Hyaluronans: Is Clinical Effectiveness Dependent on Molecular Weight?

Peter C. Vitanzo, Jr, MD, and Brian J. Sennett, MD

Abstract
The original rationale for viscosupplementation with hyaluronans was fluid replacement, suggesting that the most viscous materials (eg, those of highest molecular weight [MW]) would provide the most clinical benefits. However, it has become clear that mechanisms of action for osteoarthritis pain management are not only mechanical but also biological. After intra-articular injection, hyaluronans exert a range of biological actions within the joint. Although high- and low- to mid-MW hyaluronans (but not hyaluronans <500 kDa MW) are more or less active (depending on the specific effect examined), it is not known which actions are clinically meaningful. There is no evidence for a difference between hyaluronan products in clinical efficacy measured as pain relief, but investigators in several preclinical studies evaluating joint-structure modification in osteoarthritis models have reported advantages to using low- to mid-MW hyaluronans.

Hyaluronan intra-articular injections are effective and well tolerated for the treatment of osteoarthritis of the knee in patients who either do not respond adequately to conventional therapy or who are intolerant of nonsteroidal anti-inflammatory drugs. Patients with osteoarthritis tend to have a reduced concentration and lower mean molecular weight (MW) of hyaluronan in their synovial fluid, which led to the idea that joint fluid replacement (viscosupplementation) with exogenous hyaluronan would be beneficial. This hypothesis pre-dates discovery of both endogenous hyaladherins (now known to be responsible for natural cross-linking of hyaluronans in synovial fluid and extracellular cartilage matrix) and hyaluronan cell-surface receptors.

It has been reported that elastoviscosity and joint retention of exogenous hyaluronan increase with MW. This finding led to the proposal that duration of clinical benefit was proportional to MW on the basis of increased viscosity (mechanical and lubrication function), duration of residence in the joint, and stimulation of endogenous hyaluronan by high-MW hyaluronans. However, results of preclinical studies, in which hyaluronans of differing MWs have been compared, suggest that beneficial effects on pathogenesis and progression of osteoarthritis are seen across the range of MWs of available compounds (Table I), with some researchers finding higher levels of apparent efficacy with low- to mid-MW compounds.

CD44, a membrane-bound glycoprotein, is one of several identified hyaluronan-binding receptors seemingly involved in regulating hyaluronan synthesis and other biological activities associated with hyaluronan. Regulation of hyaluronan expression and function is complex. Three related genes of the hyaluronan synthase gene family are differentially regulated and synthesize hyaluronans of mean MW of 200 kDa or 2000 kDa. Nascent hyaluronans are bound together in the extracellular fluid by a family of hyaluronan-binding proteins termed hyaladherins, increasing their MW and resultant viscosity. Each hyaluronan molecule may have as many as 200 hyaladherin molecules associated with each chain.

Prospective, controlled, and comparative studies have yielded no consistent evidence supporting the premise that increases in MW or viscosity are associated with increases in clinical benefit.
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in clinical efficacy, as shown by outcomes such as pain relief. Data from recent clinical studies carried out in patients receiving a low- to mid-MW product have suggested that intra-articular hyaluronan therapy has disease-modifying activity and may alter progression of osteoarthritis.21-25 These issues are discussed in more detail later in this review.

PROPOSED MECHANISMS OF ACTION OF HYALURONAN

Hyaluronans are responsible for elastoviscosity of synovial fluid in joints, and elastoviscosity is higher with high-MW hyaluronans. This elastoviscosity is shear-dependent, meaning that the mechanical behavior of hyaluronan changes with the shear force applied and the speed of flow: Hyaluronan solutions behave as viscous fluids when external forces move them at low speeds but behave as elastic bodies when subjected to high rates of shear or frequency. Therefore, hyaluronans are effective as lubricants under conditions of slow movement but are effective as shock absorbers when movement is rapid.4

Clearly, this elastoviscous behavior will determine clinical activity to a large extent, but the pharmacokinetic profile of hyaluronans does not support a purely mechanical role for these substances. During movement, hyaluronan flows into the lymphatic system of the joint capsule, moves into the general circulation, and is ultimately taken up by the liver, where it is degraded to water and carbon dioxide.26 Duration of the therapeutic effect of hyaluronan, as noted in clinical studies, is also not consistent with a purely mechanical role, as treatment benefits can persist for several months after a course of injections is completed, whereas the elimination half-life of hyaluronan in the joint is measured in hours to days.27,28

"...the pharmacokinetic profile of hyaluronans does not support a purely mechanical role for these substances."

