Viscosupplementation for the Osteoarthritis of the Knee

Dr. Vladimir Bobic
Consultant Orthopaedic Knee Surgeon
Chester Knee Clinic
The Grosvenor Nuffield Hospital
Chester
UNITED KINGDOM
www.kneeclinic.info

Abstract

Osteoarthritis (OA) is a major cause of disability. Patients with OA have pain that typically worsens with weight-bearing and activity and improves with rest. Unlike the rheumatoid arthritis (RA) inflammation is usually mild and localised in the affected joint. Although the aetiology of OA remains unknown biomechanical stresses and biochemical changes in the articular cartilage, subchondral bone and synovial membrane, and genetic factors, are all important in its pathogenesis. In joints affected by OA, the synovial fluid's capacity to lubricate and to absorb impact are typically reduced. These changes are partly due to a reduction in the size and concentration of hyaluronic acid (hyaluronan) molecules naturally present in synovial fluid. Medical management of OA of the knee is effective for many patients, but significant morbidity is common for those using non-steroidal anti-inflammatory medication (NSAIDs). Gastrointestinal toxicity has been a major problem for many patients on NSAIDs, especially for geriatric patients who need to take them for extended periods to treat chronic conditions. Although only a minority of patients using NSAIDs appear to develop serious GI problems, because of widespread usage it is estimated that there are at least 16,500 NSAID-related deaths each year in the United States among patients with osteo- and rheumatoid arthritis (1, 2). Another 76,000 end up in the hospital. The economic burden of NSAID-associated gastrointestinal disorders is enormous, with an estimated cost of $500 million. Surgical treatment of the knee OA is effective but it is not appropriate for all stages of the disease or for all patients. It is also costly and not without risks. With increased understanding of the pathogenesis of OA, new therapies are being developed, one of which is viscosupplementation with hyaluronic acid. A new approach in the management of OA of the knee is to inject hyluronan or derivatives of this molecule (hylans) into the joint. In recent years, the concept of viscosupplementation has gained widespread acceptance as a new treatment for the management of OA of the knee. The safety of this treatment has been well documented in numerous clinical trials, but controversy persists regarding efficacy and cost-benefit concerns (3).

Introduction

The use of viscosupplementation is based on observation that there is a decrease in viscosity and elasticity of the synovial fluid in osteoarthritis and that the native hyaluronic acid in osteoarthritic knees has a lower molecular weight than that found in normal healthy knees. Replenishing the hyaluronic acid component of normal synovial fluid may play a role in supplementing the elastic and viscous properties of synovial fluid, which may help relieve the signs and symptoms related to osteoarthritis and improve function. In vitro studies of human synoviocytes from osteoarthritic joints have revealed that exogenous hyaluronic acid stimulates de novo synthesis of hyaluronic acid, inhibits release of arachidonic acid, and inhibits interleukin-1α induced prostaglandin E2 synthesis by human synoviocytes. (4).

Hyaluronic acid (HA) is a glycosaminoglycan that is composed of glucuronic acid and N-acetylglucosamine. It differs from other glycosaminoglycans in that it is unsulfated; also, it does not bind covalently with proteins to form proteoglycan monomers, serving

instead as the backbone of proteoglycan aggregates. It is the only glycosaminoglycan that is not limited to animal tissues, being found also in bacteria. It serves as a lubricant and shock absorber in the synovial fluid, and is found in the vitreous humor of the eye. HA is not well absorbed orally, but has been widely used intraarticularly in the treatment of OA in animals and, more recently, in humans. HA is well tolerated with no demonstrable toxicity and few side effects. Because it is injected directly into the joint, its onset of action is rapid. Conversely, its route of administration does limit its therapeutic applications to some degree, and high cost is also a factor (5).

Biochemistry

Glycosaminoglycans (GAGs) are carbohydrate polymers that are among the most abundant components of the ground substance of connective tissue throughout the body. GAG molecules are long, homogeneous, unbranched polysaccharide chains that are formed by repeating disaccharide subunits. Hyaluronate is the most abundant GAG in synovial fluid. It is produced and secreted by synoviocytes. Hyaluronate is also prevalent in the extracellular matrix of articular cartilage, where it is produced by chondrocytes and where it forms the foundation for proteoglycan aggregates. The recurring disaccharide subunit of hyaluronate consists of *N*-acetylglucosamine and glucuronate. These sugar subunits are joined by glycosidic bonds. These bonds are extremely flexible in solution; therefore, hyaluronate has no defined tertiary structure. The carboxylate group on the glucuronate sugar is negatively charged. Thus, hyaluronate is a polyanion chain. The recurring electronegative charges along the chain repel one another and attract water molecules. Hence, hyaluronate has been likened to a “molecular sponge.” These properties account for the viscosity and elasticity of the hyaluronate macromolecule.

