REVIEW ARTICLE

Drug Safety 2000 Aug; 23 (2):115-130
0114-5916/0114-596/00/0008-0115/$20.00/0

A Risk-Benefit Assessment of Injections of Hyaluronan and its Derivatives in the Treatment of Osteoarthritis of the Knee

Mark E. Adams,[1] *Andre J. Lussier*[2] and *Jacques G. Peyron*[3]

1 Department of Medicine, University of Calgary and McCaig Centre for Joint Injury and Arthritis Research, Calgary, Alberta, Canada
2 University of Sherbrooke, Sherbrooke, Québec, Canada
3 Centre de Rhumathologie, Hôpital de la Pitié, Neuilly sur Seine, France

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Abstract

Hyaluronan is critical for the homeostasis of the joint as an organ, in part, because it provides the rheological properties (viscosity and elasticity) of the synovial fluid. These properties depend upon both the concentration and the molecular weight of the hyaluronan in the synovial fluid. In osteoarthritis, the hyaluronan

is both smaller in size and lower in concentration. Thus, it is rational and physiologically meaningful to treat osteoarthritis with viscosupplementation, i.e. injection of material designed to increase the rheological properties of the synovial fluid.

It is important, though, to assess the risks and benefits of such a physiological treatment. There are various products on the market for viscosupplementation. These include hyaluronan preparations of relatively low molecular weight (Hyalgan® and ARTZ®), a hyaluronan preparation of intermediate molecular weight, but still lower molecular weight than that of the hyaluronan in normal healthy synovial fluid (Orthovisc®), and a cross-linked hyaluronan (a hylan) of high molecular weight (Synvisc®). The evidence from *in vitro* and *in vivo* models of osteoarthritis and from clinical trials to date suggests that efficacy, as would be expected by mechanistic reasoning, depends strongly upon molecular weight.

The available evidence indicates that these products differ little in the incidence and severity of adverse events (about 2 to 4%, almost always local swelling, and with no adverse sequelae). All are very well tolerated in comparison to nonsteroidal anti-inflammatory drug therapy, although direct comparisons are few. The only potentially serious adverse event is joint infection, which is rare and directly dependent upon the number of injections, among other factors. No infection has been related to contamination of any of the products.

In summary, treatment with low molecular weight preparations of hyaluronan seems to be effective. However, viscosupplementation with hyaluronan preparations may have slightly higher risk and less benefit than viscosupplementation with hylans, because the relatively lower molecular weight hyaluronan preparations require more injections which may incur higher costs and theoretically an increased chance of infection. Viscosupplementation with hylans is clearly effective, and the available evidence suggests that the benefits almost certainly outweigh the risks.

1. Osteoarthritis

Osteoarthritis is the most common and most costly type of arthritis; many studies show the very high cost of osteoarthritis.[1-5] Yet, compared with some other types of arthritis, e.g. rheumatoid arthritis, lupus and scleroderma, osteoarthritis is not associated with dramatically increased mortality. An increase in mortality has been documented,[6] but osteoarthritis also correlates with lower socioeconomic class and lower educational attainment,[7] both of which correlate with an increased mortality. The authors are unaware of any studies showing that osteoarthritis itself, irrespective of other factors, increases mortality.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat osteoarthritis, but this therapy is associated with a very high number of gastrointestinal bleeds.[8] Perhaps as many as 16 500 patients per year in the US die from NSAID-induced bleeding.[9]

Thus, it is critically important, when treating a 'benign' disease like osteoarthritis, to ensure that the risks of the treatment do not outweigh its benefits.

This article consists of, first, a description of viscosupplementation, and the experimental basis and rationale for it, and, second, reviews of the data from clinical trials showing efficacy and adverse effects for the viscosupplementation products currently marketed for osteoarthritis. Lastly, we present our interpretations of the scientific literature and conclusions drawn from it.

The article represents as objective an appraisal of the relative risks and benefits of viscosupplementation with hyaluronan and its derivatives as can be done under the present circumstances. To date, there

Table I. Viscosupplementation products

Trade name	Generic name	Average molecular weight ($\times 10^6$D)	Complex viscosity (Pa • sec at 0.02Hz)	% Elasticity (at 3Hz)	Polysaccharide concentration (μg/L)	Dosage schedule (ml × no. of wks)
Hyalgan®	Hyaluronan	0.6	<0.1	29	10	2 × 5
ARTZ®	Hyaluronan	0.75	0.3	33	10	2.5 × 3
Orthovisc®	Hyaluronan	1.55	42	63	15	2 × 3
Synvisc®	Hylan	6	213	88	8	2 × 3

have been no published trials comparing one product for viscosupplementation with another, though some completed clinical trials have been presented at scientific meetings.

This review concentrates on peer-reviewed publications and, when necessary, presents the results from verbal presentations or abstracts of completed but unpublished clinical trials.

1.1 Clinical Analyses of Efficacy and Safety

Assessments of therapeutic efficacy and safety are generally best performed using double-blind, randomised, controlled clinical trials. The control can be a placebo or an active treatment. However, with blinding for injectable material some difficulties arise. If the therapist cannot be blinded, an independent assessor should be used to maintain double-blinding. With single-blind studies the results can often be misleading, as therapies can have very large placebo effects.

