the concentration and molecular weight of HA within the synovial fluid are reduced secondary to dilution from inflammatory effusion, abnormal synoviocyte production, and molecular fragmentation.[43,78] This alteration in HA structure and concentration during the degenerative process decreases the material's ability to effectively lubricate the joint surface and distribute the stresses associated with weightbearing. Additionally, fragmented low-molecular weight HA has been shown to have a proinflammatory effect.[12,62]

Injection of HA into the joint space of an osteoarthritic knee has been shown to improve the quantitative and qualitative properties of endogenous HA, increasing joint lubrication in the short term.[13,44] Additionally, exogenous HA supplementation may provide significant anti-inflammatory effects within the joint space, affecting leukocyte function and reducing the concentration of inflammatory mediators such as prostaglandins and fibronectin.[34,37,67,83] Direct analgesic activity and chondroprotective properties of intra-articular HA injection have also been suggested by a number of recent animal studies.[2,37,39,61]

Candidates for HA Viscosupplementation

As injectable HA preparations improve and become more readily available, the quest to define the ideal candidate for this treatment is increasingly important. Although many questions remain, HA should not be administered to patients unless they have significant pain related to arthritis of the knee and are unable to receive or previously have failed to respond to other conservative treatment options such as nonsteroidal anti-inflammatory medications and physical therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been a mainstay of treatment for mild to moderate OA but are associated with significant side effects and are not well tolerated by all patients. Recent concerns related to cardiovascular risk with both nonselective and cyclooxygenase-2-selective NSAIDs have forced at least one drug off the market and have prompted further investigation.[22,33,45,54] Nonselective NSAIDs also are strongly associated with adverse gastrointestinal effects. Some analyses estimate that the risk of developing significant ulcer disease while taking even a short course (6 days to 2 weeks) of an NSAID is 16% to 22%.[42,46] Additionally, as many as 44% of patients can develop significant dyspepsia requiring medical treatment.[46]

At the present time, there has been no direct association demonstrated between the effectiveness of HA viscosupplementation and patient age, gender, or body mass index. Contraindications to HA injection include protein/avian allergies (except Euflexxa), pregnancy or nursing, pediatric patients, joint infection, bacteremia, and local overlying skin disease.

Timing of Intra-Articular HA Injection

The timing of intra-articular HA injection is important to provide maximal symptom relief for indicated patients. Multiple studies have shown that OA severity correlates well with patient response and might prove to be an important factor in the timing of these injections during the course of the disease. For maximum benefit, patients should be counseled to consider intra-articular injection early in the treatment of their disease.

Frequency of injection varies according to the particular product being used. Of the current commercially available preparations of HA, Synvisc, Orthovisc, and Euflexxa are given as 3 weekly injections, whereas 3 to 5 weekly injections may be used for Hyalgan or Supartz (Table 1).

Injection Technique

Intra-articular injection of HA is performed under sterile conditions. It is usually preceded by an aspiration to remove any effusion that may be present, decreasing the concentration of in situ inflammatory mediators and limiting the dilutional effect the effusion would have on the injected material. Preinjection arthrocentesis decreases the rate of relapse after HA viscosupplementation compared with injection alone.[76]

Multiple approaches have been described for knee aspiration and injection, including anteromedial, anterolateral, lateral midpatellar, and superolateral. Recent studies have reported that a superolateral or lateral midpatellar injection site is the most reliable for reaching the synovial joint space of the knee.[17,51,84] Our preferred approach is the superolateral aspiration and injection technique.

Clinical Outcomes

Clinical studies of intra-articular HA injection in the nonoperative management of knee OA have shown positive results; however, the reported benefits have been variable.[18,30,83] In a recent meta-analysis, Bellamy and colleagues[14] examined 76 placebo-controlled randomized clinical trials and found that intra-articular HA injection was an effective treatment for knee OA. The authors noted that HA supplementation reduced arthritis-related pain and improved knee function and overall patient assessment, with the most pronounced improvement experienced 5 to 13 weeks after injection. In a comparison of intra-articular HA injection, oral NSAID treatment, and placebo, Altman and Moskowitz[7] found that at 6-month follow-up, exogenous HA injection provided superior pain relief and functional improvement compared with placebo ($P < .03$ and $P < .05$, respectively). Although the outcomes of HA administration were better than those seen with NSAID treatment, the difference did not reach statistical significance ($P = .22$). Similar benefits were reported by Adams and associates,[1] who demonstrated that at 6-month follow-up, patients treated with either HA supplementation alone or HA supplementation combined with NSAIDs had superior outcomes to those among patients treated with NSAIDs alone ($P < .05$ for both comparisons). Caborn and colleagues[20] found in their comparison of intra-articular HA and corticosteroid injections that although the maximal benefit of steroids appeared more rapidly (within 2 weeks), pain reduction and functional improvement were significantly better ($P < .01$ and $P < .0001$, respectively) with HA supplementation during the 3- to 6-month follow-up period.