Of additional interest is the reported increase in the elastoviscous properties of synovial fluid after exogenous administration of hyaluronic acid. Mensitieri and Ambrosio29 examined synovial fluid from the knee joints of patients subjected to arthrocentesis or treatment with hyaluronan compounds of MWs ranging from 500 kDa to 730 kDa. The elastoviscosity of synovial fluid from patients who received hyaluronan was increased relative to pretreatment values, as well as to values in patients who had undergone arthrocentesis. This increase in elastoviscosity was present 1 week after administration, well after the exogenous product would have been expected to have been cleared from the joint space, suggesting that the elastoviscosity of knee synovial fluid benefits from increases in both hyaluronic acid concentration and MW.

Other potential pharmacologic mechanisms may be receptor-mediated. These mechanisms include inhibition of inflammatory mediators, inhibition of phagocytic cell function, stimulation of cartilage matrix synthesis, and decreased degradation of cartilage matrix.17,30-39

These and other potential mechanisms, and their association with MW, investigated primarily in vitro, are summarized in Table II.17,30-39 Results from in vitro evaluation of the biological actions of hyaluronans show that both high- and low- to mid-MW hyaluronans are more or less active depending on the specific effect examined. For example, mid-MW hyaluronans (500–999 kDa) appear to inhibit apoptosis more,35 offer more protection against cartilage loss,17 and suppress synovial cell proliferation more,11,17 whereas high-MW hyaluronans are more effective in inhibiting prostaglandin E2 and arachidonic acid activities.37,38 Both agents are similar with regard to effects on leukocyte chemotaxis.30 Although an “ideal” MW range should be related to the biological profile that will optimize clinical benefit for the patient, it is not well understood which of these actions are most meaningful regarding clinical benefits, such as pain relief or potential structure (disease) modification. Potential disease-modifying activities demonstrated in animal models of osteoarthritis (Table I) may provide a more meaningful picture of the benefit of low- to mid-MW hyaluronans. Even in this case, however, the activity may be distinct from the outcome of pain relief. In a review, Ghosh and Guidolin18 concluded that, based on overall preclinical and clinical data, low- to mid-MW hyaluronans used clinically for osteoarthritis may indeed have a more beneficial structure- or disease-modifying profile.

RELATIONSHIPS BETWEEN MOLECULAR WEIGHT OF HYALURONAN AND EFFICACY

In the United States, hyaluronan products marketed for treatment of osteoarthritis of the knee include Hyalgan (sodium hyaluronate; sanofi-aventis, Bridgewater, NJ), Synvisc (hylan G-F 20; Genzyme Corporation, Cambridge, Mass), Supartz (sodium hyaluronate; Smith & Nephew, Memphis, Tenn), Euflexxa (sodium hyaluronate; Ferring Pharmaceuticals, Suffern, NY), and Orthovisc (high-MW hyaluronan; DePuy Mitek, Raynham, Mass). Characteristics of these preparations are summarized in Table III.

