Hyaluronic Acid Supplementation

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As evidenced by publication of a new set of guidelines for the treatment of osteoarthritis (OA) by the American College of Rheumatology after only 5 years, modalities available for the management of OA have undergone significant changes. New therapeutic approaches include the use of cyclo-oxygenase-2 inhibitors, and intra-articular hyaluronans (HA). HA, found in a number of body tissues, is altered in the presence of osteoarthritis with decreased molecular weight and concentration resulting in impaired viscoelasticity. Hyaluronan preparations have been shown to decrease pain and increase function in patients with osteoarthritis of the knee. Mechanisms of therapeutic effect include restoration of more normal synovial fluid with improved viscoelasticity, effects on cartilage biosynthesis and degradation, anti-inflammatory effects, and direct analgesic effects. Studies in animal models, and preliminary studies in humans suggest that hyaluronans may have a structure-modifying effect in OA. Hyaluronans represent a substantive addition to the therapeutic armamentarium in osteoarthritis.

Introduction

The treatment of osteoarthritis (OA), the most common rheumatic disease, has undergone significant changes over the past decade. The rapidity of such advances is evident in the fact that guidelines for the treatment of osteoarthritis, published by the American College of Rheumatology (ACR) in 1995, have been superseded in only 5 years by a new set of guidelines based on new therapeutic advances [1•] (Fig. 1). The targets of osteoarthritis treatment include symptomatic therapy for pain, stiffness and swelling, and therapy directed at structure-modification leading to retardation, reversal, or prevention of the basic disease process.

The primary complaint of patients with osteoarthritis is usually that of pain. The etiology of such pain is multifactorial, including inflammatory and non-inflammatory causes. These multiple causes include intra-osseous increases in vascular pressure, periosteal proliferation, subchondral fractures and sclerosis, ligamentous laxity, muscle spasm, and synovitis. Of special note is that fact that cartilage is aneural; accordingly, pain associated with osteoarthritis derives from other joint structures.

Structural changes in osteoarthritis are characterized by cartilage erosion with loss of joint space, and peripheral formation of osteophytes resulting from proliferation of bone and cartilage in the form of spurs. The etiology of cartilage erosive changes is thought to relate primarily to increased catabolic activity as a result of activation of proteolytic and collagenolytic enzymes. Synthetic activity, with increases in hyaluronic acid, collagen and proteoglycan formation, is increased early in the course of osteoarthritis; it is eventually blunted, however, leading to an inability to maintain normal joint architecture.

New therapeutic agents of note introduced over the past several years include the cyclo-oxygenase-2 (Cox 2) inhibitors [2,3] and intra-articular hyaluronans (HA) [4•,5•].Cox-2 inhibitors represent NSAIDs with an increased safety profile, particularly with respect to gastropathy, with decreased potential for ulcer-related bleeding, perforation and obstruction. Intra-articular hyaluronans, utilized at this time primarily for knee osteoarthritis, have been used throughout the world for well over a decade. More recently, these agents were approved for use in osteoarthritis of the knee in the United States. The current status of intra-articular hyaluronan therapy is the subject of this review.

Intra-articular Hyaluronans—Physiology and Biochemistry

HA molecules consist of disaccharides comprised of N-acetyl glucosamine and glucuronic acid (Fig. 2). HA is found in a number of body tissues, including the aqueous of the eye, skin extracellular matrix, and cartilage; it represents a major component of synovial fluid, giving it its viscoelastic behavior. In joints, HA is produced by chondrocytes and synovial cells. In the presence of joint disease, particularly inflammation, HA becomes depolymerized with resultant decrease in molecular weight, concentration, and alteration in viscoelastic properties. In synovial fluid, hyaluronic acid is important both for joint lubrication, particularly of soft tissues, and joint nutrition.