Pharmacology of Viscosupplementation

The notion of supplementing osteoarthritic synovialfluid with exogenous hyaluronate stems fromthe fact that the molecular weight and concentrationof hyaluronate in osteoarthritic synovial fluid arereduced. This phenomenon diminishes the viscosity of osteoarthritic synovial fluid. Appropriate synovial fluid viscosity is believed to be critical for maintaining normal joint lubrication and is also believed to have chondroprotective effects. It is hypothesized that the reduced concentration and decreased molecular weight of hyaluronate in osteoarthritic synovial fluid renders articular cartilage more vulnerable to mechanical and enzymatic injury.

The goal of viscosupplementation is to increase the molecular weight and concentration of hyaluronate in arthritic joints so that the intra-articular milieu more closely resembles that of healthy synovial fluid.

The mechanism of action by which viscosupplementation alleviates arthritic knee pain is a subject of debate. It has been proposed that exogenous viscoelastic substances act biomechanically by providing a “cushioning” effect. However, some authors have suggested that viscosupplements are eliminated from the knee too rapidly to exert a significant and lasting biomechanical effect. Indeed, the half-life of hyaluronate in sheep is less than 24 hours. In vitro research suggests that exogenous hyaluronate may stimulate endogenous production of additional hyaluronate by human synoviocytes. This could lead to more durable biomechanical consequences. Other studies suggest that hyaluronate supplementation has a direct anti-inflammatory effect on synoviocytes by inhibiting arachidonic acid release or by blocking prostaglandin-E2 production. It has also been suggested that exogenous hyaluronate inhibits damage mediated by oxygen free radicals and phagocytosis. Research has also found that hyaluronate may exert a direct analgesic effect on articular nociceptors. Possible mechanisms by which HA may act therapeutically include: providing additional lubrication of the synovial membrane, and controlling permeability of the synovial

membrane, thereby controlling effusions. Other possible, though less certain, mechanisms include: promotion of cartilage matrix synthesis and reaggregation of preoteoglycans. One manufacturer has cross-linked hyaluronate chains in an effort to further enhance the molecular weight (and, hence, the viscoelasticity) of its product, Hylan G-F 20 (Synvisc™). A synthetic hyaluronic acid Arthrease™ is not cross-linked, but does have a high molecular weight. Arthrease™ has to be stored within a controlled temperature range of 2-8 C^0. It contains no animal protein and no residual cross linking reagents. Several studies have suggested that viscosupplements with higher molecular weights have greater therapeutic efficacy (6, 7).

Viscosupplements			
Substance	**Molecular Weight (daltons)**	**Treatment**	**Source**
Hyaluronate (**Hyalgan™**, Sanofi-Synthelabo)	500,000 to 730,000	1 injection per week for 5 weeks	purified from chicken combs
Hylan G-F 20 (**Synvisc™**, Genzyme Biosurgery)	6 million	1 injection per week for 3 weeks	purified from chicken combs
A synthetic hyaluronic acid (**Arthrease™**, DePuy Ltd, UK)	similar to healthy synovial fluid	1 injection per week for 3 weeks	bio-synthetic product
Hyaluronate in healthy synovial fluid	4 million to 6 million	-	natural
Hyaluronate in osteoarthritic synovial fluid	1 million to 4 million	-	natural

Anti-inflammatory Effect

Hyaluronic acid has both in vivo and in vitro effects on leukocyte function. These include inhibition of phagocytosis, adherence and mitogen-induced stimulation. These properties are dependant on the molecular size of haluronic acid. Intra-articular administration of hyaluronic acid reduces levels of inflammatory mediators, including prostaglandin and cyclic adenosine monophosphate, in the synovial fluid of patients with arthritis (3).

Analgesic Activity

It seems that intra-articular hyaluronic acid modulates pain perception directly through inhibition of nociceptors or indirectly through binding of substance P - a small peptide involved in the transmission of pain signals (3).

Chondroprotective Potential

There are some data from human and animal studies to suggest that viscosupplementation could have a chondroprotective effect. Listrat et al. suggest that repeated intra-articular injections of hyaluronan might delay the structural progression of osteoarthritis. (7). However, the chondroprotective effect of hyaluronic acid remains unproved. More research is needed to evaluate whether or not viscosupplementation

has disease-altering properties in addition to its apparent palliative characteristics. (3, 6).

