CLINICAL THERAPEUTICS

John A. Jarcho, M.D., *Editor*

Viscosupplementation for Osteoarthritis of the Knee

David J. Hunter, M.B., B.S., Ph.D.

This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

From the Rheumatology Department, Royal North Shore Hospital and Kolling Institute, University of Sydney, Sydney. Address reprint requests to Dr. Hunter at the Rheumatology Department, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia, or at david.hunter@sydney.edu.au.

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A 67-year-old woman with right-knee osteoarthritis is referred by her primary care physician for treatment of her knee pain. The patient weighs 83 kg and is 161 cm tall, and her body-mass index (the weight in kilograms divided by the square of the height in meters) is 32. She has had pain intermittently for 9 years, which has been relieved with infrequent use of naproxen. She has recently become more sedentary and is finding it increasingly difficult to play golf. A recent radiograph of her right knee reveals moderate joint-space narrowing and osteophytes, affecting primarily the medial tibiofemoral compartment and lateral patellofemoral compartment. A friend at her golf club received a hyaluronate injection and had sustained relief of her knee pain for 6 months. The patient inquires about whether this form of therapy may be appropriate for her. The specialist recommends weight loss and exercise and counsels the patient about the appropriate use of viscosupplements.

THE CLINICAL PROBLEM

Approximately 46 million people in the United States,[1] or 10 to 12% of the adult population, have symptomatic osteoarthritis.[2-4] In 2010, osteoarthritis accounted for 2.2% of global years lived with disability and 10% of global years lived with disability caused by musculoskeletal disorders worldwide, according to the Global Burden of Disease Study 2010.[5,6] Osteoarthritis is the fastest increasing major health condition; it accounts for slightly more than 17 million years lived with disability in 2010, which reflects a 64% increase during the period from 1990 through 2010.

The majority of people with osteoarthritis (64%) are of working age (15 to 64 years), and 11% of the workforce is made up of people who have osteoarthritis.[7,8] Most of the costs associated with osteoarthritis are indirect costs associated with loss of participation in work, lost productivity, sick leave, premature retirement, and substantial loss of quality of life.[9] A large component of the direct health care costs for managing osteoarthritis is the cost of total hip and knee replacements, with osteoarthritis accounting for about 95% of surgical volume for these procedures.

Recent estimates suggest that knee osteoarthritis affects approximately 250 million people worldwide.[5] Typically, knee pain limits activity and impairs quality of life. The risk of mobility disability (defined as the need for help with walking or