Complications Associated With HA Viscosupplementation

Clinical studies have demonstrated that HA viscosupplementation is generally well tolerated.[5] Although significant complications are rare, mild adverse effects have been reported to occur in 3% to 20% of patients.[5,7,27,58,65] The most common complication associated with intra-articular HA injection is an inflammatory reaction at the injection site, characterized by localized injection site pain and a knee effusion.[41,85] These injection site reactions are usually mild and self-limited, resolving without intervention within 1 to 3 days.[41] Other mild adverse effects that have been reported include postinjection itching, headaches, and calf pain.[5] Rarely, HA viscosupplementation has been reported to induce flares of crystalline arthropathy.[3,29,55]

Case reports within the orthopaedic and rheumatologic literature describe a more significant inflammatory response to intra-articular HA injection called severe acute inflammatory reaction or pseudosepsis.[4,16,23,41,59,68] This more severe adverse reaction has been defined clinically as severe joint inflammation with pain and swelling occurring 24 to 72 hours after an intra-articular injection. It usually occurs after sensitization with the second or third injection of a series or with a repeat treatment course. Septic arthritis and crystalline arthropathy are ruled out with a negative synovial fluid sample, and the reaction typically is not self-limited, requiring treatment with nonsteroidal anti-inflammatory medications or an intra-articular steroid injection. The exact cause of pseudosepsis after HA viscosupplementation is currently not well understood, although some authors believe it to occur secondary to increased immunogenicity associated with the cross-linking process used in certain HA formulations.[41] Additional study is required to enable the treating physician to identify patients at risk for this injection-related complication and to determine whether patients with a history of a pseudoseptic reaction can safely receive further HA therapy.

EXPANDING THE INDICATIONS FOR INTRA-ARTICULAR HA INJECTION FOR KNEE OA

As it becomes increasingly apparent that intra-articular HA injection has a positive effect on the clinical course of disease in OA of the knee, it is possible that providing this treatment to an alternative patient subpopulation may be beneficial. To date, the ideal patient for HA injection has yet to be defined, with the majority of clinical studies treating patients more than 60 years of age with moderate-to-severe OA. In a recent meta-analysis, Wang and coworkers[82] found that patients older than 65 years with more advanced degenerative disease were less likely to respond to HA treatment than were their younger counterparts with less severe OA.

It is the practice of one of the senior authors to use intra-articular HA injection on his younger patients with early-stage degenerative knee OA. The rationale behind this practice is to take advantage of the anti-inflammatory, anabolic, and chondroprotective effects of HA at a stage at which the overall course of the disease may be slowed or even modified. By stimulating endogenous HA production by synoviocytes, absorbing inflammatory cytokines, and inhibiting degenerative changes within chondrocytes and the cartilage matrix, supplementation in a younger, less symptomatic patient population may have significant longer-term benefits.

In a randomized study including 273 patients, Jubb and colleagues[52] reported that although no difference was noted among patients with advanced OA, intra-articular HA therapy significantly reduced the radiographic progression of joint-space narrowing in the patient subpopulation with greater joint-space width at the start of treatment ($P < .02$). The possibility of a disease-modifying effect of HA supplementation was also reported by Listrat and associates[57] in their prospective, randomized study. The authors found that intra-articular HA treatment resulted in reduced progression of structural cartilage degeneration at surveillance arthroscopy 1 year after treatment and slowed radiographic joint-space narrowing.

Although well-controlled prospective studies of the efficacy of intra-articular HA injection in younger patients are necessary, it appears logical that expanding the indications for its use will be beneficial for this population.

USE OF HA IN JOINTS OTHER THAN THE KNEE

Although HA therapy currently is not approved by the FDA for use in joints other than the knee, several trials have shown that it may have utility in treating OA pain in other joints. Unfortunately, although the majority of results are promising, most of these studies have not been placebo controlled, nor do they use equivalent dosages, injection frequencies, or efficacy measures. Additionally, most have enrolled small patient numbers.

Shoulder Pain

Some early studies have suggested that HA injection into the glenohumeral joint and the bursa is very well tolerated and may be effective in shoulder pain of various etiologies, including rotator cuff tears.[50] HA is used frequently outside of the United States to treat shoulder pain.[10] A recent study concluded that HA may offer an alternative to physical therapy and steroid injections in treating the pain and movement limitations of adhesive capsulitis.[21] Valiveti and colleagues[80] reported their practice experience with HA therapy (3 or 5 weekly injections) for 11 patients with shoulder OA. By physician assessment, 2 patients had moderate improvement, 7 mild, and 2 none. By patient assessment, 5 had moderate improvement, 5 mild, and 1 none. The average duration of improvement was 4 months.