Molecular Weight and Half-Life

Exogenous hyaluronan begins to leave the joint within 2 hours of injection, though some remains up to 3 days (this is particularly true of high-MW products). Synvisc remains up to 3 days,40 whereas Hyalgan,41 Supartz,42 Euflexxa,43 and Orthovisc44 remain less than 24 hours. Although the high-MW hylan B in Synvisc has a half-life of some weeks,26 it is biologically inert (not in solution to engage receptors). Results from a study involving 131I-radiolabeling showed that hyaluronan is eliminated from the human
knee joint in 3 distinct phases (half-lives of 1.5 hours, 1.5 days, and 4 weeks) fitting a 3-exponent function. In this study, conducted with a high-MW-nonanimal stabilized hyaluronic acid product (NASHA), it was suggested that the rapid initial phase was linked to elimination of low-MW fragments and the second phase to elimination of high-MW labeled hyaluronan. During the slow third phase, the daily decline in radioactivity was comparable to that in the urine, indicating a slow release of hyaluronan or degradation products from the gel in the knee and subsequent excretion by the kidneys. The possibility of uptake of NASHA and its products by the synovial layer and popliteal lymph nodes was also postulated. Results from another study showed increased clearance of hyaluronan with osteoarthritis but no increase in normal joints. The elimination half-life of hyaluronan increased to 23.5 hours as osteoarthritis developed but fell to 17.4 hours by the time the disease was fully established.

Molecular Weight and Tissue Penetration

The discrepancy between retention in the joint and duration of clinical effect may be attributable, at least in part, to enhanced penetration of low- to mid-MW hyaluronans into the extracellular matrices of the synovial tissues and per-

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### Table I. Preclinical Studies of Intra-Articular Hyaluronan (HA) Preparations in Animal Models of Osteoarthritis (OA)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>OA Induction Method and Subsequent Therapy</th>
<th>HA Origin (MW)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asari et al11</td>
<td>Beagle</td>
<td>ACLT, then HA x 5 wk (starting 4 wk PO)</td>
<td>Seikagaku (840 kDa or 2300 kDa)</td>
<td>Pathology ↓ significantly more with 840 kDa than with 2300 kDa. Synovial penetration of 840 kDa &gt; 2300 kDa</td>
</tr>
<tr>
<td>Ghosh et al12</td>
<td>Sheep</td>
<td>UTMM, then HA or saline x 5 wk (starting 4 mo PO)</td>
<td>Seikagaku (840 kDa); Nippon Roussel (2000 kDa)</td>
<td>Loading of operated joints ↑ and radiologic scores ↓ with HAs vs saline. Histologic scores for MTPC worse with 2000 kDa</td>
</tr>
<tr>
<td>Ghosh et al13</td>
<td>Sheep</td>
<td>UTMM, then HA or saline x 5 wk (starting 4 mo PO)</td>
<td>Seikagaku (840 kDa); Nippon Roussel (2000 kDa)</td>
<td>PG synthesis in MTPC of operated joints ↓ with HA vs placebo, but PG release ↑</td>
</tr>
<tr>
<td>Adam14</td>
<td>Sheep</td>
<td>TBLM, then HA or saline x 5 wk (starting 4 mo PO and after SF aspiration)</td>
<td>Seikagaku (840 kDa or 2300 kDa)</td>
<td>SF HA MW (determined by multiangle laser light-scattering photometry) ↑ at 5 wk PO with both HAs, but mean ↑ with 840 kDa &gt; 2300 kDa</td>
</tr>
<tr>
<td>Ghosh et al15</td>
<td>Female sheep</td>
<td>TBLM, then HA or saline x 5 wk (starting 4 mo PO and after SF aspiration)</td>
<td>Fidia (500–730 kDa); Pharmacia-Upjohn (3000–6900 kDa)</td>
<td>SF storage modulus and viscosity at 5 wk PO ↑ vs saline with both HAs. Improvement with 500–730 kDa &gt; 3000–6900 kDa</td>
</tr>
<tr>
<td>Yoshimi et al16</td>
<td>Rabbit</td>
<td>ACLT, then single-dose HA or saline</td>
<td>Hikari (200 kDa or 950 kDa)</td>
<td>Both HAs protected against histologic cartilage loss. Nonsignificant trend toward greater efficacy with 2020 kDa</td>
</tr>
<tr>
<td>Kikuchi et al7</td>
<td>Rabbit</td>
<td>PM, then HA or saline immediately PO 2w/wk x 2–4 wk</td>
<td>Seikagaku (840 kDa or 1900 kDa)</td>
<td>Cartilage histology suggested greater protection with 840 kDa than with 1000 kDa or saline</td>
</tr>
<tr>
<td>Shimizu et al17</td>
<td>Rabbit</td>
<td>ACLT, then HA x 5 wk (starting 4 wk PO)</td>
<td>Fidia (500 kDa); Seikagaku (840 kDa); Pharmacia (3600 kDa); Biomatrix (6000 kDa)</td>
<td>Protective effect in cartilage and synovium; higher MW &gt; MW 500–730 kDa. Suppression of synovial cell proliferation: 840 kDa &gt; larger HAs.</td>
</tr>
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</table>