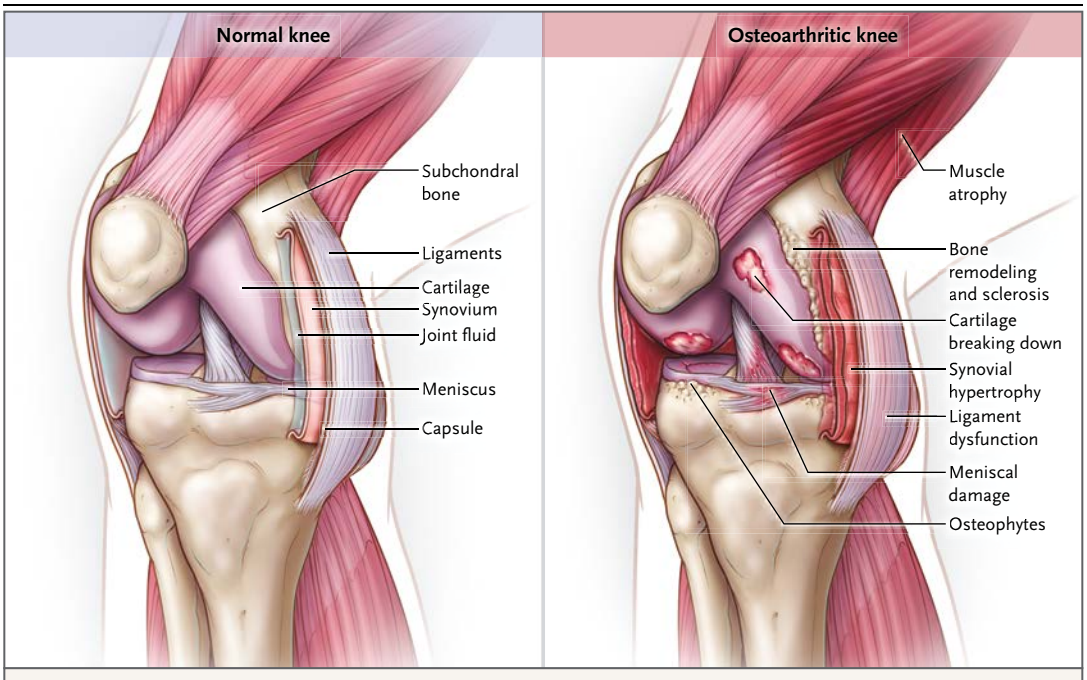

Figure 1. Schematic of the Knee Joint, Showing the Synovial Joint Tissues Affected in Osteoarthritis.

This schematic shows the way in which each structural part of the knee is affected by osteoarthritis, an observation that is consistent with the theory that osteoarthritis is a disease of the entire synovial joint.

climbing stairs) attributable to knee osteoarthritis alone is greater than that associated with any other medical condition in people 65 years of age or older.[10,11]

PATHOPHYSIOLOGICAL ASPECTS OF OSTEOARTHRITIS AND THE EFFECT OF THERAPY

The pathogenesis of osteoarthritis is perhaps best understood as excessive mechanical stress applied in the context of systemic susceptibility.[12] Susceptibility may be increased in part by genetic factors (a family history increases risk), older age, ethnic background (e.g., hip osteoarthritis is more common among white Americans than among Chinese people), nutritional factors (vitamin D or K deficiency), and female sex.[13] In persons vulnerable to the development of knee osteoarthritis, local mechanical factors such as abnormal joint congruity, joint malalignment, muscle weakness, or alterations in the structural integrity of the joint environment, such as meniscal damage or ligament rupture, can increase susceptibility to and progression of osteoarthritis. Loading can also be affected by obesity or joint injury (either acute, as in a sporting injury, or after repetitive overuse, such as in occupational exposure). The pathogenesis of osteoarthritis is characterized by progressive cartilage loss, subchondral bone remodeling, osteophyte formation, and synovial inflammation (Fig. 1).

Hyaluronate is a naturally occurring component of the cartilage and the synovial fluid. It is a polysaccharide composed of continuously repeating molecular sequences of β-D-glucuronic acid and β-D-*N*-acetylglucosamine, with a molecular mass in normal synovial fluid ranging from 6500 to 10,900 kDa.[14] Within the normal adult knee, there is approximately 2 ml of synovial fluid, with a hyaluronate concentration of 2.5 to 4.0 mg per milliliter.[15] Hyaluronate is responsible for the rheologic properties of synovial fluid, enabling it to act as a lubricant or shock absorber, depending on the forces exerted on it.[16] In osteoarthritis, synovial hyaluronate is depolymerized (molecular mass, 2700 to 4500 kDa[14]) and cleared at higher rates than normal.[17] In a normal joint, the average intrasynovial half-life of hyaluronate is approximately 20 hours.[15] In an inflamed joint, this

half-life is decreased to 11 to 12 hours. These changes reduce the viscoelasticity of the synovial fluid.