The strongest evidence to date supporting HA use for shoulder pathology comes from the first large, double-blind, randomized, saline-controlled study in the United States of HA injection for persistent shoulder pain. This study enrolled 602 patients with shoulder pain of at least 6 months' duration, caused by glenohumeral joint OA, rotator cuff tear, or adhesive capsulitis, who had not achieved pain relief with conventional therapies. Patients who received 3 or 5 weekly HA injections experienced significant pain reduction compared with those who received saline injections ($P = .036$ and $P = .012$, respectively). Patients whose shoulder pain was secondary to OA experienced the majority of benefit. At 6 months after injection, pain reduction was significant in both OA groups (3 injections: $P = .001$; 5 injections: $P = .02$).[8] It appears that HA injection is more beneficial for patients with persistent pain than for those with acute pain.[63]

Ankle Pain

Three recent pilot studies assessed the efficacy and safety of intra-articular HA injections in treating ankle pain. Altman and associates[6] enrolled 30 patients with radiographically documented ankle OA in a 12-week, double-blind, randomized study of 5 weekly injections of HA or saline into the tibiotalar joint. Patients who received HA had an average 46% improvement on the Ankle Osteoarthritis Scale (AOS) pain subscale, whereas the saline group had an average improvement of 8%. The incidence of adverse events was low and similar between groups.

Sun and colleagues[75] administered 5 weekly HA injections to 75 patients with unilateral ankle OA. Patients' pain scores on the AOS and the American Orthopaedic Foot and Ankle Society ankle/hindfoot scale were significantly ($P < .001$) superior to baseline scores at each follow-up visit (1 week, 1 month, 3 months, and 6 months after the final injection). Although 48 patients experienced increases in range of motion, these changes were not significant. Patients expressed a high level of satisfaction with treatment, with an overall patient-satisfaction rate of 86.7%. There were no serious adverse events, and the injections were well tolerated.

Salk and coworkers[70] randomized patients with OA of the ankle to receive 5 weekly injections of either HA (n = 9) or phosphate-buffered saline solution (n = 8). Although both groups reported improvement during follow-up ($P < .0001$ for within-patient differences), at 6 months after the final injection, 56% of the HA group versus 13% of the saline group had more than 30 mm of improvement on the AOS. There were no significant between-group differences in pain relief, range of motion, or quality of life. Trends in all of these areas, however, favored HA. At 6 months of follow-up, 83% of HA patients reported no problems in performing their usual activities versus 33% of the saline group, and the difference in mean scores for vitality on the Short Form-12 quality of life scale was significant (47.22 for HA and 25.00 for saline; $P = .029$).

Hand Pain

A 6-month, open-label pilot study looked at HA injections for OA at the first metacarpal-carpal joint in 16 patients who had tenderness in that joint and/or pain on thumb use. The injections were well tolerated. Mean at-rest pain scores decreased by 46%, and pain on use decreased by 27%. Maximum relief was achieved by month 5 after injection and was sustained through the sixth month.[71] More recently, injection of HA was compared with that of a glucocorticoid in a randomized single-blind study enrolling 56 patients with OA of the carpometacarpal joint of the thumb. Maximum pain relief was achieved at week 2 or 3

TABLE 2
Recent Studies of Hyaluronic Acid Viscosupplementation in Osteoarthritis of the Hip[a]

Author	Year	N	Number of Injections	Follow-up	Efficacy Measures
Vad et al[79]	2003	22	3	1 y	AAOS Lower Limb Core Scale, Visual Numeric Pain Score
Berg and Olsson[15]	2004	31	1	3 mo	WOMAC, Patient Global Assessment
Tikiz et al[77]	2005	48	3	6 mo	VAS, WOMAC, Lequesne Index, NSAID use
Pourbagher et al[66]	2005	10	3	6 mo	VAS, WOMAC
Migliore et al[60]	2006	30	1, 2, or 3	6 mo	Lequesne Index, VAS, NSAID use
Conrozier et al[25]	2006	56	1 or 2	90 d	OMERACT-OARSI Criteria (VAS, WOMAC)
Van Den Bekerom et al[81]	2006	60	1, 2, or 3	6 mo	VAS, NSAID use

[a]AAOS, American Academy of Orthopaedic Surgeons; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, visual analog scale; NSAID, nonsteroidal anti-inflammatory drug; OMERACT-OARSI, Outcome Measures in Clinical Trials–Osteoarthritis Research Society International.

with the steroid and at week 26 with the HA. On a visual analog scale, 88% of the HA group and 79% of steroid patients reported long-term pain improvement (after 26 weeks), and those in the HA group demonstrated significantly superior lateral pinch power ($P = .02$).[36]

