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Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity

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Summary

Objective: Although available nonsurgical pharmacotherapies for treatment of osteoarthritis (OA) are considered to be solely symptom-modifying agents, recent advances have been made in the search for agents that may modify disease progression. Intra-articular hyaluronan (HA) therapy is one symptom-modifying approach that has been found to be safe and effective for reducing pain due to OA of the knee. Presented here is a review of the evidence that HAs may also modify the rate of OA disease progression in addition to providing symptomatic efficacy.

Design: A review of the literature based on a MEDLINE search through June 2004, using the terms HA, sodium hyaluronate, hyaluronic acid, hylan, hylan G-F 20, OA, disease modification, structure modifying and joint structure.

Results: Evidence for disease-modifying activity of HAs stems from 1) the complex biochemical effects of HAs in the synovium and extracellular matrix of the articular cartilage, including interactions between exogenously administered HA and articular cartilage, subchondral bone, matrix proteoglycans, and collagens; 2) the effects of HA administration in animal models of OA, including total or partial meniscectomy and anterior cruciate ligament transectomy; 3) results of clinical trials using one HA, Hyalgan® (sodium hyaluronate, molecular weight 500–730 kDa) that evaluated structural outcomes, such as joint-space width, chondrocyte density and vitality, and arthroscopic evaluation of chondropathy.

Discussion: Growing preclinical and clinical evidence supports the notion that, in addition to relieving the symptoms of OA, HAs also modify the structure of the diseased joint and the rate of OA disease progression, at least early in the evolution of the disease process.

Key words: Hyaluronans, Osteoarthritis, Knee, Disease-modifying.

Introduction

SYMPTOM MODIFICATION VS MODIFICATION OF DISEASE PROGRESSION IN THE TREATMENT OF OSTEOARTHRITIS

Nonsurgical treatments for osteoarthritis (OA) may be characterized as symptom-modifying or disease-modifying drugs. As defined by the Osteoarthritis Research Society (OARS), disease-modifying drugs are those that are intended to prevent, retard, stabilize, or reverse development of the morphological changes of OA[1]. At present, no pharmacological treatments for OA are approved for the indication of modifying the rate of OA disease progression. However, evaluation of novel agents and agents with established symptom-modifying activity for disease-modifying effects has become a major focus of research in musculoskeletal diseases. The orally administered supplements glucosamine and chondroitin sulfate, natural components of articular cartilage, are examples of nutritional agents which may both reduce the symptoms of pain associated with OA and have an impact on OA disease progression as measured by effects on joint-space width (JSW)[2–4].

Intra-articular (IA) hyaluronan (HA) is currently indicated only as a symptom-modifying treatment for OA of the knee. However, there is substantial evidence suggesting that HA in certain patient populations can also have disease-modifying activity. This possibility was initially suggested by the finding that the pain-relieving benefit of IA HA generally persists for considerably longer than its half-life within the injected joint, which has been estimated to be as short as 18 to 24 h in animal studies[5]. For example, clinical efficacy in randomized, controlled trials (RCTs) has been demonstrated to last for at least 26 weeks for Hyalgan®*

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*We have chosen to include the branded names, not as an endorsement or condemnation of a brand, but to offer clarity regarding clinical data, utilization, and recommendations. The members of this class can be differentiated by administered dose, dosing regimens, molecular weight, labeling and supporting clinical data. However, they share similar terminology for their generic names with the names that describe the class, and in addition some share the same generic device name. This can lead to confusion and misinterpretation, and we have felt compelled to clarify.

(sodium hyaluronate, average molecular weight [MW] 500–730 kDa)[6,7†], and may last as long as a year or more in some patients[8,9]. Similarly, Synvisc® (hylan G-F 20, average MW >6000 kDa)[10] (Genzyme Biosurgery, Cambridge, MA), Supartz® (sodium hyaluronate, average MW 630–1120 kDa)[11] (Seikagaku Corporation, Tokyo, Japan), and Orthovisc® (sodium hyaluronate, average MW 1900–3000 kDa)[12] (Anika Therapeutics, Woburn, MA) have also demonstrated months of pain relief. All of these products are approved for use in the US, although there are clear distinctions in dose, dosing regimen and labeling for repeat treatment[12–15].