Exogenous intraarticular hyaluronate is available as a treatment for the symptoms of knee osteoarthritis. It can be either synthesized by means of bacterial fermentation or extracted from animal tissues (e.g., rooster comb). The injected polymers range in size from 100 to 10,000 kDa. The therapeutic goal of administration of intraarticular hyaluronate is to provide and maintain intraarticular lubrication, which increases the viscoelastic properties of synovial fluid[18]; this form of therapy is therefore sometimes termed "viscosupplementation." It is also claimed that hyaluronate exerts antiinflammatory, analgesic, and possibly chondroprotective effects on the articular cartilage and joint synovium.[15] The clinical benefits of treatment with intraarticular hyaluronate, which may persist well beyond the intraarticular residence time of the product, have been suggested to be caused by the reestablishment of joint homeostasis as a result of an increase in the endogenous production of hyaluronate that persists long after the exogenous injected material has left the joint.[17]

CLINICAL EVIDENCE

Despite numerous trials and meta-analyses, the efficacy of hyaluronate-related agents in patients with knee osteoarthritis remains debated and uncertain. In one trial, Chevalier et al.[19] found that intraarticular injection of hylan G-F 20, a high-molecular-mass (mean, 6000 kDa) hyaluronate derivative, resulted in a significant but clinically modest reduction in knee pain, as compared with intraarticular injection of a saline placebo. As in many of the other trials of hyaluronates, there was a large placebo effect in this trial.[20] Meta-analyses assessing the efficacy of this form of therapy[21-29] have had discordant findings,[30,31] possibly because each review used different search strategies and selection criteria to identify trials for inclusion in the analysis.[30] Methodologic quality was not always formally assessed, and some of the systematic reviews raised concerns regarding the significant heterogeneity across studies and regarding publication bias.

There is also controversy over whether the molecular mass of hyaluronate influences efficacy. For example, Berenbaum et al. found that treatment with an intermediate-molecular-mass hyaluronate (GO-ON [Rottapharm]; 800 to 1500 kDa) was significantly superior to low-molecular-mass hyaluronate (Hyalgan [Fidia Pharma]; 500 to 730 kDa) for knee osteoarthritis symptoms ($P=0.047$).[32] A higher proportion of patients with treatment response was observed with GO-ON than with Hyalgan (73.3% vs. 58.4%, $P=0.001$). In another trial, however, the effect size for symptom relief was found to be broadly similar with high-molecular-mass and intermediate-molecular-mass products.[33] In sum, the effectiveness of intraarticular hyaluronate is at best modest and at worst, in some of the aforementioned meta-analyses, indistinguishable from that of placebo.

CLINICAL USE

Comprehensive management of osteoarthritis should always include a combination of treatment options that are directed toward the common goal of alleviating pain and improving function.[34,35] The recommended hierarchy of management should consist of nonpharmacologic methods first (such as weight loss, exercise, braces, and assistive devices such as canes); then analgesic medication, including nonsteroidal antiinflammatory drugs (NSAIDs); and finally surgery.[36-38] Too frequently, the first step is forgotten or not emphasized sufficiently, to the patients' detriment.[39]

The use of local therapy for osteoarthritis management has inherent appeal, because it may mitigate some of the serious concerns regarding the side effects associated with systemic therapies, including gastrointestinal bleeding and myocardial infarction. Local therapies include topical agents, such as topical NSAIDs and capsaicin, as well as intraarticular glucocorticoids and intraarticular hyaluronate. The currently available evidence suggests that viscosupplementation may be as effective as NSAIDs and results in fewer systemic adverse events; in comparison with intraarticular glucocorticoids, it has a delayed onset of effects and a longer-lasting benefit.[40]

The hyaluronates listed in Table 1 are approved by the Food and Drug Administration (FDA) as class III medical devices for persons with osteoarthritis of the knee whose condition has not responded adequately to conservative nonpharmacologic treatment and simple analgesics. Different hyaluronate formulations are available worldwide, from a low-molecular-mass preparation (range,

Table 1. Hyaluronates Approved by the Food and Drug Administration for Knee Osteoarthritis.