Hip Pain

Hyaluronic acid therapy has been studied more extensively in hip OA than in other nonknee joints. Of issue with the use of HA in hip OA are the potential for systemic reactions to the contrast media used in fluoroscopic guidance for needle placement and the danger of repeated exposure to radiation. A possible solution is the use of ultrasonography to guide injection placement.[26] A number of recent studies have evaluated the efficacy of intra-articular HA injection in the nonoperative management of hip OA (Table 2), of which 2 used sonographically guided injections.[60,66]

In a single-center study, significant ($P < .05$) improvement was seen in 22 patients with mild to moderate OA pain 1 year after they had received 3 injections of high-molecular-weight HA, with an overall success rate of 84%; success rates were 90.5% and 50% among patients with mild to moderate and severe OA, respectively.[79] Similarly, patients in another study had significant ($P < .001$) improvement on measures of pain, as well as significant ($P < .001$) reduction in consumption of NSAIDs at 6 months after the third injection of high-molecular-weight HA.[60] Conrozier and colleagues[25] retrospectively applied the Outcome Measures in Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria to the results of a pilot study in which they had administered 1 or 2 injections of high-molecular-weight HA to 56 patients with moderate to severe hip OA. At 90 days after injection, 58.9% of patients met the OMERACT-OARSI response criteria. In the absence of a control group, this observation provided support for the potential benefit of fewer injections of high-molecular-weight HA.

In a study comparing the effects of low- and high-molecular-weight HA in hip OA, both formulations caused significant ($P < .001$) reductions on pain scores, and both resulted in significant ($P < .0001$) reductions in NSAID use. There were no significant between-group differences in efficacy and no serious adverse effect of either form of HA.[77] In a small trial of low-molecular-weight HA, patients also experienced significant ($P < .05$) pain relief by the 6-month follow-up.[66] Another study assessed the effects of 2 avian-derived HAs of different molecular weights (n = 20 each) and a synthetic HA analog (n = 20). Nonsteroidal anti-inflammatory drug use decreased by 59% overall, and by 6 months after injection, 45% of patients had not required surgery. No between-group differences in efficacy were observed.[81] Berg and Olsson[15] performed a pilot study of 1 injection of nonanimal stabilized HA. At 3 months after injection, improvements were significant ($P < .0007$) by both objective and patient assessments.

POTENTIAL FOR DISEASE-MODIFYING ACTIVITY OF HA

It has been thought for some time that HA may have disease-modifying properties. Although its half-life ranges from 1 to 3 days to 7 to 10 days depending on the specific formulation used, studies have noted that the effects of injected HA substantially outlast its half-life in the joint.[40] Thus, it has been hypothesized that intra-articular HA does not simply provide viscosupplementation but also may affect the underlying pathologic factors associated with OA symptoms.[38] Numerous studies using rabbits, dogs, and sheep have supported the hypothesis that exogenous HA reduces cartilage degeneration and promoted tissue repair.[40]

Several clinical studies also provide evidence for the disease-modifying potential of HA. In one study, 3 sets of 3 weekly injections of low-molecular-weight HA, at 3-month intervals, were administered to 19 patients with knee OA, and their 1-year outcomes were compared with 17 patients with knee OA who did not receive HA. Although deterioration was seen in both groups on radiographs and arthroscopy, it was less extensive in the HA-treated group.[57] As part of a study comparing low-molecular-weight HA with a corticosteroid, arthroscopic and microscopic evaluations were performed, at baseline and 6 months after the last of 5 weekly injections, on the knees and tissue samples of 48 patients. Both treatments reduced inflammation and resulted in reparative structural changes.[64] In another study, Bagga and colleagues[11] observed that at 3 months

after 3 weekly injections of high-molecular-weight HA, the mean HA concentration in the synovial fluid of 27 patients had increased by 13% ($P < .0008$). By the 6-month follow-up, the HA concentration of approximately half of the patients was still above baseline values. This suggests that HA injections may have stimulated production of endogenous HA and thus altered disease progression.

FUTURE DIRECTIONS

As reports in the literature continue to demonstrate the symptomatic and possible disease-modifying benefits of intra-articular HA injection in knee OA, the off-label use of this therapy has increased. There has also been interest generated in the use of this treatment for patients with other lesions affecting the knee.

During arthroscopic knee procedures, in addition to washing out debris and inflammatory cytokines, the irrigation fluid removes the native synovial fluid and the lubricating HA layer covering the articular surface.[44] In vitro and animal studies have demonstrated that arthroscopy irrigation fluid can have a detrimental effect on chondrocyte metabolism after arthroscopic surgery.[19,69] It is possible that intra-articular injection of HA after arthroscopy may have a positive effect on postoperative pain and improve the efficacy of treatment secondary to aiding the rapid restoration of the lubricating and protective HA layer. In a randomized study including 80 patients, Hempfling[44] evaluated the efficacy of HA injection immediately after knee arthroscopy. He found that compared with controls, patients who received HA injections after arthroscopy maintained the pain-relieving and functional benefits of the surgical procedure to a greater extent at both 1- and 2-year follow-up. Additionally, recent animal studies have demonstrated that HA injection after experimental meniscal tear results in more rapid healing with better defect fill and more normal-appearing repair tissue, suggesting the potential use of HA injection after cases of meniscal repair.[9,49,73]

Patients undergoing anterior cruciate ligament reconstruction may be another group who would benefit from postprocedure HA injection. A recent animal study demonstrated that HA treatment had positive effects on tendon-to-bone healing in a ligament-reconstruction model.[86] The authors found that specimens treated with HA had histologically better tendon-to-bone healing and biomechanical failure strength than did untreated controls.