*Investigations shown are those in which HAs with differing MWs were compared directly. Compounds were administered intra-articularly in all studies. MW indicates molecular weight; ACLT, anterior cruciate ligament transection; PO, postoperatively; UTMM, unilateral total medial meniscectomy; MTPC, medial tibial plateau cartilages; PG, proteoglycan; TBLM, total bilateral lateral meniscectomy; SF, synovial fluid; PM, partial meniscectomy.
haps the cartilage. There is some evidence—from a canine osteoarthritis model evaluating increased expression of prostaglandin E2, thickening of synovial lining layers, and vacuolar changes in lining cells, together with fluorescein staining of hyaluronan—that low- to mid-MW hyaluronans (ie, 840 kDa) penetrate diseased tissues more effectively than high-MW hyaluronans (ie, 2300 kDa). Pathologic changes suggested more accessibility of synovial tissues to the 840-kDa product.11 However, there remains no direct evidence that this phenomenon correlates with or explains a clinical benefit.

**Molecular Weight and Elastoviscosity**

Increasing the mean MW of hyaluronan clearly increases the elastoviscous properties of the solution.4 Although this result would be advantageous if the mechanism of pain relief were only mechanical, it seems counterintuitive when biological mechanisms are involved. It does not follow that cellular activation of the precisely regulated hyaluronans and other associated pathways would occur in response to a higher concentration and higher than normal MW of hyaluronan in the knee. Within the cartilage matrix, structural properties of the extracellular matrix are determined by aggregates of endogenous hyaluronan and proteoglycans that include aggregan and link proteins.47 Hyaluronan MW seems to be determined by the binding of elongating nascent hyaluronan to a receptor. Saturation of these receptors may stall elongation of the nascent hyalu-

<table>
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<th>Table II. Molecular Weight and Effect* on Biological Activity of Hyaluronan</th>
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<tr>
<td><strong>Biological Activity</strong></td>
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<tr>
<td>In vitro data</td>
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<tr>
<td>Inhibition of leukocyte chemotaxis30</td>
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<tr>
<td>Inhibition of phagocytosis30</td>
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<tr>
<td>Inhibition of lymphocyte proliferation31</td>
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<tr>
<td>Oxygen-derived free radical scavenging32</td>
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<tr>
<td>Enzymatic cartilage degradation33,34</td>
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<tr>
<td>Inhibition of apoptosis35</td>
</tr>
<tr>
<td>Stimulation of endogenous hyaluronan production36</td>
</tr>
<tr>
<td>Inhibition of prostaglandin E2 and arachidonic acid activities37,38</td>
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<tr>
<td><strong>In vivo animal studies</strong></td>
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<tr>
<td>Analgesia39</td>
</tr>
<tr>
<td>Protection against cartilage loss11,17</td>
</tr>
<tr>
<td>Suppression of synovial cell proliferation11,17</td>
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</tbody>
</table>

*Minus sign (–) indicates no significant effect; plus sign (+), mild effect; ++, moderate effect; ++++, marked effect; NT, not tested.

†Smith and Ghosh36 found that maximal stimulation of hyaluronan synthesis of human synovial cells was achieved using preparations of MW 500 kDa to approximately 4000 kDa; preparations of MW less than 500 kDa had no effect; with preparations of MW 4700 kDa or more, stimulation declined with increasing HA concentration.