It is difficult, though not impossible, to assess efficacy from open trials, i.e. with no comparison to either placebo or active drug. Open studies can also be used for safety data but it is difficult to be certain that adverse effects that are known to be common in placebo arms of clinical trials are due to the product. If a specific event has been defined as related to the product with a defined temporal sequence and is uncommon otherwise, then quite reasonable data concerning the related effect can be obtained. Historical controls can be used, if these are well defined and if there has been no other significant change in the therapeutics of the disease in question since the data for the historical controls had been gathered.

2. Viscosupplementation

2.1 What Is It?

The use of intra-articular injections of high elastoviscous solutions of hyaluronan or hylans (cross-linked derivatives of hyaluronan) to treat arthritis is called viscosupplementation.[10] The aim of viscosupplementation is to restore the rheological properties (viscosity and elasticity) of the synovial fluid (molecular weight of hyaluronan in healthy synovial fluid is about 3 to 4 $\times 10^6$D). These products also have other effects, such as free radical scavenging, especially with the hylans,[11] and antinociceptive effects,[12] and may promote the normalisation of the hyaluronan synthesis[13] (see section 2.3).

2.2 Types of Products

The clinical use of hyaluronan was made possible by the development of a sterile, noninflammatory preparation with sufficient purity, molecular weight and elastoviscous properties to be medically useful. The first of these preparations with a high molecular weight was developed in the 1960s by Balazs[14] and was called by its acronym NIFNaHA (noninflammatory fraction sodium hyaluronan). This preparation is now marketed as under the name Healon® for ocular surgery but it is not marketed for osteoarthritis.

Several preparations of hyaluronan are in use for the treatment of osteoarthritis of the knee. These are, listed in increasing molecular weight, Hyalgan®, ARTZ®, Orthovisc®, and a cross-linked derivative of hyaluronan (Synvisc®). These 4 products are considered in this article and their general properties are listed in table I.

2.3 Effects of Viscosupplementation *In Vitro* and in Animals

2.3.1 *In Vitro* Effects

In vitro, high viscosity solutions of hyaluronan have effects on inflammatory cells, including inhibition of lymphocyte transformation,[15] the phagocytic activity of macrophages and leucocytes, and the release of prostaglandins.[13,16,17] *In vitro*, both hyaluronan and hylan protect chondrocytes or cartilage explants from degradation by enzymes, interleukin-1, and oxygen-derived free radicals, and this action is viscosity (molecular weight) dependent.[18] In addition, in bovine cartilage, hyaluronan stimulates the production of tissue inhibitor of metalloproteases-1.[19] In general, these cellular protective activities, as well as the protection against physical damage, are dependent upon both the concentration and the molecular weight of hyaluronan.[13,15-19]

It is observed that hyaluronan and hylan products have effects that last longer than their residence times in the joints. Hyaluronan solutions influence the synthesis of hyaluronan in synovial cell cultures.[13] This effect reaches a maximum 48 hours after hyaluronan is added to the culture medium and is also concentration- and molecular weight-dependent. A proposed possible explanation is that this stimulatory effect results from simultaneous activation of multiple cell-surface receptors, thus requiring a particular molecular weight and conformation. This persistent effect might also result from scavenging of free radicals, thus allowing production of a larger form of hyaluronan, a process that would be at least partially self-perpetuating. The prolonged effect of the hylan-based product may also partially be explained by the presence of hylan B (see section 3.4) in the joint for as long as 30 days.[20]

Interleukin-1 also stimulates hyaluronan synthesis in cultured fibroblasts.[21] However, much of this newly synthesised hyaluronan has a very low molecular weight,[21] and this, as the authors of this report suggest, may partially account for the smaller size of hyaluronan in osteoarthritis.

In summary, hyaluronan solutions display many regulatory and protective effects on cells and tissues that are related to their molecular weight and their elastoviscous properties.

2.3.2 Animal Model Studies

There is an increasing body of evidence from animal model studies (using rabbit, mouse, dog, etc.) showing that hyaluronan can protect cartilage from physical damage. There are no studies showing this effect in humans. This is largely due to the pragmatic reasons of the cost of such studies, the necessary study duration and thus the rate of dropouts, and especially the lack of a sufficiently precise method of assessing the cartilage structure *in vivo* in humans.

As with the *in vitro* studies, many of the animal studies show that the higher the molecular weight of the product (hyaluronan or hylan), the better the effect on the cartilage protection. Viscosupplementation, to our knowledge, has not been well studied in immobilisation of the human knee, though this would seem to be worthwhile.

Among the earliest studies was one performed with Healon® by Rydell and Balazs.[22] Two types of experiments were done on joints. In the first, horses with spontaneous traumatic or degenerative arthritis were injected with Healon®, methylprednisolone, or both. All horses improved, but the horses treated with both agents did substantially better. In another set of experiments using both dogs and owl monkeys, the lateral femoral condyles were wounded surgically. Healon® was injected every fourth day for 4 weeks, and the animals were sacrificed after 6 to 8 weeks. The injected joints were reported to be smoother and to show less signs of reaction than the noninjected joints.