Clinical Effectiveness

Viscosupplementation is a proven adjunct to the treatment armamentarium of general practitioners and surgeons. A number of recent clinical trials have evaluated the efficacy and safety of intra-articular hyaluronic acid injections (8, 9, 10, 11, 12, 13, 14, 15). The reports of these studies were among those presented to the Food and Drug Administration (FDA) in the course of the process that resulted in the release of this treatment modality. The American College of Rheumatology has included viscosupplementation in the treatment algorithm for osteoarthritis of the knee (4, 16, 17).

Study	Intervention	Design	Clinical Assessment Parameters	Conclusion	Comment
Listrat et al., 1997	3 injections of Hyalgan, every 3 months, for a year	Randomised, prospective	VAS (pain), Lequesne's index (functional impairment), $AIMS_2$ (quality of life)	This study suggests that repeated injections of hyaluronan might delay structural progression of the disease.	Industry-sponsored study. Small sample size
Adams et al., 1995	Hylan G-F 20 vs continuous NSAIDs	Randomised, single-blind, prospective, muticenter	VAS (pain)	Hyalgan equivalent to continuous NSAIDs at 12-week follow-up	Industry-sponsored study
Wobig et al., 1999	Hylan G-F 20 vs a low molecular weight hyaluronate	Randomised, double-blind, prospective, multicenter	VAS (pain)	Hylan G-F 20 significantly better than low molecular weight hyaluronate at 12 week follow-up	Industry-sponsored study
Bellamy et al., 2001	Appropriate Care (according to ACR guidelines) with or without hylan G-F 20 injections	Randomised, prospective, multicentre	WOMAC, and SF-36	Results provide strong evidence for adoption of treatment with hylan G-F 20 in patients with knee OA. Good value for money.	Industry-sponsored study

Cost-effectiveness

In clinical trials of intraarticular hyaluronan preparations, pain relief among those who completed the study was significantly greater than that seen after intraarticular injection of placebo, and comparable with that seen with oral NSAIDs. In addition, pain relief among those who completed the study was comparable with greater than that with intraarticular glucocorticoids. Although pain relief is achieved more slowly with

hyaluronan injections than with intraarticular glucocorticoid injections, the effect may last considerably longer with hyaluronan injections (17).

The price for the course of HA ranges from approx. £200 to £300 in the UK. In our own experience on 104 patients, in Liverpool and Chester (with Hyalgan™, Synvisc™, Orthovisc™ and Arthrease™), from 1999 to 2002, the average duration of pain relief was seven months, but approximately 10% of patients did not experience any significant pain relief. We did not observe any significant complications. The only reported adverse effects were injection site pain in five patients (lasting less than 24 hours), and exacerbated knee effusion in two patients.

Safety

The risk of introducing infection into an OA joint is extremely low if standard aseptic technique is used. The lack of systemic side effects make the use of viscosupplementation an appealing option for the management of the knee OA. Extensive safety and toxicity tests were performed on Synvisc™ before the first clinical trials. Preclinical studies showed that Synvisc™ is nonantigenic, nontoxic, noninflammatory, and does not elicit foreign body reactions. Hyaluronan, from which hylan is derived, has been safely used in ophthalmic and orthopedic applications in millions of patients. There have been no systemic side effects attributed to Synvisc. No cases of anaphylaxis or anaphylactoid reactions have been reported in connection with Synvisc™ treatment. However, anaphylactic-like reactions have been reported following intra-articular Hyalgan™ injections (18).

Unwanted Effects

In clinical trials, transient redness, local pain, warmth, and effusion, usually lasting up to three to four days, may occur. Occasionally, severe synovitis may occur requiring treatment with intra-articular corticosteroids.

Precautions

Patients should consult their doctor or surgeon if they have a history of hypersensitivities to hyaluronan preparations or are allergic to avian proteins, feathers and egg products. Intra-articular viscosupplements should not be given to patients with an infection or skin disease around the injection site, and should not be used if venous or lymphatic stasis is present in the leg, or if the joint is severely inflamed (18).