Hyaluronic acid injection may also be a useful adjunctive treatment modality for patients with osteochondral defects. In addition to the potential improvement in the quality of repair tissue and incorporation with adjacent cartilage after microfracture, abrasion arthroplasty, or osteochondral grafting of full-thickness defects, HA supplementation may also provide a chondroprotective effect on the surrounding cartilage, limiting the detrimental effects associated with edge loading during weightbearing. Tytherleigh-Strong and colleagues,[78] using a sheep mosaicplasty model, reported that intra-articular HA injection resulted in improved integration of implanted osteochondral grafts with the surrounding tissue. Additionally, the authors found that glycosaminoglycan levels and the aggregate moduli (a measure of cartilage stiffness under loading conditions) of the repair tissue in the treated group were significantly higher than that seen in the control specimens ($P < .05$ for both comparisons), leading them to believe that intra-articular HA treatment after mosaicplasty improves graft chondrocyte survival and metabolic activity.

Patients with isolated patellofemoral pain may be another population who would benefit from intra-articular HA therapy. The anterior knee pain associated with isolated patellofemoral disease is often disabling and refractory to both conservative and operative treatment methods.[24] In an open pilot study of 43 patients with isolated patellofemoral symptoms, Clarke and coworkers[24] found that HA injection provided significant improvements in overall knee pain and in the extent of pain with stair climbing compared with baseline ($P < .01$ for both comparisons). Additionally, these improvements were maintained for up to 1 year postinjection.

Timing of Delivery

The appropriate number and timing of HA injections have yet to be determined. Single-injection HA therapy has been used in Europe (Durolane, Smith & Nephew Inc, Memphis, TN) and is currently being investigated clinically in the United States. The US Food and Drug Administration has approved repeat courses of intra-articular HA injection; however, many insurance plans require at least a 6-month interval between treatments.[18] In an early study evaluating the efficacy of HA supplementation, Dixon and colleagues[31] found that up to 11 injections over a 23-week period provided significant improvement compared with baseline in OA knee pain ($P < .02$). It is possible that once the exact mechanism of action of intra-articular HA treatment is understood, timing of delivery will be optimized. Further investigations are needed to determine the efficacy of intra-articular HA injections given over greater time intervals.

Cellular Mechanisms of Action

In vitro and animal studies are ongoing in an effort to determine the effects of exogenous HA administration on chondrocyte metabolism and its effect on the pathogenesis of OA. In a canine model of OA, Echigo and coworkers[32] demonstrated that intra-articular HA injection suppressed chondrocyte apoptosis compared with control specimens. Similar results were seen by Diaz-Gallego et al[28] in a rabbit OA model. These authors concluded that the chondroprotective action of HA supplementation occurred secondary to an inhibition of the production of nitric oxide, a mediator suspected to contribute to cartilage degeneration and chondrocyte death. Other studies have shown that HA treatment may limit the progression of OA lesions by stabilizing proteoglycan structure, limiting the fragmentation and enzymatic breakdown associated with degenerative arthritis.[48,72] Once the mechanism of action of HA is elucidated, additional issues, such as the effect of

differences in HA preparation molecular weight and half-life in the synovium, will be better understood.

Long-term Delivery Systems

In a normal joint, the average intrasynovial half-life of HA is approximately 20 hours.[35,83] In an inflamed joint, this half-life is significantly decreased to the 11- to 12-hour range. Studies of the various HA products available on the market have shown that the fluid forms of injectable HA have half-lives ranging from 1 to 3 days to 7 to 10 days, whereas cross-linked versions have been reported to be present for up to 30 days. Future research into possible structural modifications of the injected HA preparations (cross-linking, fluid-gel ratios) or longer-term delivery systems (controlled-release carriers) may improve the duration of action of intra-articular HA treatment. If the therapeutic window for each HA treatment is extended, the number of required injections and perhaps the overall cost of therapy may decrease.