In an interesting editorial commentary entitled “Hyaluronan Is Not Just a Goo!” Toole [6•] describes important hyaluronic acid-cell-matrix interactions, emphasizing important functions of hyaluronic acid in body metabolism. Molecular functions of HA fall into three overlapping categories. These include the influence of HA

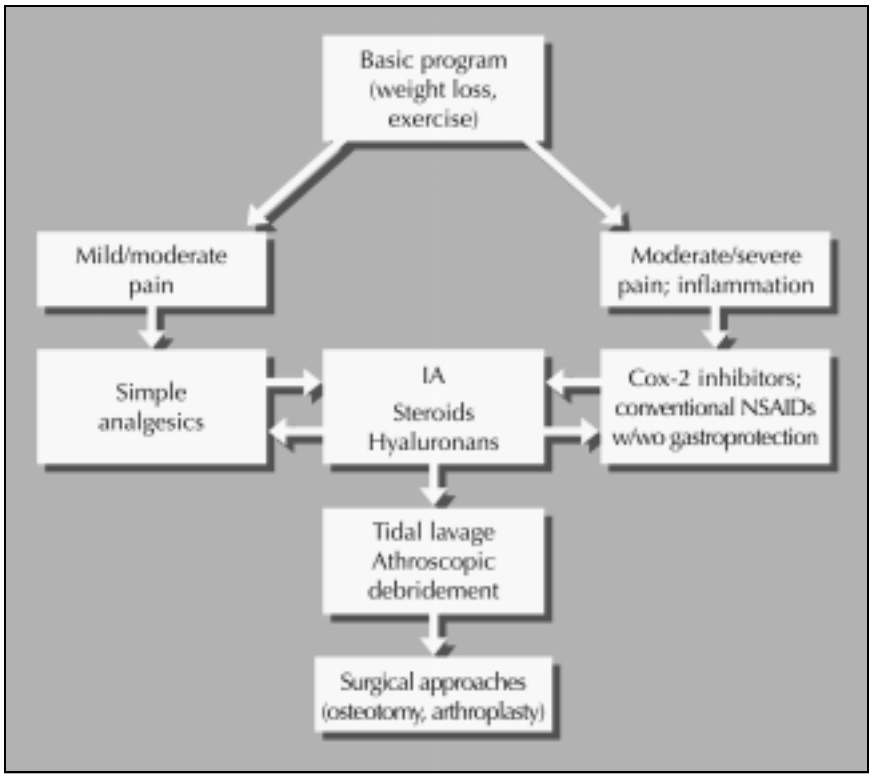

Figure 1. Schematic outline of OA management.

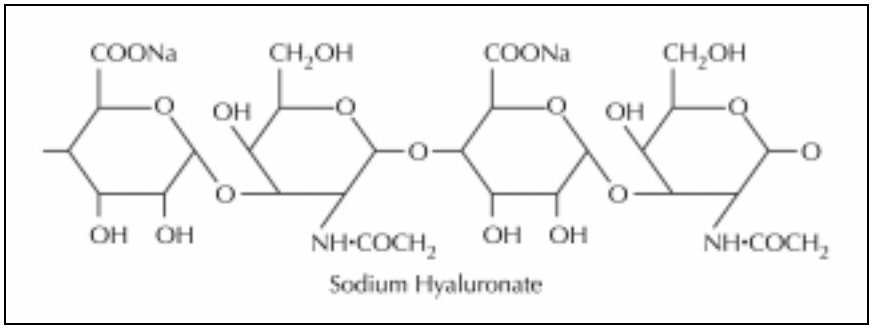

Figure 2. Chemical structure of hyaluronans comprised of repeated N-acetyl glucosamine and glucuronic acid residues.

on hydration and physical properties of tissues due to its large hydrodynamic domain; its interaction with other extracellular matrix macromolecules, including proteoglycans such as aggrecan and versican; and, finally, interaction with cell surface receptors, notably CD44, which influence cell behavior. The ability of HA to form a pericellular coat as a cellular environment illustrates the interplay of these three functions.

A number of hyaluronic acid preparations are available throughout the world for clinical use. Preparations available in the United States include sodium hyaluronan (Hyalgan, Sanofi Synthelabo Inc., New York, NY), and hylan GF-20 (Synvisc, Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA). These preparations are not identical, differing particularly in molecular weight and viscosity. Current preparations are derived from rooster combs; new preparations being studied investigationally include those derived from hyaluronans secreted by streptococci.

Hyalgan is a viscous solution of the sodium salt of hyaluronic acid. It has a molecular weight between 500,000 and 730,000 daltons, and is a highly purified fraction of natural sodium hyaluronate. Synvisc is chemically cross-linked with formaldehyde and vinyl sulfone; its average molecular weight is 6,000,000 daltons. Hyalgan has been most commonly administered in a cycle comprised of five injections over a 4-week period. More recently, approval has been given by the Food and Drug Administration (FDA) for a three-injection series. Synvisc is used in a course of one injection weekly for a total of three injections.