Using a model of immobilisation of the knee of the rabbit, Kikuchi et al.[23] reported that treatment with a relatively high molecular weight hyaluronan (SL-1010; molecular weight = 2.02×10^6D produced by bacterial fermentation) resulted in a significantly better range of motion than did treatment with either a lower molecular weight hyaluronan (molecular weight = 9.8×10^5D) or with saline. Using a similar rabbit model, Sakakibara et al.[24] showed that treatment with hyaluronan of molecu-

lar weight 2.02×10^6D was more potent at reducing the loss of range of motion and the histological changes in the knees than hyaluronan of 9.8×10^5D molecular weight or saline.

Again, using a similar model, Kido et al.[25] used SL-1010 and a hyaluronan of 9.5×10^5D molecular weight or saline as controls and reported that the SL-1010 resulted in a significantly higher range of motion and content of sulphated glycosaminoglycans than did the control treatments.

Kikuchi et al.[26] used a rabbit partial meniscectomy model to test the effect of hyaluronan 1.9×10^6D molecular weight, hyaluronan 8.0×10^5D molecular weight (ARTZ®) or saline on cartilage degeneration. Both of the hyaluronan preparations significantly inhibited cartilage degeneration compared with saline, and the effect of the higher molecular weight preparation was better than that of the lower molecular weight preparation, significantly so for the femoral condyle.

Armstrong et al.[27] studied the effect of ARTZ® in an ovine meniscectomy model of osteoarthritis. The animals treated with ARTZ® had significantly less severe histological changes and less severe, though not significantly so, changes in the subchondral bone compared with the animals treated with saline.

Williams et al.,[28] used a rabbit model of osteoarthritis induced by injection of fibronectin fragments in the knee. The test knees were given pretreatment with ARTZ® 1 day before injection of the fibronectin fragments and showed less severe changes at 1 week, but no differences at 4 weeks, compared with knees that were not pretreated with ARTZ®.

In a model using intra-articular papain to induce slight degenerative changes in the cartilage, Obara et al.[29] showed that injection of a hyaluronan of 1 to 2×10^6D molecular weight resulted in significantly decreased friction of the joint surface and histological changes compared with animals who did not receive hyaluronan. In this article the results of a study in 4 rabbits with anterior cruciate ligament transection were also presented. The hyaluronan injections reduced the friction in 3 of the 4 joints, but no statistical tests were done on this small group of animals.

In a study by Yoshioka et al.[30] 99 rabbits received either injections of either hyaluronan (ARTZ®), or vehicle carrier, or no injection. The hyaluronan injections resulted in an amelioration of the histological changes, and a partial preservation of the cartilage thickness, surface roughness, and thickness of the synovial lining layer compared with vehicle. There were, however, no changes in the biochemical measures (water content, glycosaminoglycan content, DNA content).

Also using anterior cruciate ligament transection in rabbits, Yoshimi et al.[31] compared the effects of a higher molecular weight hyaluronan (2.02×10^6D), a lower molecular weight hyaluronan (9.5×10^5D), and saline. This resulted in improvements in the gross, histological, and histochemical measurements, with both hyaluronan preparations versus saline, some of which were significant for the group injected with the higher molecular weight hyaluronan.

Abatangelo et al.[32] reported on changes in lameness, radiographs, and biochemistry in dogs with an anterior cruciate ligament transection and weekly injections of Hyalgan®, either beginning at the first week or the seventh week, compared with untreated control dogs. The animals were sacrificed at 7, 13, and 17 weeks. These investigators reported decreases in lameness and in radiographs, but performed no statistics on these results. There were no statistically significant changes in the biochemical measures. In an accompanying article, Schiavinato et al.[33] reported that the morphological changes were improved in the 17-week dogs that started treatment at week 7.

Marshall[34] reported in a non–peer reviewed article that changes were *'significantly milder'* in a bilaterally anterior cruciate ligament transected dog model after injections of Synvisc®; however, this article has not yet appeared in a full length peer-reviewed journal.

Though really a clinical trial in equine veterinary medicine, the results of a comparison of 5 different preparations of hyaluronan ranging from molecular weight 1.5×10^5 to 3.5×10^6D by Phillips[35]

Table II. Rheological parameters of synovial fluid in the young, the aged and in individuals with osteoarthritis[38]

Patient group	Complex viscosity (Pa • sec at 0.02Hz)	% Elasticity (at 3Hz)
Young	137	94
Old	33	71
With osteoarthritis	0.4-5	36-73

are presented here. The 2 preparations of molecular weight 3.5×10^6D resulted in about 3 times longer duration of increased soundness in the joints (a combined measurement of range of motion, lameness, joint effusion and heat in the joint) than preparations of molecular weight 1.5×10^5 to 2×10^6D.

Asari et al.[36] presented data that a lower molecular weight preparation of hyaluronan penetrated arthritic synovium more than a higher molecular weight preparation.

In contrast to the other evidence presented, a review published in 1994[37] suggested that, based on the available literature at the time, the clinical effect of hyaluronan may not be dependent upon the molecular weight.

Studies in animals and animal models, then, suggest that hyaluronan can be effective in ameliorating the changes in various models of osteoarthritis. When compared, higher molecular weight preparations of hyaluronan have almost always been shown to be more effective than lower ones.