Presented here is a review of preclinical and clinical evidence that HAs, in addition to relieving pain associated with OA, also may modify the rate of OA disease progression.

Methods

References reviewed were taken from MEDLINE, based on a search through June 2004, using the terms HA, sodium hyaluronate, hyaluronic acid, hylan, hylan G-F 20, OA, disease modification, structure modifying and joint structure. Papers were subjectively evaluated for inclusion based on relevance to the objectives of this review. Data reported at professional conference proceedings were also considered. Only a limited selection of nonclinical, biochemical data on HA effects in the joint were included, as a thorough review of this extensive area was beyond the scope of this article; an emphasis was placed on studies that evaluated joint structure outcomes in animal models of OA and in patients with OA. No ''data on file'' information was considered in this review.

Results

PROPERTIES OF HAs

HAs are found in synovial fluid and many other extracellular matrices, and play a major role in the pliable and resilient nature of articular cartilage[16] and for maintenance of the viscoelastic and lubricating properties of the synovial fluid[17]. The finding that HA concentration and chain length (MW) are both reduced in patients with OA of the knee[17] led to the hypothesis that decreased viscosity of the synovial fluid may cause the wear and pain associated with the disease. This formed the initial premise for the development of IA injections of HA as a fluid replacement treatment termed ''viscosupplementation'', as therapy for the treatment of pain associated with OA[18]. IA HA therapy with various products of MW greater than 500 kDa has been shown to be safe and effective in clinical trials[6,7,11,19–24] and clinical practice experience[25–28] for the relief of pain associated with OA of the knee.

Aside from the established symptomatic efficacy of exogenously administered HAs in OA, it has become increasingly clear that these molecules do more than simply lubricate and protect the joint from a biomechanical standpoint. There is now a large body of nonclinical evidence for complex effects of HAs on joint biochemistry, as well as preclinical data for all products and clinical evidence for disease-modifying activity of at least one HA product, Hyalgan (sodium hyaluronate, MW 500–730 kDa)[14].

Effects of HAs on joint biochemistry

HAs have been shown to regulate many processes in the synovial fluid, the articular cartilage, and the subchondral bone, through effects on the matrix proteoglycans, collagens, and hyaladherins in synoviocytes, chondrocytes and inflammatory cells (reviewed in Ref.[29–32]). By virtue of these complex effects, potential disease-modifying effects of exogenously administered HA include regulation of joint repair by effects on chondrocyte growth and metabolism; regulation of endogenous HA, proteoglycan and collagen synthesis; inhibition of expression and function of chondrodegrading enzymes; regulation of programmed cell death (apoptosis); and inhibition of destructive inflammatory responses (Table I). Although it is beyond the scope of this article to thoroughly review the complex biochemical activities of HA, some key examples of studies that have investigated these effects in *in vitro* and animal models of OA are discussed here or in referenced reviews.

Creamer *et al.*[33] evaluated the effects of 5 weekly IA injections of Hyalgan (sodium hyaluronate, MW 500–730 kDa) on concentrations of keratan sulfate, chondroitin sulfate, and C-propeptide of type II collagen (biochemical markers of cartilage degradation) in the synovial fluid of 12 patients with OA of the knee. Over the 6-week study period, HA produced a trend toward reduced concentrations of keratan sulfate in the treated knees, although the difference was not statistically significant, perhaps because of the small sample size or the short time course of the study. In a rabbit model of OA, IA injections of Artz® (sold as Supartz in US, sodium hyaluronate, MW 620–1170 KDa)[15] following anterior cruciate ligament transectomy (ACLT) were found to suppress synovial expression of proinflammatory cytokine IL-1β and the matrix metalloproteinase-3 (MMP-3; stromelysin), which degrades extracellular matrix components proteoglycan and type II collagen[34]. A more recent study further demonstrated that treatment of human articular cartilage explants with an 800-kDa form of sodium hyaluronate inhibited IL-1β-stimulated production of three degradative enzymes, MMP-1, MMP-3, and MMP-13, possibly through interaction between the HA and CD44 on chondrocytes[35]. Expression of these molecules in the synovial fluid and cartilage correlates with inflammatory destruction of cartilage in patients with OA[36,37]. In studies using the ACLT model in rabbits, HA injections were also shown to inhibit chondrocyte apoptosis and histomorphologically measured cartilage degradation[38,39]. A recent study using a rabbit partial meniscectomy model of OA demonstrated that injection of Orthovisc