Mechanisms of action

Multiple mechanisms of action have been proposed to explain the therapeutic efficacy of the hyaluronan agents. Such mechanisms include effects on physical and biomechanical properties of joint structures [7,8], effects on cartilage biosynthesis and degradation [9,10], anti-inflammatory effects [11,12], and direct analgesic effects related to interaction with pain receptors [13,14]. Intra-articular hyaluronic acid restores the viscoelasticity of synovial fluid, improving joint fluid flow and the nutrient environment.

Studies in which human synoviocytes from osteoarthritic joints were incubated with exogenous HA demonstrated de novo synthesis of HA, suggesting augmentation of endogenous HA production [15]. Similarly, synoviocyte cell lines derived from patients with OA synthesized more HA, and HA of higher molecular weight, when HA was added to the medium [16].

Cartilage breakdown in OA is mitigated by HA-related inhibition of degradative enzyme induction and activation [10,17]. Anti-inflammatory effects are characterized by inhibition of interleukin-1α-induced prostaglandin E_2 synthesis by human synoviocytes [11], an influence on leukocyte adherence, proliferation and phagocytosis [18], and protection against superoxide radicals [12].

Takahashi and colleagues [19•] evaluated the effect of intra-articular hyaluronan on chondrocyte apoptosis and nitric oxide (NO) production. They created an experimental model of osteoarthritis using anterior cruciate ligament transection in rabbits. Animals administered intra-articular hyaluronic acid had less severe osteoarthritis than those receiving a vehicle carrier of HA, or no injection. The number of apoptotic chondrocytes was significantly lower in the HA group, although NO production was not altered. Using this same experimental model, this investigative group demonstrated decreased extent and grade of cartilage damage in an hyaluronan injection group as compared to control [17]. In synovium, expression of matrix metalloproteinase-3 (MMP-3) and IL-1β-mRNA was suppressed in the mild grades of OA in the hyaluronan injection group. Results suggested that one of the therapeutic mechanisms of the hyaluronan related to down-regulation of MMP-3 and IL-1β in synovium during early development of OA. In a partial meniscectomy model of osteoarthritis in rabbits, total proteoglycan synthesis in an HA treatment group was significantly higher than in controls [20]. Studies of mRNA expression revealed that HA inhibited matrix metalloproteinase-3 (MMP-3) and tissue inhibition of metalloproteinase-1 (TIMP-1) production; MMP-1 production were not affected.

Hyaluronan was shown to be effective in blocking the catabolic action of fibronectin fragments in explant cultures of bovine cartilage, and in an experimental in vivo model of damage to the rabbit knee joint [10]. Fibronectin fragments induced catabolic cytokines, which, in turn, inhibited proteoglycan synthesis. Studies demonstrated that hyaluronan completely blocked fibronectin fragment-mediated decreases in proteoglycan content. Hyaluronan appeared to block damage in part by blocking penetration of fibronectin fragments and slowing metalloproteinase expression. However, enhancement of proteoglycan synthesis was considered possibly a more important mechanism in the response to hyaluronan exposure.

In studies of "limiting viscosity" following injection of hyaluronan, limiting viscosity values were higher than both baseline values and that of the HA preparation injected [21,22]. Additional studies demonstrated that the median viscosity and elasticity of synovial fluid were increased following injections of hyaluronan as compared to saline-treated patients [8]. In trials in which horses were administered hyaluronan intravenously, examination revealed decrease in lameness scores, decrease in synovial fluid concentration of prostaglandins, and less severe synovial abnormalities on histopathologic study [23].

Structural effects of Hyalgan administered in a dose of 20 mg per week for five injections were evaluated by microarthroscopy and morphologic analysis of biopsy samples taken at baseline and after 6 months, following administration to patients with osteoarthritis of the knee [24]. Studies at 6 months compared to baseline revealed a statistically significant reconstitution of the superficial amorphous layer of the cartilage, increased chondrocyte density, and a statistically significant decrease in synovial inflammation. Significant and persistent improvement in joint pain and mobility were also observed after treatment. The authors suggested that the sustained effect of Hyalgan was attributable to the effects of Hyalgan on the cellular and tissue components of the joint, rather than a temporary restoration of synovial fluid viscosity.