2.4 Rationale for Viscosupplementation in Patients with Osteoarthritis

The molecular weight and rheological properties of naturally occurring hyaluronan in the synovial fluid are decreased with ageing and osteoarthritis (fig. 1, table II). Consequently, the ability of hyaluronan to protect the joint, both chemically and rheologically, is impaired.[38] Thus, viscosupplementation, or supplementation of the synovial fluid with a high viscosity hyaluronan or hyaluronan derivative makes excellent physiological sense.[39,40]

The concentrations of all the preparations for viscosupplementation differ less in their concentration than in their molecular weight (table I). Thus, the differences in their rheological properties are mostly dependent upon their molecular weight (table I). From the *in vitro* and animal model studies cited above, it would be expected that preparations with higher molecular weight would have better effects. We feel that analysis of the clinical data also shows that the higher molecular weight, the better the response (see section 3).

3. Clinical Efficacy of Viscosupplementation Products

3.1 Hyalgan®

3.1.1 Description of the Product

Hyalgan® is a 1% solution of hyaluronan extracted from rooster combs, as is the hyaluronan used in all 4 of the preparations discussed. It has a molecular weight of 5 to 7.3×10^5D. The recommended treatment consists of 5 injections of 20mg (2ml) given once-weekly.[41-47]

As a consequence of its relatively low molecular weight (though paradoxically it has been described as 'high molecular weight hyaluronan'), its viscoelastic properties are low relative to other preparations (table I) and are even as low or lower than that of synovial fluid from aged individuals (table II).

3.1.2 Clinical Trials

Eight placebo-controlled studies have been published (table III), as have 3 studies comparing

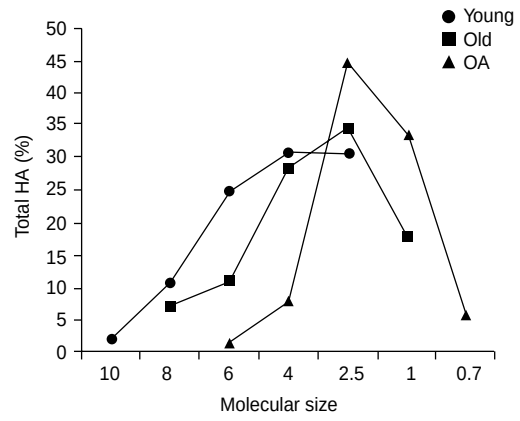

Fig. 1. Molecular weight of hyaluronan in synovial fluid of young, old, and osteoarthritic individuals. **HA** = hyaluronan; **OA** = osteoarthritis.

Table III. Clinical trials with Hyalgan®

References	Trial duration (wks)	No. of patients	No. of injections	Results	Remarks
Bragatini et al.,[41] Grecimoro et al.[42] & Carrabba et al.[43]	8	195	3-5	75-88% Hyalgan® responders *vs* 30-50% placebo responders	3 or 5 injections better than 1. Single injection of 40mg no better than 20mg
Henderson et al.[44]	20	91	5	No statistical difference between Hyalgan® and placebo recipients except for use of escape NSAID	Numerous patients withdrew. Numerous adverse effects
Dixon et al.[45]	48	63	4	Patients receiving Hyalgan® did statistically better than patients receiving placebo	Patients improved more for pain at rest than for pain on movement or activity
Dougados et al.[46]	52	95	4	Patients receiving Hyalgan® did better than patients receiving placebo at 7 wks; few differences at 52wks	Blinding not specified
Listrat et al.[47]	52	36	9	Arthroscopic evaluation at 1yr, but no control treatment specified over 6mo-1y. Patients receiving Hyalgan® had better arthroscopic results	Investigated progression
Altman et al.[48]	26	495	5	Patients receiving Hyalgan® did statistically better than patients receiving placebo with analysis of covariance and repeat measures analysis. Patients receiving Hyalgan® did no better than patients receiving naproxen	Comparisons with placebo and naproxen

NSAID = nonsteroidal anti-inflammatory drug.

Hyalgan® with corticosteroid injections.[46,49-51] The results for efficacy have not been entirely consistent. Short term controlled studies[41-43] totalling 195 patients show that approximately 75 to 88% of the patients respond to Hyalgan® injections compared to 30 to 50% who respond to placebo. There was no significant advantage to increasing the dose to 40mg per injection,[41] but it was clear that a series of 3 or 5 injections had a better result over 2 months than a single injection.[43]

One 5-month study of a 5-injection regimen[44] failed to show a significant advantage of hyaluronan over placebo except for a decrease in the use of rescue NSAIDs. A 48-week trial[45] found that Hyalgan® was very effective compared with placebo for rest pain and mildly effective for pain on movement.

A study of 95 patients[46] (47 receiving Hyalgan®, 4 injections) was carried out for 1 year. The study was controlled, but no mention is made in the published paper about blinding, so it must be assumed that this was an open-label study. At 7 weeks (4 weeks after the last injection) the patients who had been given Hyalgan® were better for all parameters measured. At 1 year, the Hyalgan® and control patients were not different with respect to VAS pain at rest or after exercise, but were better by physician's global assessment and the Lequesne index. In another study of 1 year[47] 36 patients (19 given Hyalgan®, 17 control) were given 3 courses of 3 injections of Hyalgan®, for a total of 9 injections. In addition to clinical parameters, the study entailed an arthroscopic evaluation of the joint before the treatment and 1 year later. At that time, the progression of the arthroscopically evaluated joint lesions was less in the Hyalgan®-treated patients than in the control group, thus raising the possibility of a retarding effect on joint degradation.[47] However, the study states that the patients in the placebo arm were administered 'conventional therapy'; no control aspirations and injections were stated to be administered in the

later portion of the trial, making it difficult to interpret the results.