Table I
Potential disease-modifying activities of hyaluronans

Promotion of healing and repair
Stimulation of chondrocyte growth and metabolism
Maintenance of chondrocyte vitality (decreased apoptosis)
Stimulation of synthesis of articular cartilage matrix components (e.g., collagen, proteoglycans, including endogenous hyaluronan, hyaladherins)
Inhibition of destruction
Inhibition of expression and activity of chondrodegradative enzymes (e.g., metalloproteinase)
Inhibition of matrix-destructive inflammatory processes

†Fidia SpA, Padua, Italy. Note that discussion of hyaluronans in this review is primarily limited to US-approved products.

(sodium hyaluronate, MW 2000 kDa) prevented changes in proteoglycan content[40] in the tibial condylar articular cartilage, compared to injection of vehicle.

Anti-inflammatory properties of exogenously administered HAs include inhibition of leukocyte migration, inhibition of leukocyte phagocytosis, inhibition of lymphocyte proliferation, inhibition of prostaglandin production, prevention of oxidative damage by free radicals, and inhibition of the expression of inflammatory cytokines[31]. The effects of Hyalgan (sodium hyaluronate, MW 500–730 kDa) injections on inflammatory mediators in the synovial fluid have also been demonstrated in patients with OA. In a randomized, double-blind, saline-controlled study involving 40 patients with OA of the knee, Corrado *et al.*[41] found that five IA injections significantly decreased the numbers of activated macrophages and lymphocytes in synovial fluid, compared with saline injections. Likewise, Dougados *et al.*[20] demonstrated that at 4 weeks after the last of four IA injections, patients who received Hyalgan (sodium hyaluronate, MW 500–730 kDa) had significantly less synovial effusion, indicating a lesser degree of destructive inflammation.

Any or all of the biochemical effects of HA discussed here could form the basis for modification of OA disease progression. Moreover, these activities of HA have implications for other joint disease processes that result in cartilage damage. The results of a number of preclinical studies, described in the following section, provide evidence that these or other activities of HA have the potential to modify the OA disease process.

PRECLINICAL: ANIMAL STUDIES OF JOINT STRUCTURE MODIFICATION BY HA

A number of animal models have been developed to experimentally induce changes associated with OA, such as the degradation of collagen and proteoglycans of the articular cartilage, and increased inflammation. The most commonly studied models have been total or partial meniscectomy and ACLT, and it should be noted that these models are quite aggressive in that the degenerative changes can occur within a few months after induction. Potential disease-modifying activities of exogenously added HAs have been demonstrated in several species using these approaches (Table II).

The disease-modifying effects of HA have been evaluated using a meniscectomy model in rabbits and sheep. Administration of Artz (sodium hyaluronate, MW 620–1170 kDa), after partial meniscectomy in rabbits or sheep significantly inhibited cartilage degeneration[42,43]. Five weekly IA injections of sodium hyaluronate, initiated immediately after partial or total meniscectomy, significantly enhanced collagen remodeling compared with saline treatments[44,45].

Wiig *et al.*[46] reported that a single injection of Healon® (sodium hyaluronate, MW 1900–3900 kDa) (Pharmacia & Upjohn, Uppsala, Sweden) given immediately after ACLT in rabbits significantly enhanced tissue repair, increased collagen synthesis, increased angiogenesis, and decreased inflammation compared with a single injection of saline. A course of 5 weekly injections of Artz (Supartz, sodium hyaluronate, MW 620–1170 kDa) protected chondrocytes from apoptotic cell death following ACLT in rabbits[38]. Administered to either rabbits or dogs after ACLT, Artz (Supartz, sodium hyaluronate, MW 620–1170 kDa) also reduced the degree of damage to the femoral cartilage and helped to preserve articular cartilage and synovial tissue integrity[39,47]. In a study that evaluated the effects of Synvisc (hylan G-F 20, MW $\approx$ 6000 kDa) (Biomatrix, Montreal, Canada) in a dog ACLT model, gross morphological and histological damage within joints that received injections was significantly milder than that seen in control joints[48].