SUMMARY

Intra-articular HA injection is gaining popularity as part of the nonoperative management of patients with OA. The anti-inflammatory, anabolic, and chondroprotective actions of HA have been shown in recent clinical studies to reduce pain and improve function. With evidence mounting in support of the efficacy of this treatment modality for patients with OA, its potential use in additional patient populations and other pathologies affecting the knee is being investigated. Although continued study is needed, intra-articular HA injection is proving to be a safe, effective, and evolving tool for clinicians treating patients with symptomatic OA.

REFERENCES

1. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage*. 1995;3(4):213-225.
2. Adams ME, Brandt KD. Hypertrophic repair of canine articular cartilage in osteoarthritis after anterior cruciate ligament transection. *J Rheumatol*. 1991;18(3):428-435.
3. Ali Y, Weinstein M, Jokl P. Acute pseudogout following intra-articular injection of high molecular weight hyaluronic acid. *Am J Med*. 1999;107(6):641-642.
4. Allen E, Krohn K. Adverse reaction to Hylan GF-20. *J Rheumatol*. 2000;27(6):1572.
5. Altman RD. Intra-articular sodium hyaluronate in osteoarthritis of the knee. *Semin Arthritis Rheum*. 2000;30(2 Suppl 1):11-18.
6. Altman RD, Cohen MM, Hollstrom R, et al. Efficacy of intra-articular hyaluronan (Hyalgan) in a double-blind study for osteoarthritis of the ankle. *Osteoarthritis Cartilage*. 2006;14(suppl B):S170.
7. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. *J Rheumatol*. 1998;25(11): 2203-2212.
8. Altman RD, Moskowitz R, Jacobs S, et al. Double-blind, randomized trial of intra-articular injection of sodium hyaluronate (Hyalgan) for the treatment of chronic shoulder pain. *Arthritis Rheum*. 2005;52 (suppl):S461.
9. Amiel D, Toyoguchi T, Kobayashi K, Bowden K, Amiel ME, Healey RM. Long-term effect of sodium hyaluronate (Hyalgan) on osteoarthritis progression in a rabbit model. *Osteoarthritis Cartilage*. 2003;11(9): 636-643.
10. Andrews JR. Diagnosis and treatment of chronic painful shoulder: review of nonsurgical interventions. *Arthroscopy*. 2005;21(3): 333-347.
11. Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol*. 2006;33(5):946-950.
12. Balazs EA. The physical properties of synovial fluid and the specific role of hyaluronic acid. In: Helfet AJ, ed. *Disorders of the Knee*. Philadelphia: J B Lippincott; 1982:61-74.
13. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol Suppl*. 1993;39:3-9.
14. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006;2:CD005321.
15. Berg P, Olsson U. Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: a pilot study. *Clin Exp Rheumatol*. 2004;22(3):300-306.
16. Bernardeau C, Bucki B, Liote F. Acute arthritis after intra-articular hyaluronate injection: onset of effusions without crystal. *Ann Rheum Dis*. 2001;60(5):518-520.
17. Bliddal H. Placement of intra-articular injections verified by mini air-arthrography. *Ann Rheum Dis*. 1999;58(10):641-643.
18. Brockmeier SF, Shaffer BS. Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc*. 2006;14(3):155-162.
19. Bulstra SK, Kuijer R, Eerdmans P, van der Linden AJ. The effect in vitro of irrigating solutions on intact rat articular cartilage. *J Bone Joint Surg Br*. 1994;76(3):468-470.
20. Caborn D, Rush J, Lanzer W, Parenti D, Murray C. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. *J Rheumatol*. 2004;31(2):333-343.
21. Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? *Rheumatol Int*. 2006;26(6):536-540.
22. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006;113(12):1578-1587.
23. Chen AL, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee: a report of six cases. *J Bone Joint Surg Am*. 2002;84(7):1142-1147.
24. Clarke S, Lock V, Duddy J, Sharif M, Newman JH, Kirwan JR. Intra-articular hylan G-F 20 (Synvisc) in the management of patellofemoral osteoarthritis of the knee (POAK). *Knee*. 2005;12(1):57-62.
25. Conrozier T, Bertin P, Bailleul F, et al. Clinical response to intra-articular injections of hylan G-F 20 in symptomatic hip osteoarthritis: the OMERACT-OARSI criteria applied to the results of a pilot study. *Joint Bone Spine*. 2006;73(6):705-709.
26. Conrozier T, Vignon E. Is there evidence to support the inclusion of viscosupplementation in the treatment paradigm for patients with hip osteoarthritis? *Clin Exp Rheumatol*. 2005;23(5):711-716.
27. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain: a one-year double-blind, placebo-controlled study. *Arthritis Rheum*. 1994;37(4):521-528.
28. Diaz-Gallego L, Prieto JG, Coronel P, Gamazo LE, Gimeno M, Alvarez AI. Apoptosis and nitric oxide in an experimental model of osteoarthritis in rabbit after hyaluronic acid treatment. *J Orthop Res*. 2005;23(6):1370-1376.
29. Disla E, Infante R, Fahmy A, Karten I, Cuppari GG. Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection. *Arthritis Rheum*. 1999;42(6):1302-1303.
30. Divine JG, Zazulak BT, Hewett TE. Viscosupplementation for knee osteoarthritis: a systematic review. *Clin Orthop Relat Res*. 2007;455: 113-122.

31. Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Curr Med Res Opin*. 1988;11(4):205-213.
32. Echigo R, Mochizuki M, Nishimura R, Sasaki N. Suppressive effect of hyaluronan on chondrocyte apoptosis in experimentally induced acute osteoarthritis in dogs. *J Vet Med Sci*. 2006;68(8):899-902.
33. Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension*. 2005;46(3):500-507.
34. Forrester JV, Balazs EA. Inhibition of phagocytosis by high molecular weight hyaluronate. *Immunology*. 1980;40(3):435-446.
35. Fraser JR, Kimpton WG, Pierscionek BK, Cahill RN. The kinetics of hyaluronan in normal and acutely inflamed synovial joints: observations with experimental arthritis in sheep. *Semin Arthritis Rheum*. 1993;22(6 Suppl 1):9-17.
36. Fuchs S, Monikes R, Wohlmeiner A, Heyse T. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. *Osteoarthritis Cartilage*. 2006;14(1):82-88.
37. Ghosh P. The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. *Clin Exp Rheumatol*. 1994;12(1):75-82.
38. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? *Semin Arthritis Rheum*. 2002;32(1):10-37.
39. Ghosh P, Read R, Numata Y, Smith S, Armstrong S, Wilson D. The effects of intraarticular administration of hyaluronan in a model of early osteoarthritis in sheep: II. Cartilage composition and proteoglycan metabolism. *Semin Arthritis Rheum*. 1993;22(6 Suppl 1):31-42.
40. Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis Cartilage*. 2005;13(3):216-224.
41. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. *Clin Orthop Relat Res*. 2004;419:130-137.
42. Goldstein JL, Aisenberg J, Lanza F, et al. A multicenter, randomized, double-blind, active-comparator, placebo-controlled, parallel-group comparison of the incidence of endoscopic gastric and duodenal ulcer rates with valdecoxib or naproxen in healthy subjects aged 65 to 75 years. *Clin Ther*. 2006;28(3):340-351.
43. Greenwald RA. Oxygen radicals, inflammation, and arthritis: pathophysiological considerations and implications for treatment. *Semin Arthritis Rheum*. 1991;20(4):219-240.
44. Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. *Knee Surg Sports Traumatol Arthrosc*. 2007;15(5):537-546.
45. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol*. 2006;98(3):266-274.
46. Hollenz M, Stolte M, Leodolter A, Labenz J. NSAID-associated dyspepsia and ulcers: a prospective cohort study in primary care. *Dig Dis*. 2006;24(1-2):189-194.
47. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum*. 2006;54(1): 226-229.
48. Hulmes DJ, Marsden ME, Strachan RK, Harvey RE, McInnes N, Gardner DL. Intra-articular hyaluronate in experimental rabbit osteoarthritis can prevent changes in cartilage proteoglycan content. *Osteoarthritis Cartilage*. 2004;12(3):232-238.
49. Ishima M, Wada Y, Sonoda M, Harada Y, Katsumi A, Moriya H. Effects of hyaluronan on the healing of rabbit meniscus injured in the peripheral region. *J Orthop Sci*. 2000;5(6):579-584.
50. Itokazu M, Matsunaga T. Clinical evaluation of high-molecular-weight sodium hyaluronate for the treatment of patients with periarthritis of the shoulder. *Clin Ther*. 1995;17(5):946-955.
51. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am*. 2002;84(9):1522-1527.
52. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *Int J Clin Pract*. 2003;57(6):467-474.
53. Kawasaki K, Ochi M, Uchio Y, Adachi N, Matsusaki M. Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels. *J Cell Physiol*. 1999;179(2):142-148.
54. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302-1308.
55. Kroesen S, Schmid W, Theiler R. Induction of an acute attack of calcium pyrophosphate dihydrate arthritis by intra-articular injection of hylan G-F 20 (Synvisc). *Clin Rheumatol*. 2000;19(2):147-149.
56. Kujawa MJ, Caplan AI. Hyaluronic acid bonded to cell-culture surfaces stimulates chondrogenesis in stage 24 limb mesenchyme cell cultures. *Dev Biol*. 1986;114(2):504-518.
57. Listrat V, Ayral X, Patarnello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage*. 1997;5(3):153-160.
58. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Ann Rheum Dis*. 1996;55(7):424-431.
59. Martens PB. Bilateral symmetric inflammatory reaction to hylan G-F 20 injection. *Arthritis Rheum*. 2001;44(4):978-979.
60. Migliore A, Tormenta S, Martin LS, et al. The symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip: clinical data of 6 months follow-up. *Clin Rheumatol*. 2006;25(3):389-393.
61. Miyakoshi N, Kobayashi M, Nozaka K, Okada K, Shimada Y, Itoi E. Effects of intraarticular administration of basic fibroblast growth factor with hyaluronic acid on osteochondral defects of the knee in rabbits. *Arch Orthop Trauma Surg*. 2005;125(10):683-692.
62. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther*. 2003;5(2):54-67.
63. Moskowitz RW, Blaine TA. An overview of treatment options for persistent shoulder pain. *Am J Orthop*. 2005;34(12 Suppl):10-15.
64. Pasquali Ronchetti I, Guerra D, Taparelli F, et al. Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. *Rheumatology (Oxford)*. 2001;40(2):158-169.
65. Peyron JG. Intraarticular hyaluronan injections in the treatment of osteoarthritis: state-of-the-art review. *J Rheumatol Suppl*. 1993;39:10-15.
66. Pourbagher MA, Ozalay M, Pourbagher A. Accuracy and outcome of sonographically guided intra-articular sodium hyaluronate injections in patients with osteoarthritis of the hip. *J Ultrasound Med*. 2005;24(10):1391-1395.
67. Punzi L, Schiavon F, Cavasin F, Ramonda R, Gambari PF, Todesco S. The influence of intra-articular hyaluronic acid on PGE2 and cAMP of synovial fluid. *Clin Exp Rheumatol*. 1989;7(3):247-250.
68. Puttick MP, Wade JP, Chalmers A, Connell DG, Rangno KK. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. *J Rheumatol*. 1995;22(7):1311-1314.
69. Reagan BF, McInerny VK, Treadwell BV, Zarins B, Mankin HJ. Irrigating solutions for arthroscopy: a metabolic study. *J Bone Joint Surg Am*. 1983;65(5):629-631.
70. Salk RS, Chang TJ, D'Costa WF, Soomekh DJ, Grogan KA. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind pilot study. *J Bone Joint Surg Am*. 2006;88(2):295-302.
71. Schumacher HR, Meador R, Sieck M, Mohammed Y. Pilot investigation of hyaluronate injections for first metacarpal-carpal (MC-C) osteoarthritis. *J Clin Rheumatol*. 2004;10(2):59-62.
72. Smith GN Jr, Myers SL, Brandt KD, Mickler EA. Effect of intraarticular hyaluronan injection in experimental canine osteoarthritis. *Arthritis Rheum*. 1998;41(6):976-985.