Product	Dose and Number of Injections
Hyalgan, Fidia Pharma (sodium hyaluronate)	Weekly injections of 20 mg, for a total of five injections
Supartz, Bioventus (sodium hyaluronate)	Weekly injections of 10 mg, for a total of five injections
Orthovisc, DePuy Mitek (high-molecular-mass hyaluronate)	Weekly injections of 30 mg, for a total of three to four injections
Euflexxa, Ferring Pharmaceuticals (1% sodium hyaluronate)	Weekly injections of 20 mg, for a total of three injections
Synvisc One, Sanofi-Aventis (hylan G-F 20)	A one-time injection of 48 mg
Synvisc, Sanofi-Aventis (hylan G-F 20)	Weekly injections of 16 mg, for a total of three injections
Gel-Syn, Institut Biochimique (sodium hyaluronate)	Weekly injections of 17 mg, for a total of three injections

500 to 730 kDa) to more recent intermediate-molecular-mass formulations (range, 800 to 2000 kDa) and even cross-linked, high-molecular-mass formulations (mean, 6000 kDa), including hylans, non–animal-derived hyaluronate, and others.[32] There is no reliable evidence of the superiority of any one brand of viscosupplement to other brands.

There is no clear evidence supporting any specific clinical criteria to select patients who will be most likely to benefit from hyaluronate injections. However, trial data suggest that patients with late-stage disease (such as those with marked joint-space narrowing) who are older than 65 years of age are less likely than younger patients or patients with earlier disease to have any benefit.[27] This treatment is contraindicated in persons with known hypersensitivity to hyaluronate products, women who are pregnant or nursing, pediatric patients, patients with bacteremia, or patients with infections in or around the target knee, although these recommendations are not necessarily based on reports of adverse events.

The diagnostic workup before administration of hyaluronate should include ensuring that the patient has knee osteoarthritis. The clinical presentation of knee osteoarthritis is often confused with other sources of knee pain, such as anserine bursitis, patellar tendonitis, and popliteal (Baker's) cyst, as well as referred pain from the hip or lower back.[41] If there is concern that another condition may be responsible for the pain, a radiograph can provide confirmatory proof and assist in ruling out other diagnostic possibilities.[42] Because osteoarthritis is a noninflammatory form of arthritis, laboratory findings are expected to be normal.

Intraarticular injections should always be performed under sterile conditions; the aseptic technique must be followed to avoid joint infection. The procedure is usually performed in an outpatient setting, with the patient lying supine with the knee in full extension. Aspiration of any effusion before injection is highly recommended to prevent dilution of the injected hyaluronate. The same needle used for aspiration can be left in place and used for the injection. Ideally, joint injections should be delivered into the joint space and not into the fat pad or the synovial tissues. Multiple approaches have been described for knee aspiration and injection, with studies reporting that the superolateral injection site is the most consistently reliable site for reaching the synovial joint space of the knee[15,43,44] (Fig. 2). Subcutaneous local anesthetic can be administered, although the hyaluronate should not be mixed with anesthetic when injected. Ultrasonographic guidance of the intraarticular injection may be needed, particularly for obese patients. The injection technique involves insertion of a 22-gauge, 1.5-in. needle at an angle of 45 degrees directed toward the center of the knee joint.[43]

Patients should be advised to avoid strenuous or prolonged weight-bearing activities for approximately 48 hours after treatment. However, there is no routine need for the use of crutches or treatment with analgesics immediately afterward. Typically, the most pronounced improvement is expected from 5 to 13 weeks after injection[21] with some residual effect still present at 24 weeks.[23] It is reasonable to follow up at 6 months after the procedure to determine the next suitable steps for management. For patients whose condition does not respond, it is important to continue treatment with nonpharmacologic methods and analgesics and, if necessary, to consider the next