Similar results were obtained in rabbits and dogs using Hyalgan (sodium hyaluronate, MW 500–730 kDa). A course of 5 weekly Hyalgan injections, starting at 4 or 13 weeks after ACLT, significantly reduced the degree of articular degeneration at evaluations 26 weeks after surgery. In this study, rabbits that received 10 injections showed less disease progression than did rabbits treated with five injections, suggesting that sequential courses of Hyalgan therapy may provide long-term benefits for altering the disease course[49]. In dogs, initiation of weekly IA injections of sodium hyaluronate starting at 3, 6, or 12 weeks after ACLT (the Pond-Nuki model of OA) significantly inhibited formation of a fibroblast-like cell layer on the articular cartilage and increased mean chondrocyte density and area in the middle and deep layer of the articular cartilage[50]. Hyalart® (sodium hyaluronate, MW 500–750 kDa)[‡] significantly reduced cartilaginous lesions when given starting at 3, 6, or 12 weeks after ACLT in dogs (Pond-Nuki model of OA)[51].

MW OF HAs AND BIOLOGICAL ACTIVITY

Initial evidence that the MW of injected HA can have a substantial impact on its biological activity was demonstrated by Smith and Ghosh[52]. They found that synthesis of HA by human synovial cell lines was increased by the addition of exogenous HA, and that a maximal effect was achieved using HA preparations with MW between 500 and approximately 4000 kDa; preparations of less than 500 kDa had no effect, and with HA preparations of 4700 kDa or more, the stimulation declined with increasing HA concentration. These investigators proposed that with exogenously added HA of MW $<$500 kDa, only weak binding of HA to cell surface HA receptors can occur; between 500 and 4000 kDa, HA binding to its receptors is optimal; at MWs $>$4000 kDa, steric hindrance by the large domains of the HA molecules prevents optimal receptor occupation.

A recent preclinical study provided further *in vitro* findings that the MW of the HA preparations used may have an influence on their potential disease-modifying effects. Ghosh *et al.*[53] reported that IA treatment of meniscectomized sheep with Hyalgan (sodium hyaluronate, MW 500–730 kDa) but not Hylartil® (sodium hyaluronate, MW 3000–6900 kDa, a veterinary product) (Pharmacia & Upjohn, Uppsala, Sweden), improved the elasticity and viscosity of synovial fluid in the experimentally induced osteoarthritic joints at 5 weeks after administration of the last of five IA injections (week 26 of the study).

For example, in another *in vitro* study, Lisignoli *et al.*[54] found that Hyalgan (sodium hyaluronate, MW 500–730 kDa), but not purified HAs with MW 40–65 kDa or 1000 kDa, exerted an inhibitory effect on anti-Fas-induced chondrocyte apoptosis. The effect was mediated by specific HA binding to surface-expressed CD44 and ICAM-1. In another *in vitro* study, a low-MW HA (200 kDa) enhanced eosinophil production of transforming growth factor, while a high-MW HA (3000–5800 kDa) had a substantially lesser impact[55].

[‡]Bayer AG, Leverkusen, Germany; sold as Hyalgan® in most of Europe and US.

Table II
Preclinical animal models of OA: disease-modifying effects of hyaluronans