73. Sonoda M, Harwood FL, Amiel ME, Moriya H, Amiel D. The effects of hyaluronan on the meniscus in the anterior cruciate ligament-deficient knee. *J Orthop Sci*. 2000;5(2):157-164.
74. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290(18):2443-2454.
75. Sun SF, Chou YJ, Hsu CW, et al. Efficacy of intra-articular hyaluronic acid in patients with osteoarthritis of the ankle: a prospective study. *Osteoarthritis Cartilage*. 2006;14(9):867-874.
76. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Intra-articular injection of high molecular weight hyaluronan after arthrocentesis as treatment for rheumatoid knees with joint effusion. *Rheumatol Int*. 2002;22(4):151-154.
77. Tikiz C, Unlu Z, Sener A, Efe M, Tuzun C. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. *Clin Rheumatol*. 2005;24(3):244-250.
78. Tytherleigh-Strong G, Hurtig M, Miniaci A. Intra-articular hyaluronan following autogenous osteochondral grafting of the knee. *Arthroscopy*. 2005;21(8):999-1005.
79. Vad VB, Sakalkale D, Sculco TP, Wickiewicz TL. Role of hylan G-F 20 in treatment of osteoarthritis of the hip joint. *Arch Phys Med Rehabil*. 2003;84(8):1224-1226.
80. Valiveti M, Reginato AJ, Falasca GF. Viscosupplementation for degenerative joint disease of shoulder and ankle. *J Clin Rheumatol*. 2006;12(3):162-163.
81. Van Den Bekerom MP, Mylle G, Rys B, Mulier M. Viscosupplementation in symptomatic severe hip osteoarthritis: a review of the literature and report on 60 patients. *Acta Orthop Belg*. 2006;72(5):560-568.
82. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *J Bone Joint Surg Am*. 2004;86(3):538-545.
83. Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg*. 2000;8(5):277-284.
84. Wind WM Jr, Smolinski RJ. Reliability of common knee injection sites with low-volume injections. *J Arthroplasty*. 2004;19(7):858-861.
85. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther*. 1998;20(3):410-423.
86. Yagishita K, Sekiya I, Sakaguchi Y, Shinomiya K, Muneta T. The effect of hyaluronan on tendon healing in rabbits. *Arthroscopy*. 2005;21(11):1330-1336.