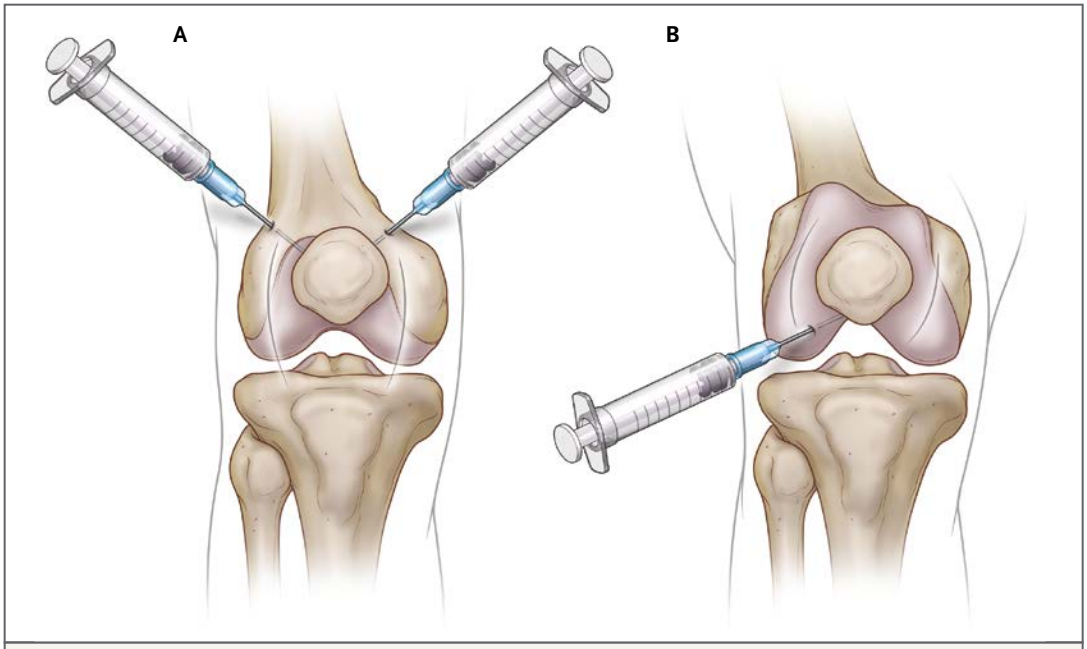

Figure 2. Injection Sites.
Panel A shows the superomedial and superolateral injection sites. These injections are performed with the knee extended. Panel B shows the lateral joint line injection site, with the right knee flexed 90 degrees.

steps; these may include treatment with tramadol, duloxetine, or opioids, as well as joint replacement. One study suggests that a lack of response to an initial course of intraarticular hyaluronate does not necessarily mean that a repeat course will not be effective.[45] The FDA has approved repeat courses of intraarticular hyaluronate; however, many insurance plans require at least a 6-month interval between treatments.

The average cost of a hyaluronate product for an injection course is approximately $500. This does not include the cost of the visit or an associated fee for injections, which is charged by some facilities. Costs may be further increased by the treatment of adverse effects, such as pseudoseptic reactions, which may require repeat visits, aspiration, culture, and sometimes provisional antibiotic treatment while culture results are pending.

ADVERSE EFFECTS

Minor side effects include pain at the injection site (which occurs in 1 to 33% of patients), local joint pain and swelling (in <1 to 30%), and local skin reactions (in 3 to 21%).[46] More serious side effects can occur. Pseudoseptic reactions (occurring in 1 to 3% of patients), which are characterized by inflammation and swelling of the joint that are not caused by infection, can be severe and may require further medical treatment. These reactions usually occur after sensitization with the second or third injection of a series or with a repeat treatment course. True joint infections have also been reported, but these appear to be rare.[47]

Some forms of hyaluronate may cause these adverse effects more frequently than others. A meta-analysis of adverse events showed that the frequency of flares of pain and swelling was higher after intraarticular injections of high-molecular-mass hylan (a modified form of hyaluronate) than after injections of the standard form of intraarticular hyaluronate (relative risk, 2.04; 95% confidence interval [CI], 1.18 to 3.53).[25] Euflexxa (Ferring Pharmaceuticals) is a synthetic derivative form of hyaluronate that does not appear to induce hypersensitivity reactions.

A recent review by Rutjes et al.[48] raised concerns about an increased risk of serious adverse events (relative risk, 1.41; 95% CI, 1.02 to 1.97), including gastrointestinal and cardiovascular adverse events and cancer. It is difficult to interpret these data[31] because of limitations of transparency

in the study reporting and the biologic implausibility of some of the adverse events (especially with regard to cancer[49]) relative to the timing of treatment administration.