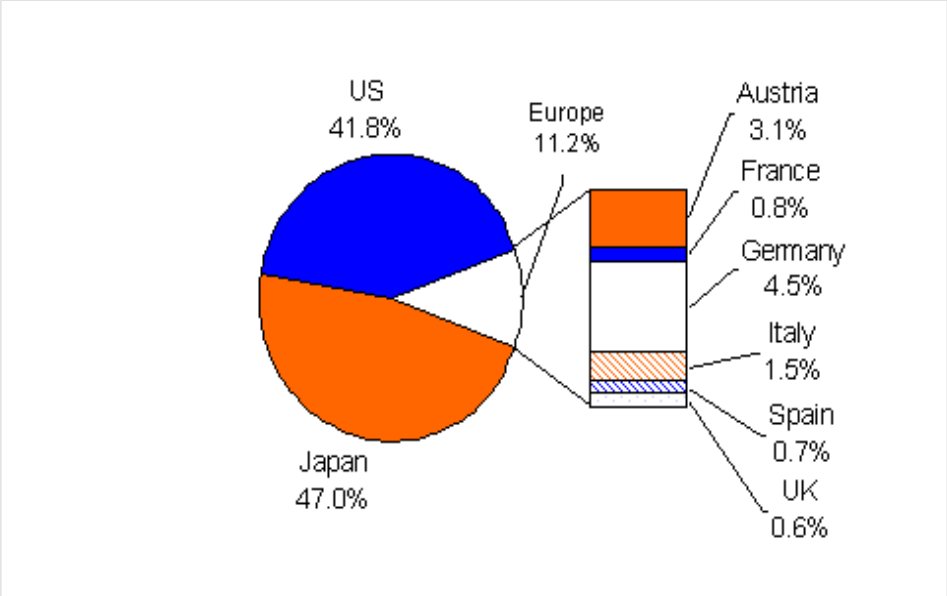
Market Analysis[19]: the reimbursement of hyaluronic acid therapy varies greatly from market to market, particularly in Europe, and has become more important in some of these markets than efficacy or product reputation. Despite claims and reasonable clinical evidence from manufacturers of efficacy and specific product advantages, many end-users remain sceptical that hyaluronic acid viscosupplementation is truly an effective treatment for osteoarthritis of the knee. Therefore companies must increase physician and surgeon confidence through detailed clinical studies specifically designed to address these concerns.

The US will become the largest market for HA manufacturers and distributors, valued at $235 million in 2001, despite per capita usage of only 8.5% of that seen in Austria. The Austrian market is growing at a very slow pace, because of extremely high per capita usage. In contrast, the UK market is growing at a higher rate, but surgeon and GP scepticism, infrastructure problems, and lack of funds interfere with wider acceptance of viscosupplement therapy. In the UK there are additional difficulties with “evidence-based-medicine” approach of some NHS Trusts, which are unnecessarily restrictive, and in reality based on rationing policies. At the same time most orthopaedic surgeons recommend and use a wide range of expensive oral NSAIDs, a combination of intra-articular steroids and local anaesthetic injections, and arthroscopic debridements and washouts, without any restrictions.

As evident from the table below, the $563.9 million global market for hyaluronic acid is dominated by Japan and the US, with the European market accounting for a comparatively small level of sales. While Japan accounted for 47% of the global market value in 2001, nearly 86% of the total number of HA injections were administered in Japan. Low prices in Japan, and high prices in US, account for the discrepancy between comparative market values and comparative market volumes.

Global Market Share by Value, %, 2001

Global Market Value: $563.9 million



Source: Datamonitor (www.datamonitor.com) **D A T A M O N I T O R**

In France, the product is only reimbursed at 50% of the price, with only one product reimbursed in 2001. In Spain, the use of hyaluronic acid is very low, due to lack of reimbursement. In Italy, the market is fairly mature, with hyaluronic acid viscosupplementation first utilized in 1987 when Fidia launched Hyalgan to the market. Fidia's product continues to dominate the market, which reached 345,000 injections in 2001. The largest HA market in Europe is Germany. The German HA market continues to exhibit impressive growth despite a relatively high market volume, forecasted to approach 1,000,000 units sold in 2002. The young US market remains the fastest growing market, and in 2002 will become the highest value HA market in the world. Only three products currently competing on the US market are contributing to increased awareness and acceptance of hyaluronic acid among end-users and patients.

Conclusion

The economic costs of OA of the knee are enormous. If viscosupplementation does indeed reduce and defer the need for surgical procedures like arthroscopic knee washouts and debridements, and total knee replacements, the cost savings will be considerable. Even more important will be the diminution of the risks associated with anaesthetic and surgical procedures. However, 3 or 5 weekly injections are quite awkward for most clinicians and patients. One single injection, which lasts long

enough, would be much more useful.

There is no doubt that viscosupplementation represents valuable addition to current treatments for osteoarthritis and an alternative treatment when other forms of medical treatment are contraindicated or have failed.

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