††The 2 studies showed marked differences. Protection against cartilage loss was only mild with the 500-kDa hyaluronate or the 3600-kDa hyaluronate but was marked with the 800-kDa hyaluronate in the study by Shimizu and colleagues.17

In the study by Asari and colleagues,11 protection against cartilage loss was moderate with the 800-kDa hyaluronate but was marked with the 1900-kDa hyaluronate.

<table>
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<tr>
<th>Table III. Details of Hyaluronans Commercially Available in the United States</th>
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<tbody>
<tr>
<td><strong>Compound</strong></td>
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<tr>
<td><strong>Generic name</strong></td>
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<tr>
<td><strong>Manufacturer</strong></td>
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<tr>
<td><strong>Molecular weight (kDa)</strong></td>
</tr>
</tbody>
</table>

Figure. In vitro synthesis of hyaluronan by synovial fibroblasts is influenced by concentration and molecular weight (MW) of exogenous hyaluronan (HA). The signal for synthesis is provided by HA in the MW range of 500 to 4000 kDa in a concentration-dependent manner. Figure adapted with permission from Smith MM, Ghosh P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. Rheumatol Int. 1987;7:113-122
Molecular Weight and Receptor Binding

It is thought that hyaluronan concentration is monitored by synovial fibroblasts and that homeostasis is maintained through specific cell-surface receptors. These receptors have also been shown in vitro to be activated by exogenous hyaluronan, with maximal responses being elicited by exogenous hyaluronans of certain size ranges. In one study, investigators found the most marked response by synovial fibroblasts from an osteoarthritic joint exposed to hyaluronan of MW >500 kDa, whereas smaller molecules had little or no effect. The investigators also found that a high-MW hyaluronan (4700 kDa) was less effective in stimulating synthesis than a compound of MW 3800 kDa. They thought this finding indicates that synovial fibroblasts do not increase synthesis of endogenous hyaluronans in the presence of functionally acceptable (ie, very high MW or high concentration) hyaluronans.

Study results have shown that hyaluronan binding at the cell surface is a complex interplay of multivalent binding events affected by the size of the multivalent hyaluronan ligand, the density of cell-surface CD44, and the CD44 activation state. The most significant feature distinguishing CD44 from other hyaluronan-binding proteins is that, with CD44, binding to hyaluronan takes place at the cell surface, where multiple, closely arrayed CD44 receptor molecules interact with the highly multivalent repeating disaccharide chain of hyaluronan. The actual affinity of a single CD44–hyaluronan binding domain for hyaluronan is likely to be very low. Thus, binding of a CD44-positive cell to a soluble hyaluronan molecule must involve multiple weak receptor–ligand interactions, dependent on the relative valency of the native hyaluronan molecule. In high-MW hyaluronan polymers, each molecule interacts with more than one receptor-binding site, and this increases the likelihood that the molecule will remain bound to the receptor, thereby increasing the receptor affinity (avidity) of the molecule. Beyond a certain limit, however, very large hyaluronan molecules will be less efficient in engaging multiple receptors because of steric hindrance—hence the bimodal nature of many biological activities. This suggests that the maximal response would be produced by hyaluronans within a specific size range (neither too big nor too small). The existence of isoforms of the hyaluronan receptors may also contribute to differential binding. However, these ideas remain speculative at this time, and the exact mechanism of receptor binding is not known. Either the response may be proportional to the number of receptors bound, or it may be an “all-or-nothing” phenomenon that depends on the simultaneous binding of 2 or more receptors.

In addition, biological activation is also balanced with “bioavailability,” the ability to penetrate into diseased tissues. Again, larger hyaluronan molecules may be less efficient in penetrating into the synovium (see Figure).