Recently, a 3-arm study was published comparing 5 weekly injections of Hyalgan® with 5 placebo injections and naproxen.[48] Using the sophisticated and valid statistical methods of analysis of covariance, combined with repeat measures analysis, differences between Hyalgan® and placebo were shown in the primary efficacy measure, which was pain on a 50-foot walk. While these differences were statistically significant, they were not large in absolute terms. No difference was shown between Hyalgan® and naproxen.

However, in our opinion, this cannot be used to say that Hyalgan® was equivalent, because in the naproxen group no arthrocentesis was performed. Arthrocentesis is thought by many to be an effective treatment, accounting for some of the improvement versus baseline seen in the 'placebo' arms of studies of viscosupplementation. Thus, the naproxen arm may have suffered a negative bias. The authors stated they had not powered the study for an intent-to-treat analysis, but used only a 'completers' analysis. That this was not an intent-to-treat analysis becomes important when trying to make comparisons, particularly between Hyalgan® and Synvisc® (see section 3.4). For the latter drug, almost all of the studies used an intent-to-treat analysis.

Three studies have compared corticosteroid injections with Hyalgan®. Two[49,50] were open studies using 6-methylprednisolone acetate (40mg) injections and showed that the pain decrease with Hyalgan® was slower but ultimately as effective as the corticosteroid and lasted considerably longer.[49,50] The third study[51] was a double-blind controlled trial with 63 patients. However, there was a high dropout rate, and an intent-to-treat analysis failed to show any significant differences. Analysis of the patients who remained in the trial was reported to show a non-significant trend in favour of hyaluronan. It is notable that double-blind controlled trials of corticosteroids in osteoarthritis of the knee are few, and some of these do demonstrate its efficacy but show that the duration is almost always less than 2 months.[52,53]

3.2 ARTZ®

3.2.1 Description of the Product

ARTZ® is a 1% solution of hyaluronan extracted from rooster combs with an average molecular weight of 6 to 8 × 10^5D. Like Hyalgan®, it too is often referred to as 'high molecular weight hyaluronan', though its molecular weight is clearly less than that of the hyaluronan in normal synovial fluid.

The recommended treatment consists of 5 once-weekly injections of 25mg (2.5ml).[54] As a consequence of its slightly higher molecular weight than Hyalgan®, its viscoelastic properties are slightly higher than are those of Hyalgan® but are low relative to other preparations (table I) and even to synovial fluid from aged individuals (table II).

3.2.2 Clinical Trials

The results of the clinical trials for efficacy of ARTZ® have been mixed. Some clinical trials show efficacy for a treatment series of 5 to 16 injections, depending on the patient population and the investigators. Clinical trials are summarised in table IV.

Early short term trials[54-57] in 466 patients showed that about 50 to 84% of the patients who received ARTZ® improved and about 20 to 38% were graded 'excellent'. In 1 controlled trial in which 60% of the patients responded to hyaluronan, 34% were also improved by placebo injections.[56] One study using multiple injections over 6 months[58] showed 80% responders (43.5% graded 'excellent') but an average of 13.7 injections was used per patient. This suggests that many repeat injections may necessary to increase the magnitude and duration of the effect.

A recent 14-week placebo-controlled trial[59] showed a significant benefit of ARTZ® as measured by the Lequesne index (an algofunctional index). However, a 1-year trial[62] in patients selected by arthroscopic criteria found significant benefit for ARTZ® only in the subgroup of patients more than 60 years of age and with a Lequesne index[63] greater than 10. The intent-to-treat analysis showed no difference between ARTZ® and placebo.

Taken together, the studies with ARTZ® and with Hyalgan®, 2 preparations of similar molecular weight, show that a unit dose is 20 to 25mg, and a

Table IV. Clinical trials with ARTZ®

References	Trial duration (wks)	No. of patients	No. of injections	Results	Remarks
Oshima et al.,[54] Namiki et al.,[55] Shichikawa et al.[56] & Honma et al.[57]	4-8	466	1-16	50-84% responders; 20.4 to 38% 'excellent'	Summary of 4 early short-term studies. Only 1 was placebo controlled, with 60% responders to ARTZ® *vs* 34% responders to placebo[56]
Igarashi et al.[58]	26	33	7-20	88% responders; 45.5% excellent	Study of multiple injections; average, 13.7 injections per patient
Puhl et al.[59]	14	95	5	Lequesne index improved by 4.4 in ARTZ® group, 2.8 in placebo group	$p < 0.005$
Dahlberg et al.[60]	52	28	5	Improvement from baseline not statistically different from placebo	Patients all had prior arthroscopy
Lohmander et al.[61]	70	96	5	Improvement from baseline not statistically different from placebo	ARTZ® was only significantly better than placebo in the patient subgroup aged ≥60y, having a Lequesne index of ≥10

series of 5 or more consecutive weekly injections is generally necessary to produce a significant effect over several weeks or months. Used in this way, these hyaluronan injections are generally, but not always, more effective than placebo injections. The effect lasts longer than that of corticosteroids (whose effect has been well documented to be short). The studies tend to show that symptoms, such as pain, are better influenced than clinical signs, and that the best results are obtained in patients with mild to moderate radiographical changes (Kellgren Lawrence grades II and III) and with no or only small effusions.