Study	Species	Model	Product/Regimen	Results
Kikuchi *et al.*[42]	Rabbit	Partial meniscectomy	Artz® [Supartz®]*/IA injections 2×/week immediately after surgery vs saline	HA produced a significant inhibition of cartilage degeneration in femoral condyle and tibial plateau 2 and 4 weeks after surgery
Armstrong *et al.*[43]	Sheep	Meniscectomy	Artz® [Supartz®]/5 weekly IA injections starting at 16 weeks postsurgery	HA limited development of changes in articular cartilage and subchondral bone
Wiig *et al.*[46]	Rabbit	ACLT	Healon®†/single injection immediately after surgery vs saline	HA produced pronounced tissue repair, increased synthesis of collagen, increased angiogenesis, and decreased inflammation
Takahashi *et al.*[38]	Rabbit	ACLT	Artz®[Supartz®]/5 weekly IA injections vs starting at 4 weeks postsurgery vs saline	HA protected against chondrocyte apoptosis
Amiel *et al.*[49]	Rabbit	ACLT	Hyalgan®‡/5 weekly IA injections starting at 4 or 13 weeks postsurgery vs saline, with follow-up at 26 weeks postsurgery	Single and repeat courses of HA injections reduced the degree of articular degeneration; repeat course were best
Schiavinato *et al.*[50]	Dog	ACLT (Pond-Nuki model)	Hyalgan®/weekly IA injections vs no surgery or no HA treatment, assessed at 7 or 13 weeks postsurgery	HA inhibited formation of fibroblast-like cell layer on the articular cartilage and significantly increased mean chondrocyte density and area in middle and deep layer
Wenz *et al.*[51]	Dog	ACLT (Pond-Nuki model)	Hyalart® [Hyalgan®]/5 weekly IA injections starting at 3, 6, or 12 weeks after surgery vs saline	HA significantly reduced cartilaginous lesions
Marshall *et al.*[48]	Dog	ACLT	Synvisc®§/3 weekly IA injections, starting 1 week after surgery	HA significantly improved gross morphology and histopathology

ACLT, anterior cruciate ligament transection; HA, hyaluronan; IA, intra-articular.
*Sodium hyaluronate, MW 620–1170 kDa, Seikagaku Corp., Tokyo, Japan.
†Sodium hyaluronate, MW 1900–3900, Pharmacia & Upjohn Corp., Uppsala, Sweden.
‡Sodium hyaluronate, MW 500–730 kDa, Fidia SpA, Padua, Italy.
§Hylan G-F 20, Biomatrix, Montreal, Canada.

In contrast to studies in which HAs of intermediate MW appeared to exert greater biological activity than HAs of very low or high MW, two preclinical studies that used a rabbit ACLT model of OA found otherwise. Shimizu *et al.*[56] compared the effects of three native HAs, Hyalgan (sodium hyaluronate, MW 500–730 kDa), Artz (Supartz, sodium hyaluronate, MW 800 kDa), Healon (sodium hyaluronate, MW 3600 kDa)§, with a crosslinked form, Synvisc (hylan G-F 20, MW 6000 kDa), on gross morphology and histopathology. All of these HA forms exerted significant chondroprotective effects, but these effects were numerically superior in the groups receiving Synvisc and Healon. In a similar rabbit ACLT study, Kikuchi *et al.*[42] found that whereas both forms of tested HAs produced significant chondroprotection, a fermented HA form of 1900 kDa exerted superior protective protects compared with Artz (Supartz, sodium hyaluronate, MW 800 kDa) in some measures; for example, global femoral histopathologic scores were superior in rabbits that received the higher-MW HA form ($P < 0.05$). Similar biochemical experimental evidence for a crucial role of HA MW in its biological activity is accumulating rapidly, and is the subject of a recent in-depth review[30].

In the treatment of patients with OA of the knee, there is no substantive clinical evidence to support the notion that differences in MW (within the range of 500 to 6000 kDa) has any impact on clinical efficacy. Aviad and Houpt[57] examined this issue in a review of published HA clinical studies and concluded that there was no substantive evidence to suggest that differences in MW (within the range of approved products on the market) had any relationship to clinical efficacy. The same conclusion was reiterated in the American College of Rheumatology 2000 Treatment Guidelines for OA of the Knee[58]. However, this issue has yet to be directly explored in the context of potential disease-modifying activity.

§Pharmacia & Upjohn, Kalamazoo, MI; a form of sodium hyaluronate indicated for intraocular use.