Clinical Efficacy

There have been several reviews on the clinical efficacy of intra-articular hyaluronans in the treatment of pain associated with osteoarthritis—including, most recently, publication by the Cochrane Collaboration of the most comprehensive meta-analysis of this class. However, there have been no reports of any well-controlled, randomized clinical studies directly comparing hyaluronans across a wide range of MWs (500–6000 kDa). Several clinical studies have compared 2 or more hyaluronans of differing MWs. Wobig and colleagues reported on a study that was said to compare hylan G-F 20 (MW >=6000 kDa) with sodium hyaluronate (MW = 800 kDa) and find the high-MW hyaluronan superior. However, it was subsequently noted that the original study was a 4-arm trial that also included another sodium hyaluronate (MW = 2300 kDa) and a control group of a degraded, nonelastoviscous hylan G-F 20 preparation. In the total analysis, it was shown that none of the hyaluronans was statistically different from the control group. A retrospective clinical practice report compared hylan G-F 20 with sodium hyaluronate (MW = 615 kDa) and found that, for both products, all patients reported a statistical improvement in pain after treatment. The report further suggested that, compared with sodium hyaluronate, hylan G-F 20 had a superior response in many parameters. However, it was subsequently reported that significant limits in the scope and design of the study called its conclusions into question.

Three recent prospective studies from clinical practice also compared the clinical efficacy of hylan G-F 20 (MW =6000 kDa) with that of sodium hyaluronate (MW 500–730 kDa): Brown and colleagues (N = 54) reported no evidence for a benefit of either product over the other, and Garcia (N = 51) and Richardson and colleagues (N = 90) reported in 2 separate studies that the short-term efficacy of hylan G-F 20 (MW = 6000 kDa) and sodium hyaluronate (MW 500–730 kDa) could not be distinguished. However, all 3 reports documented a product-specific pseudoeptive reaction to hylan G-F 20—also termed severe acute inflammatory reaction (SAIR). None of these studies reported any SAIRs to the sodium hyaluronate injections. Incidence of SAIRs in these reports ranged from 5.3% to 20.7% of the patients injected. Similarly, Hamburger and colleagues reported that in clinical practice study of 171 patients, 5 weekly injections of sodium hyaluronate (MW 500–730 kDa) had a mean duration of benefit of 447 days, whereas 3 weekly injections of hylan G-F 20 had a mean duration of 370 days (P = .018 in favor of sodium hyaluronate). Furthermore, incidence of SAIRs was 16.3% with hylan G-F 20 versus 0% for sodium hyaluronate (P<.0001).
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Karlsson and colleagues recently reported on a multi-center, randomized, saline-controlled study comparing the clinical efficacy of hylan G-F 20 (MW ≈ 6000 kDa) or sodium hyaluronate (MW ≈ 890 kDa) with that of an intra-articular saline control. Patients with knee osteoarthritis treated with injection of hyaluronan or saline showed clinical improvement during the first 26 weeks of treatment, though neither hyaluronan preparation demonstrated any significant difference from the saline control. Collectively, the limited clinical trial evidence suggests that there is no definitive difference in efficacy (symptomatic relief) between hyaluronans ranging in MW from 500 kDa to 6000 kDa, though there seem to be clear differences in safety profiles and other clinically relevant benefits (eg, disease-modifying) in several studies.

Kirschner and Marshall compared the safety and effectiveness of sodium hyaluronate (MW 2400-3600—kDa) prepared by biological fermentation with those of avian-derived hyaluronan (hylan G-F 20 (MW ≈ 6000 kDa)). The effectiveness was not inferior and there was a significantly higher incidence of post-injection effusions in hylan G-F 20.54

This conclusion was reiterated in the American College of Rheumatology 2000 treatment guidelines, in which it was recommended that intra-articular hyaluronan therapy be considered a possible therapy for knee osteoarthritis: “To date, differences in clinical efficacy between these preparations [Hyalgan and Synvisc] as a function of molecular weight have not been demonstrated.” In agreement, the Cochrane meta-analysis concluded that no evidence would lead one to conclude that hyaluronan products differ in pain-relieving efficacy, though it was acknowledged that few well-designed, head-to-head studies have been conducted.55