3.3 Orthovisc®

Orthovisc®, like the other preparations, is derived from rooster combs. Its concentration is slightly higher than that of the other preparations (table I), but its viscoelastic properties are still lower than that of the hyaluronan in normal healthy synovial fluid (table II).

Although Orthovisc® is available in Canada, there are few publications from which to assess its efficacy. A literature search revealed no peer-reviewed publications of its efficacy or tolerability in osteoarthritis of the knee, though some clinical trials have been conducted. It is, therefore, difficult to say more about this preparation in this indication.

3.4 Synvisc®

3.4.1 Description of the Product

Recently, more elastoviscous derivatives of hyaluronan have been made available to clinical medicine. Hylans are polymers of hyaluronan that have been cross-linked through their hydroxyl groups.[64,65] They are very highly hydrated,[66] are very powerful scavengers of hydroxyl radicals and are more stable to the action of these agents than are noncrosslinked hyaluronan.[11]

Synvisc® (hylan G-F 20) is a mixture of 2 hylan polymers, 80% by volume hylan A fluid and 20% by volume hylan B gel. It was specifically developed for the treatment of human osteoarthritis by viscosupplementation. The average molecular weight of Synvisc® is 6×10^6D. Hylan B is a viscoelastic gel in a microparticulate form that is also derived from hyaluronan. Because it is a gel, it has an infinite molecular weight. It is extremely hydrated (≈99.5% solvent content) but is not water-soluble, but is in suspension with the hylan A in the vehicle.

The elastic modulus of Synvisc® (table I) is greater than that of normal synovial fluid (table II). Its residence time in the joint fluid space and tissues is longer than that of natural hyaluronan,[20,67] as would be expected from its larger molecular size and cross-linking. Residence time is about 23 hours

Table V. Clinical trials with Synvisc®

References	Trial duration	No. of patients	No. of injections	Results	Remarks
Scale et al.[68]	12wk	80	2 or 3	Both the 2-injection and 3-injection treatments were statistically superior to placebo	3-injection treatment regimen statistically superior to 2-injection regimen
Adams[69]	26wk	118	3	Synvisc® was statistically superior to placebo for all outcome measures	At 6mo more of the Synvisc® patients still had 'excellent' improvement' *vs* placebo
Adams et al.,[70] Adams[71]	26wk	93	3	Synvisc® was as good or better than continuous NSAIDs	Synvisc® was statistically superior to NSAID therapy when using a repeat measures analysis corrected for covariates
Lussier et al.[72]	2.5y (retrospective)	336 (122 treated bilaterally)	3	77% of patients rated 'much better' or 'better'	Mean time to retreatment was 8.2mo. Improvement lasted more than 6mo in the majority of patients

NSAIDs = nonsteroidal anti-inflammatory drugs.

for a 1% solution of hyaluronan and about 20 to 30 days for a 0.4% solution of hylan B. Hylan B contributes much to the elastoviscosity of Synvisc® as well as to the increase in the residence time of the this combination product in the joint. The unit dose of Synvisc® is 2ml (16mg of hylan), and the recommended therapeutic regimen is once weekly for 3 injections.

3.4.2 Clinical Trials

Several clinical studies of Synvisc® have been reported (table V).[68-72] Two dose-ranging, placebo-controlled, double-blind trials[68] showed that 2 injections of Synvisc® are statistically significantly better than placebo according to most criteria, but that 3 injections were significantly better than 2 injections at 8 and 12 weeks. Some statistical differences from placebo were evident after the first Synvisc® injection. A follow-up telephone survey at 26 weeks suggested that Synvisc® was still effective at this time. It was concluded that a 3-injection schedule is the optimum treatment schedule.[68]

A double-blind, placebo-controlled, multicentre study in 118 patients[69] confirmed that most efficacy outcome measures were significantly improved after the first injection. This effect increased and continued at least up to week 12, and was reported to be increased in a telephone interview at week 26. At 12 weeks, for all outcome measures, many more of the Synvisc®-injected than placebo-treated patients had an 'excellent' result (using visual analogue scale pain scores, <20mm). At 6 months, based on a telephone interview, this was still true.

In a double-blind, multicentre, randomised, controlled trial in Canada, Synvisc® was compared to continuous NSAID therapy in 93 patients.[70] In 1 group the patients continued their usual NSAID therapy and received 3-weekly arthrocenteses as an intra-articular control. In a second group the patients continued their usual NSAID therapy, but, in addition, received 3 Synvisc® injections; in the third group the patients discontinued their usual NSAIDs and instead received 3 Synvisc® injections.