CLINICAL STUDIES OF JOINT STRUCTURE MODIFICATION BY HAs

The OARS has made a set of recommendations for the conduct of clinical trials designed to investigate disease-modifying drugs for the treatment of OA[1]. The primary outcome of such trials should be a measure of joint structure or morphology. Imagery (e.g., radiography or magnetic resonance imagery) or direct visualization (e.g., arthroscopy) can be used. Studies that make use of surrogate markers of cartilage destruction as an outcome (such as in the study conducted by Creamer *et al.*[33]) are considered helpful but not sufficient for establishing disease-modifying activity. Trials of at least 1 year in length and, if possible, evaluation of patients at high risk for progression are considered advantageous, as disease-modifying effects may be slow-acting. For example, a review of longitudinal studies using radiographs to follow joint-space narrowing in osteoarthritic patients found the average rate of change to be approximately 0.1 mm/year[59].

Table III
Clinical studies: disease-modifying activity of hyaluronans in knee OA

Study	Design	Product/Treatment	Structural outcome parameter	Results
Listrat *et al.*[60]	Randomized, 1-year, no injection controlled ($n = 36$)	Hyalgan®/arthroscopy followed by 3 weekly IA injections every 3 months	Joint-space narrowing/ radiograph and arthroscopy	HA-treated patients showed less deterioration of joint space than did controls; difference did not achieve significance
Frizziero *et al.*[61]	Open, 6-month study ($n = 40$)	Hyalgan®/5 weekly IA injections	Microarthroscopy and morphological assessment of paired biopsy samples	HA produced significant reconstitution of superficial amorphous cartilage layer ($P = 0.0039$), improvement in chondrocyte density and vitality ($P = 0.0023$ and $P = 0.05$), and reduction in synovial inflammation ($P = 0.001$)
Pasquali Ronchetti *et al.*[62]	Randomized, open, active-controlled, 6-month study ($n = 24$)	Hyalgan®/5 weekly IA injections vs methylprednisolone/3 weekly injections	Arthroscopy with light and electron microscopy	Both treatments significantly decreased inflammatory score and edema; HA reduced number and aggregation of lining synoviocytes, methylprednisolone decreased number of mast cells ($P \leq 0.05$)
Guidolin *et al.*[63]	Randomized, open, active-controlled, 6-month study ($n = 24$)	Hyalgan®/5 weekly IA injections vs methylprednisolone/3 weekly injections	Analysis of paired cartilage biopsies by electron microscopy	HA produced significant reconstitution of superficial layer, improved chondrocyte density and metabolism
Jubb *et al.*[65]	Multicenter, randomized, placebo-controlled, double-blind 1-year study ($n = 319$)	Hyalgan®/3 courses of 3 weekly IA injections vs saline	Change in joint space measured by digital image analysis of weight-bearing radiographs	HA reduced progression of joint-space narrowing in patients with greater joint-space width at entry ($P = 0.02$)

HA, hyaluronan; IA, intra-articular. Hyalgan® [Hyalart®] (sodium hyaluronate, MW 500–730 kDa), Fidia SpA, Padua, Italy.

However, the rate of joint space loss may not be linear throughout all stages of OA.

Recently results have become available from a number of clinical studies that evaluated disease-modifying effects of Hyalgan (sodium hyaluronate, MW 500–730 kDa). Each of the studies described here used joint structure (assessed via arthroscopy or radiographs) or morphology as the outcome parameter, and several were carried out over at least a 1-year period (Table III).

Arthroscopic and histomorphometric analysis

In a randomized, blinded, clinical trial carried out by Listrat *et al.*[60], a total of 39 patients with OA of the knee and chondropathy underwent a baseline arthroscopic examination and were then treated with three cycles of 3 weekly IA injections of Hyalgan (sodium hyaluronate, MW 500–730 kDa) or 3 weekly saline injections, at 4-month intervals. A follow-up arthroscopic examination was performed at the end of the 1-year study. Recorded videos of the baseline and end-of-study arthroscopic examinations were scored by blinded arthroscopists using a validated scoring system of chondropathy (SFA) as the primary outcome measure. This 1-year outcome measure is consistent with those advocated by the OARS guidelines; both blinded arthroscopy and radiography were evaluated. The results demonstrated that patients who received sodium hyaluronate had significantly less progression of chondropathy (visual analog scale [VAS] score of chondropathy, $P = 0.016$; SFA score, $P = 0.05$) and a trend toward less joint-space narrowing (not statistically significant due to small patient numbers), than did patients who were treated with saline injections. In addition, even though the primary outcome measure was progression of chondropathy, the secondary outcome of clinical improvement based upon the Arthritis Impact Measurement Scale (AIMS) was significantly better for the sodium hyaluronate treatment group ($P < 0.05$) at 1 year. There was also a two-fold less usage of rescue medication (paracetamol) by the HA group, and a statistically significant reduced usage of NSAIDs ($P = 0.016$).