AREAS OF UNCERTAINTY

The actual overall efficacy of intraarticular hyaluronate, if any, is an area of ongoing uncertainty. A summary of the current conflicting literature would suggest that hyaluronate has, at best, a small treatment benefit. The positive or supportive meta-analyses consistently show this small effect,[21,26-28] whereas the negative reviews highlight the absence of a definite difference from placebo, the heterogeneity of the published literature, and the potential for publication bias.[22,24,25] Although there are some data suggesting that younger patients and patients with less-severe disease may have greater benefit from this treatment than do older patients and those with more advanced disease,[16,27] further evidence is required to support this claim.

The effect of intraarticular hyaluronate on the structural progression of osteoarthritis, especially after repeat administration over longer intervals, remains an open question, with some pilot evidence suggesting positive effects.[50,51] Jubb et al.[50] conducted a secondary analysis after adjusting for baseline differences in the width of the joint space and found a protective effect in the subgroup of persons with milder disease. A magnetic-resonance-imaging study by Wang et al.[51] provided evidence suggesting a beneficial effect on knee cartilage, although it was a small study involving 78 patients, and the results were based on an analysis that included only participants who completed the trial, in which there was a dropout rate of approximately 30% and a higher rate of surgical intervention in the hylan G-F 20 group. At present, these studies are best described as suggestive of an effect, but the results are in need of replication before any conclusive clinical recommendations can be made.

The current consensus is not to advocate for the use of hyaluronate.[36,52] However, it is a treatment that is used regularly by both orthopedists and rheumatologists, as well as by other health professionals. At present, the management of osteoarthritis is best characterized as palliative, with numerous missed opportunities for more beneficial intervention[34] and typical clinical practice that does not reflect guideline recommendations.[39,53-56] The treatment of osteoarthritis is not unique in this regard.[57]

GUIDELINES

Consistent with the contradictory meta-analyses, available guidelines also have conflicting recommendations, despite being based on the same research evidence. The 2010 Osteoarthritis Research Society International (OARSI) guidelines recommended intraarticular hyaluronate as potentially useful in patients with knee or hip osteoarthritis, with a modest effect size for pain relief.[37] A more recent update of the evidence from the OARSI suggested that the data from the more rigorous trials did not show a significant difference between the effect of hyaluronate and that of placebo; as a result, it was not recommended for the treatment of either knee or multiple-joint osteoarthritis.[58] In the American Academy of Orthopaedic Surgeons clinical practice guideline, it was determined that the evidence was inconclusive and a recommendation could not be made for or against the use of intraarticular hyaluronate.[52] Similarly, the 2012 American College of Rheumatology recommendations do not advocate the use of intraarticular hyaluronate for the initial management of knee osteoarthritis. However, if a patient does not have a satisfactory response to acetaminophen or NSAIDs, then the use of tramadol, duloxetine, or intraarticular hyaluronate is conditionally recommended.[36]

RECOMMENDATIONS

In this clinical setting of a prevalent disabling disease, for which the therapy in question has, at best, modest efficacy for relief of pain, the tolerance for treatment expense and adverse events is limited. Therefore, the current evidence base would not advocate the use of intraarticular hyaluronate for the management of knee osteoarthritis. Similarly, although there are some data suggesting a benefit of high-molecular-mass products as compared with low-molecular-mass preparations, the data are inconsistent. For the case in question, this patient was counseled to lose weight and undertake a strengthening exercise program and was counseled against the use of intraarticular hyaluronate.

Are there any narrower therapeutic indications

for which the use of intraarticular hyaluronate may be justified? At this point in time, there is not sufficient evidence to indicate that younger patients with less severe disease, or other patient subgroups, have a more favorable outcome.

The comments and opinions expressed herein represent those of the author and do not reflect those of any official scientific role that the author holds or institution with which he is affiliated.

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