At 12 weeks, the patients were evaluated in the physicians offices or clinics. In all 3 treatment groups, patients had improved compared with baseline. There were differences between the groups only for pain at rest; the Synvisc®-only group showed more improvement compared with the other groups. At 26 weeks, telephone-evaluated outcome measures were significantly better in the 2 Synvisc®-injected groups than in the NSAID-alone group. It was concluded that 3 Synvisc® injections were as good or better than continuous NSAID therapy and could be used to replace continuous NSAID therapy, providing pain relief for more than 6 months. No interference between the 2 treatments was observed.

At the request of the US Food and Drug administration, a more detailed analysis of this study was performed using repeated measure analysis corrected for covariates. When analysed this way, the Synvisc® group was not only equivalent but was significantly better than the NSAID group.[71]

In a retrospective study, case reports of all patients treated by 5 Canadian rheumatologists were collected during a period of 2.5 years and analysed.[72] The files of 336 patients (458 knees) were reviewed. 56 knees were given a second treatment. 76% of patients responded to the treatment after the first series and 84% after the second. About half of the patients were graded 'much better'. Clinical benefits after a first treatment lasted >3 months in 65% of the patients and >6 months in more than half the patients. The mean time before the patients requested a second treatment was 8.2 months.

Lastly, a double-blind, double-control comparison of viscosupplementation with Synvisc® against diclofenac and placebo control in knee osteoarthritis has recently been presented and published as an abstract.[73] There were 3 groups: group 1, arthrocentesis + Synvisc® + placebo capsules (the Synvisc® group', 43 patients); group 2, arthrocentesis + diclofenac retard 100 mg/day (the 'diclofenac group', 42 patients); and group 3, arthrocentesis + placebo capsules (the 'double-control' group, 49 patients). After the 12-week trial, the patients were allowed to enter a follow-up evaluation, with up to 4 additional courses of Synvisc®.

Synvisc® was statistically superior ($p < 0.05$) to the double-control treatment for the Lequesne Index, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) A pain score, the WOMAC C functional score, and the WOMAC A/C composite score. The diclofenac group was not statistically superior to the double-control group for any of the measurements. Synvisc® was statistically superior to diclofenac ($p < 0.05$) for walking pain, pain at night, and pain at rest. The mean time between treatments 1 and 2 in the follow-up phase was 13 weeks and between courses 2 and 3 it was 17 weeks.[73]

The rate of local reactions with Synvisc® (2 to 4%) was comparable to that reported in previous studies. In the diclofenac group 32% of patients had gastrointestinal symptoms, compared with 9 and 7% of the patients treated with Synvisc® and arthrocentesis, respectively ($p < 0.005$). A possible criticism of this study is that the diclofenac dose may have been submaximal, leading to a possible efficacy bias favouring Synvisc®; however, the rate of gastrointestinal symptoms would be expected to be higher if the maximal diclofenac dose of 150mg had been used.

4. Safety of Hyaluronan and Hylan Injections

Safety is a major concern for a therapy used for a chronic nonlife-threatening condition that may require many repeat administrations. A comprehensive review of available data shows that the incidence of adverse events is low after local injections of hyaluronan or hylans (table VI).

Tolerability of hyaluronan and hylan, in general, has proved to be very good. This type of treatment has gained wide acceptance in countries where it is available. However, long term studies evaluating repeat treatments and possible influence of this therapy on the natural history of knee osteoarthritis need to be done. In 1 report, involving only 22 patients, the rate of adverse events was 27%.[74] However, there were several statistically anomalous results in the data.[75] In the 1-year study by Altman et al.,[48] injection site pain occurred at a rate of 23 *vs* 13% in the placebo group, emphasising the importance of correct placement of the injection.[76,77] In addition, it is important to aspirate as completely as possible any synovial fluid which may be present.

The only adverse effects of significance are transient local reactions in the injected joint, which are typically benign, short lived, without sequelae, and similar to those observed with any intra-articular treatment. The mean prevalence of local adverse effects in controlled clinical trials is generally between 2 and 4% of the injections. In controlled clinical studies, the frequency of adverse effects after control injections (usually saline) falls within the same range. Intra-articular injections of corticoste-

Table VI. Rates of local adverse effects (AEs) reported for the available hyaluronan and hylan products[40]

Product	Rate (%) of local AE per injection (range)		Patients who discontinued clinical trials (%)
	clinical trials	postmarketing surveys	
Hyalgan®	4.2 (2-4.4)	0.5	1.4
ARTZ®	2.6 (1.6-15)	0.4[a]	3.4
Synvic®	2.3 (0-3.5)	0.16	1.5

a Calculated from the rate per patient, assuming 5 injections per course of treatment.

roids are known to cause painful reactions at an incidence of approximately 3%.[62,78]

These local adverse effects are very much the same with all intra-articular injection products. The adverse effects include joint pain that occurs from a few hours to 2 days after the injection. The joint may be swollen, but is rarely warm. An effusion may be present and, in a few instances, has been reported to be abundant and rich in mononuclear cells. These symptoms, in most cases, resolve spontaneously in a few days, often before the next weekly injection. Rest, cold packs, analgesics, NSAIDs, and occasionally corticosteroid injections or arthrocentesis to remove the effusion have been helpful. This local reaction does not necessarily recur with subsequent injections, so discontinuation of the treatment is generally unnecessary and clinical benefits can often be significant after the local reaction subsides.