An open-label study involving 40 patients with OA of the knee was carried out to evaluate the effects of 5 weekly injections of Hyalgan (sodium hyaluronate, MW 500–730 kDa) on synovial membrane and cartilage structure[61]. Outcomes were measured 6 months after initiation of treatment. Microarthroscopic assessment, a visualization process that allows magnifications of up to 150 times the normal arthroscopic field, showed that 60% of patients exhibited no progression and 32.5% of patients exhibited improvement compared with baseline. Only 7.5% of patients evaluated showed a worsened condition. Evaluation of cartilage biopsy samples indicated a statistically significant reconstitution of the superficial amorphous layer of the cartilage ($P = 0.0039$), an anatomical feature widely applied in assessment of clinical condition in OA[61], improved chondrocyte density in cartilage biopsies ($P = 0.0023$) and vitality (a measure of chondrocyte metabolic activity) ($P = 0.05$), and reduction in synovial inflammation ($P = 0.0001$).

A randomized, open-label study conducted in 99 patients with either primary or secondary OA of the knee compared the effects of five IA injections of Hyalgan (sodium hyaluronate, MW 500–730 kDa) with those of three injections of methylprednisolone acetate[62]. The primary outcome of this study, evaluated 6 months from the start of treatment, was alteration in synovial membrane histopathology, assessed using electron microscopic evaluation of cartilage biopsies. Both active treatments significantly decreased inflammation and produced favorable

modifications in several structural aspects of the synovial membrane. Edema was decreased, and the amount of collagen present in the membranes was increased. Sodium hyaluronate, but not methylprednisolone, also significantly reduced the numbers of synoviocytes aggregating on the synovial membrane, whereas methylprednisolone significantly decreased the numbers of mast cells present. When cartilage biopsies were taken from a subset of 24 patients with primary OA, results indicated that sodium hyaluronate significantly improved chondrocyte density ($P = 0.002$ and 0.049 for zones I and II, respectively) and overall matrix appearance ($P = 0.02$), compared with methylprednisolone treatment. Chondrocyte metabolism in HA-treated subjects was also significantly improved, as evidenced by increased extension of synthetic structures and mitochondria[63].

A second report described results of arthroscopic and efficacy evaluations of the 30 HA-treated and 25 methylprednisolone-treated patients from the same study[64]. At the 6-month follow-up, a statistically significant difference in favor of HA was achieved for the reduction in lesion extent in the medial tibial plateau ($P < 0.03$) and in lesion grade in the patellar compartment ($P < 0.02$), but not for patients in the methylprednisolone group. There was a tendency for better improvement in the HA group for all other compartments as well, which did not achieve statistical significance. Structural differences between the two treatment groups were also maintained when evaluating patients with primary OA separately. Although initially methylprednisolone produced a more immediate pain reduction effect measured using VAS (evaluated at day 35 after treatment), the symptomatic effect of HA appeared to be longer-lasting based on VAS measurements at the 6-month follow-up. The somewhat delayed, long-lasting, and pain-reducing effect of HA as compared with methylprednisolone could reflect the longer-term mechanisms of action that relate to an impact on disease progression.