Clinical Studies

Clinical responses from five weekly injections of Hyalgan were compared to placebo or oral naproxen in a 26-week, double-blind, masked observer, multicenter trial of 495 patients with idiopathic OA [4•]. Patients receiving Hyalgan improved more with respect to pain on a 50-ft walk outcome measure as compared to placebo at week 26; 56% of Hyalgan-treated patients, compared to 41% of placebo-treated patients, had greater or equal to 20-mm reduction in the visual analog scale (VAS) for pain from week 5 continuously through week 26. At 26 weeks, more Hyalgan-treated patients (47.6%) had slight pain or were pain-free in contrast to placebo-treated or naproxen-treated patients. Injection-site pain was more common in the Hyalgan-treated than in the placebo-treated group (23% versus 13%). This study demonstrated that intra-articular Hyalgan was associated with relief of pain and improvement in patient function, and was at least as effective, with fewer adverse reactions as continuous treatment with naproxen, for 26 weeks.

In a similar study, the efficacy, safety and patient satisfaction of intra-articular Hyalgan in patients with osteoarthritis of the knee were examined [25]. Primary efficacy criteria were pain on walking, measured with a visual analog scale, and the Lequesne Index. Completor and intent-to-treat analyses both demonstrated a significant benefit favoring hyaluronic acid-treated patients at month 6. This study once again demonstrated the efficacy of Hyalgan compared to placebo with symptomatic benefit, which persisted for up to the 6 months of the study.

Multiple studies have demonstrated long-term duration of efficacy following three to five weekly injections of Hyalgan, 20 mg per injection [4•,26–28]. In one such study, symptom relief of knee OA was seen following the treatment cycle in 68% of patients; in 55% of these patients, relief was maintained until the end of the 12-month follow-up [28]. Administration of repeated cycles of Hyalgan demonstrated repeated efficacy with no increase in local or systemic adverse events [28,29•,30,31]. In the longest such study, administration of a repeat cycle of five injections every 6 months over a period of 25 months led to a decrease in pain after the first treatment course, with continued decrease up to the end of the study, at which time there was 55% improvement in pain compared with baseline values [31].

Potential for structural-modification by hyaluronan (Hyalgan) was evaluated in a prospective, controlled study, of 1 year's duration, in humans [29•]. After randomization, either conventional therapy or three cycles of three intra-articular injections of Hyalgan were administered at 3-month intervals. Arthroscopic assessment revealed decreased deterioration in structural parameters in the Hyalgan-treated group, suggesting that repeated intra-articular injections might delay disease progression.

Investigations with hylan GF-20 (Synvisc), a highly cross-linked hyaluronan, were performed using three intra-articular injections over a 2-week period [5]. Differences between Synvisc and saline treatment as a control were significantly different statistically for all outcome measures related to pain. Improvement occurred early, and was sustaine during follow-up in a substantial number of patients. Rescue therapy was required by 11% of the hylan-treated patients in contrast to 53% of saline-treated patients. In other trials with hylan GF-20, improvement in osteoarthritis pain and response to the drug was observed. In one the these studies, a multicenter randomized masked patient/masked evaluator study, viscosupplementation with hylan GF-20 was compared with continuous NSAID therapy [32]. Hylan GF-20 was at least as effective for pain during motion as was NSAID therapy at 12 weeks, and was significantly better than NSAID therapy at 26 weeks.

Acute local reactions following intra-articular injection of hylan GF-20 have been described [33–37]. In a retrospective review of patients with OA of the knee who were treated with hylan GF-20, the total were 22 patients, 88 injections, and 28 treated knees in all [33]. Six patients had reactions within 24 hours of injection, characterized by pain, warmth, and swelling lasting up to 3 weeks. Crystal studies and cultures were negative. The mechanisms of such reactions were unclear, but may include an immunologic response to the altered cross-linked hyaluronan [37], endotoxin, or a crystal-like response to large hyaluronan particles.