On very rare occasions, an adverse reaction may be so severe as to mimic a joint infection, even with white cell counts of $>1 \times 10^5$ cells/mm^3 in the synovial fluid. However, these too are self-limiting events that do not require any emergency surgical intervention, unless it is clearly demonstrated that the joint is septic on the basis of microbiological studies.

The mechanism of these local adverse effects is poorly understood. The absence of recurrence after further injections seems to preclude allergic mechanisms. The events may result from misplacement of the injections, which is common[76,77] and could cause tissue swelling. Reactions might be caused by blockage of the synovial outflow by these viscous substances. In a few cases, large and highly cellular effusions have been reported and the possibility of crystal arthritis has been raised.[79,80] Presently, these mechanisms remain conjectural.

No alteration of blood or urine tests related to the hyaluronan or hylan products has been observed. No interaction with drugs taken by the patients for coincident conditions are known, nor are they expected because intra-articular hyaluronan has no systemic pharmacological activity.

All of the manufacturers correctly insist on strictness of aseptic conditions while performing the injections. Reports of septic arthritis after hyaluronan or hylan injections are very rare, and have never been traced to a contamination in the product itself.

Finally, it is notable that no case of viral infection has been reported during hyaluronan use in several million patients who received hyaluronan or hylan preparations intra-articularly in Japan, Italy, Canada, Sweden, Germany, and many other countries in the past 10 years, as well as in an estimated 40 million people treated with hyaluronan preparations in ophthalmic surgical procedures worldwide during the past 25 years.

5. Discussion

As discussed above, all of the hyaluronan products have an excellent safety profile, with no or extremely rare systemic adverse effects. Local adverse effects are self-limiting, do not diminish efficacy and do not seem to be caused by an immunological reaction. It is essential to bear in mind the importance of full aspiration of any synovial fluid that is present and meticulous attention to needle placement, in order to optimise efficacy and minimise adverse effects.

All of the products for viscosupplementation have been shown in clinical trials to be effective. The

results may well differ between various products but directly comparative trials are not available.

As well, all hyaluronan products may be cost effective versus NSAIDs, because of the high cost of NSAID-associated gastrointestinal bleeds, but no formal pharmacoeconomic analyses have investigated this aspect of therapy. Relative cost effectiveness of various treatments may change if the cyclooxygenase (COX)-2 selective inhibitor NSAIDs live up to their expectations and are not very expensive.

The hyaluronan products may also differ from each other with respect to cost effectiveness. The acquisition cost of Synvisc® is not, or not substantially, greater than that of the lower molecular weight hyaluronan preparations,[81] yet its efficacy seems to be more consistent and possibly greater. In addition, the full course of Synvisc® is a 3-injection rather than a 5-injection protocol. Overall, based on the preclinical and clinical data, it may make more economic and clinical sense to use a preparation that requires only 3 injections. Use of the lower molecular weight preparations of hyaluronan entails an increase in the physician's and patient's cost because of greater number of injections required and therefore the increased possibility of infection. However, formal studies comparing these products have not been published.

Unfortunately, no studies have been published that accurately assess the impact of viscosupplementation on the direct and indirect costs of osteoarthritis, though we are aware of such studies being done. It is hoped that such studies will be published in the near future, giving us guidance as to the cost effectiveness of viscosupplementation in the treatment of osteoarthritis.

When should these products be used in treatment of osteoarthritis? As the clinical trial evidence suggests that all the products are effective and have no devastating or potentially fatal adverse events, it would seem to be sensible to use them before starting NSAIDs, and after conservative measures have been tried (exercise, bodyweight loss, physiotherapy, occupational therapy, simple analgesics, patient education, etc.). In addition, Synvisc® appears to be at least as good as, and possibly better than, NSAIDs and requires only 3 injections.

It is clear, though, that not all physicians agree with this proposed strategy. This may be on the basis of immediate cost, with some NSAIDs having low initial costs. However, with possible exception of the COX-2 specific NSAIDs, the cost of the adverse events associated with NSAIDS needs to be considered. As viscosupplementation generally is more effective in patients with mild to moderate osteoarthritis, though it certainly can be effective in advanced disease, its use could be considered either before, or concurrently with, the initiation of NSAID therapy.

6. Conclusions

Intra-articular therapy with elastoviscous solutions of hyaluronan or hylans (viscosupplementation) is one of the best tolerated, most effective treatments for osteoarthritis of the knee. It reduces pain and improves joint function for several months after a series of 3 to 5 injections. Also, it can significantly decrease the patient's dependence on NSAIDs and corticosteroid injections and their associated hazards. Most, but not all, evidence from both preclinical and clinical studies suggests that the greater the elastoviscosity (molecular weight) of the viscosupplementation product, the greater the effectiveness of the treatment.

By re-establishing elastoviscous homeostatic conditions in the joint, viscosupplementation has the potential to influence the natural course of osteoarthritis. However, studies to show this directly need to be performed, as do formal cost-effectiveness studies.

Acknowledgements

The help of Nancy Immel and Jennifer Bagley is gratefully acknowledged.

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Correspondence and offprints: Dr *Mark E. Adams*, Department of Medicine, University of Calgary and McCaig Centre for Joint Injury and Arthritis Research, Calgary, Alberta, Canada T2N 4N1.
E-mail: adams@ucalgary.ca