**RELATIONSHIP BETWEEN MOLECULAR WEIGHT AND TOLERABILITY**

As a class, the hyaluronans have a well-documented tolerability profile, with no known systemic effects and few contraindications or drug interactions. The most common side effect noted in most clinical studies has been injection-site pain. Although any intra-articular injection can elicit an inflammatory response, a clinically distinct reaction known as pseudosesis or SAIRs has emerged after hyaluronan injections. Although it is not clear whether pseudoseptic reactions can occur with any hyaluronan, all published reports to date have been linked to hylan G-F 20 (Synvisc). Whereas the manufacturing practices for all hyaluronan products have similar quantitative specifications for the amount of allowable proteins within the products (general-ly <0.1%), qualitatively the protein contaminants in hylan G-F 20 that have been exposed to potential cross-linking by formaldehyde and vinylsulfone have been shown to be immunologically distinct.67-69 Indeed, cross-linking is known to enhance or modify the immunogenicity of antigens, and rabbit studies have demonstrated an inflammatory reaction to hylan but not to sodium hyaluronate preparations after injection into the joint space.70 Interestingly, there have been several case reports of patients having a SAIR to hylan G-F 20 and subsequently being treated with sodium hyaluronate with good clinical results and without further sequelae,71 adding further support for a hylan G-F 20–specific reaction.

Antibodies to hylan have been noted in the sera of some patients.71 In addition, the immunologic response may progress to more serious conditions such as granulomatous reactions. Cases of hylan G-F 20–related granulomatous reactions have been reported in patients who had knee osteoarthritis treated with intra-articular injections of this agent.71 The reactions take the form of chronic inflammation of the perisynovial area and surrounding tissues and are shown by histologic evaluation to include histiocyte and foreign body giant cells. A recent report also characterized this response as a pseudosarcoma.72 A recent animal study comparing the biocompatibility of sodium hyaluronate and saline with hylan G-F 20 has confirmed these clinical observations.73 After intradermal injection in guinea pigs and intramuscular injection in rabbits, hylan G-F 20 induced definitive macroscopic changes in guinea pigs by day 14 and in rabbits by day 28. Severe granulomatous inflammation in guinea pigs and acute inflammation with minimal infiltration of macrophages and foreign body giant cells in rabbits were seen on histologic assessment. Furthermore, specific antibodies against hylan G-F 20 were demonstrated in guinea pigs by passive cutaneous anaphylaxis, and substantial deposits of immunoglobulin G on hylan G-F 20 were evident by immunohistochemistry.73

**CONCLUSIONS**

Data on intra-articular hyaluronan therapy for osteoarthritis—pain—which have been accumulating for almost 2 decades—have shown that the original (1980s) hypothesis of a link between hyaluronan MW and duration of efficacy is not borne out by preclinical and clinical evidence. It is instead likely that the mechanism of action of hyaluronan is based on several probable biological activities mediated through receptor-based pharmacologic mechanisms that go beyond the physical, mechanical, and elastoviscous properties of these products.

Current evidence suggests that there is an optimal MW range for induction of various biological activities. In primarily in vitro analyses, some of these activities are induced more effectively by high-MW hyaluronans, whereas others are induced by low- to mid-MW hyaluronans. In contrast, preclinical studies evaluating joint-structure outcomes in animal models of osteoarthritis indicate that low- to mid-MW hyaluronans may have more potential for disease modification. There is no solid evidence for a difference between hyaluronan products in clinical efficacy as indicated by pain reduction. However, additional head-to-head studies should be considered to firmly establish any possible benefits in terms of efficacy between products of differing MWs, particularly in distinct patient populations. It would be particularly important also to evaluate any differences with regard to a potential impact on osteoarthritis.
disease progression, which has been described for low- to mid-MW sodium hyaluronate (500–730 kDa). When risk–benefit assessment is used in making treatment decisions, lack of evidence for a superior clinical benefit from use of high-MW hyaluronans versus low- to mid-MW hyaluronans should be considered together with the finding that cross-linked polymer products may be associated with increased risk of adverse events in the knee, specifically SAIRs and granulomas.

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**References**

8. Armstrong S, Read R, Ghosh P. The effects of intrarticular hyaluronan on cartilage and subchondral bone changes in an ovine model of early osteoarthri-

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