Precipitation of acute pseudogout has been described with both Hyalgan and Synvisc [38–41]. Acute attacks occur in a range that spans from hours to 1or 2 days following hyaluronan injection. The mechanisms by which HA injections might induce acute attacks are not clear. Shedding of CPPD crystals may be a mechanical complication of the joint injection procedure with associated joint injury. HA injections may initiate a fall in synovial fluid calcium related to phosphate buffer present in the injection agent, similar in mechanism to acute pseudogout following parathyroidectomy [42]. Although it appears that induction of acute pseudogout flares may be related to hyaluronan use, this occurrence is unusual [43]. Chondrocalcinosis was not a contra-indication to inclusion of patients for study in the investigations by Altman and Moskowitz [4•]; no cases of acute pseudogout were noted in the Hyalgan-treated group in that study. Accordingly, the presence of chondrocalcinosis or a past history of pseudogout does not mitigate against the use of these agents.

My own clinical experience with the use of hyaluronan has demonstrated significant efficacy and safety. Their use merits consideration in patients who have limited response to a baseline program of nonpharmacologic therapy and simple analgesics. Not infrequently, patients are able to decrease or discontinue use of nonsteroidal anti-inflammatory agents or, if such agents are continued, an additive symptomatic response is frequently noted. Failure of response to HA therapy is often the result of using these agents in late stage, rather than in earlier moderate stage disease. In the above-mentioned study by Altman and Moskowitz [4•], patients with stage II or stage III Kellgren-Lawrence radiologic changes could not be differentiated as to response. In patients with stage IV "bone-on-bone" disease, intra-articular hyaluronan therapy is, as noted, less likely to be of benefit; nevertheless, other clinicians and I have noted that patients with advanced disease may at times respond. Such use is reasonable in individuals who have comorbid illnesses that contravene use of other agents, or in whom other agents have been less than optimally effective. Sufficient numbers of patients with severe disease will respond to make use of intra-articular hyaluronans appropriate for consideration.

I differentiate the indications for use of intra-articular steroids versus intra-articular hyaluronans. Intra-articular corticosteroids appear most efficacious in patients whose symptoms are in reasonable control, but whose knees flare following joint overuse. This applies, for example, to patients following a period of vacation travel, prolonged periods of shopping, or a mild injury. IA hyaluronan therapy, on the other hand, appears more reasonable for use in patients who have persistent moderate levels of pain that are not responding to usual therapeutic programs. The response to the hyaluronan injections is slower than with corticosteroids, but more lasting in duration [44]. I have effectively employed a procedure in which intra-articular corticosteroids are followed in 3 or 4 weeks by a series of hyaluronan injections. The advantages of this procedure are that the patient has fairly rapid onset of relief of symptoms, following which more prolonged relief is initiated by the hyaluronan cycle. In addition, suppression of inflammation by the intra-articular steroids may allow a

decreased rate of loss of hyaluronate from the joint, thereby intensifying and prolonging its efficacy.

Although in the United States reimbursement for intra-articular hyaluronan therapy is provided primarily for treatment of knee OA, hyaluronan therapy appears to be beneficial when injected into other OA-affected joints. Clinicians have investigationally noted what appear to be good clinical responses to intra-articular hyaluronan in the first carpometacarpal joint, using 0.5 cc of Hyalgan in a five-injection series. Similarly, the hyaluronans are being evaluated in other joints including the hip, ankle, and shoulder with what appear to be preliminary beneficial effects. Controlled trials of these agents in such articulations other than the knee are in progress.

Disease Modification

Although not FDA-approved for use as a disease modifier, studies in animal models have demonstrated salutary effects on osteoarthritic changes following hyaluronan injection [17,19,40,45]. As noted earlier, studies in man have suggested a structure-modifying activity of Hyalgan in OA of the knee when evaluated arthroscopically [29•]. Several additional trials of hyaluronans as a disease modifier are in progress.

Conclusions

In summary, hyaluronans appear to be efficacious and safe [1•]. As with other therapeutic agents, not all patients will respond, nor will all patients have a 100% response. Use of these agents at an earlier stage of osteoarthritis pathology is likely to be associated with a higher rate of therapeutic success. Their efficacy and safety are noted in the recent updated ACR Guidelines for the treatment of osteoarthritis [1•]. Further studies will define their role in the management of OA of joints other than the knee, and their possible efficacy as disease-modifying agents. Hyaluronans represent a substantive addition to the therapeutic armamentarium in OA of the knee.

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