Radiography and JSW analysis

Because of the encouraging effects observed in these small studies, a multicenter, double-blind, randomized study involving 408 patients with OA of the knee was carried out recently to assess the disease-modifying effects of Hyalgan (sodium hyaluronate, MW 500–730 kDa)[65]. The primary outcome parameter was the difference in JSW over 1 year, measured using digital image analysis of standard weight-bearing radiographs. Patients received three courses of 3 weekly IA injections of sodium hyaluronate or placebo (saline) every 4 months, and were assessed at 1 year after initiation of the treatment. A total of 319 patients completed the 1-year study, but only 273 patients had paired evaluable radiographs at baseline and at the 1-year follow-up based upon prospective quality standards and that were assessed by blinded radiologists. Prospectively, the patient population (paired evaluable radiographs) was divided into subpopulations for subsequent statistical analysis based upon a mean JSW above the mean (less severe OA) and those below the mean JSW (more severe OA), and an analysis of covariance of these 273 patients demonstrated that the response to treatment was indeed a function of the baseline JSW. The study further demonstrated that sodium hyaluronate treatment, compared with placebo, significantly reduced progression of loss of JSW in the subset of patients who had higher joint-space area at study entry (>4.6 mm); the HA group exhibited a mean loss of -0.13 mm, whereas the placebo group showed a mean loss of -0.55 mm ($P = 0.021$). There was no statistical difference between treatment groups when comparing the change in JSW in the patients with more severe OA based upon less JSW at entry (<4.6 mm). Although all patients were allowed to maintain their standard analgesic medications (paracetamol, NSAIDs, etc.), the study also demonstrated statistically significant incremental benefits of pain relief (beyond oral analgesic use) compared with the control group at 2–4 months following each course of Hyalgan (sodium hyaluronate, MW 500–730 kDa) injections.

Discussion

Taken together, available clinical trial results form a solid body of evidence in support of the ability of the one sodium hyaluronate product evaluated in patients to modify OA disease progression, and are consistent with a large body of preclinical data demonstrating equivalent benefits in animal models for a number of HA products. Note that these clinical studies made use of the OARS recommended guidelines for the design of studies intended to demonstrate disease modification: the primary outcomes were based on prospective evaluations of either imaged or directly visualized measures of joint structure and morphology; in half of the studies, outcomes were evaluated at the 1-year timepoint (recommended duration)[60,65]. One important issue that requires further information is the possible impact of HA MW on disease-modifying activities. Current animal data suggest that MW may be an important consideration, but clinical data supporting disease modification are essentially limited to one HA product at present. Comparative trials evaluating structural outcomes of treatment with HA products of different size and manufacture are needed to further investigate this issue.

The presumed underlying basis for disease-modifying activity of HAs—which could include effects on synoviocyte and chondrocyte function, cartilage degradation, endogenous HA synthesis, and inflammatory processes—may also have important implications for therapeutic areas other than OA. These include the use of HAs in related degradative joint diseases such as chondromalacia, trauma injuries, post-arthroscopy and post-surgical recovery, and for wound healing. As an example, a recent study reported on the beneficial effects of sodium hyaluronate administered post-arthroscopy or after open-knee joint procedures[66]. HA mitigated inflammation, provided pain relief (assessed by VAS), and enhanced range of motion. Other pilot studies have also demonstrated benefit of HA therapy in improving function and/or reducing pain in patients following knee immobilization[67] or acute knee injury[68], and in the treatment of inflammatory arthropathies[69]. Definitive RCTs in each of these indications are currently in progress.

The search for disease-modifying agents to treat OA has become a priority in the field of orthopedics. The nutritional supplements glucosamine and chondroitin sulfate are promising oral agents under evaluation. IA HAs have been shown to be safe and efficacious for treatment of pain of OA of the knee; preliminary work supports HA use for OA pain relief in other joints as well. Based on preclinical data, there is evidence to support the notion that all the approved HAs in the US may have some disease-modifying properties. Growing clinical evidence also indicates that Hyalgan (sodium hyaluronate, MW 500–730 kDa) may alter the progression of OA. It would be of interest to see if similar clinical benefits can also be demonstrated with other HAs. The possible underlying disease-modifying mechanisms of action of HA, such as stimulation of chondrocyte growth and

metabolism, inhibition of chondrodegradation, inhibition of chondrocyte apoptosis, and suppression of destructive inflammation, in conjunction with the unique physiochemical properties of HA, may also allow applications to other orthopedic therapeutic uses, such as post-arthroscopy therapy, wound healing, and generation of synthetic matrices for use in reconstructive surgery. Work is ongoing in these areas.

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