

Intra-articular use of hyaluronic acid in the treatment of osteoarthritis

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Abstract: Osteoarthritis is one of the leading causes of disability in the elderly. The changes in the lubricating properties of synovial fluid lead to significant pain and loss of function. More than ten years have passed from the first studies. Up till now many authors have supported intra-articular hyaluronan (HA) therapy as not only a symptom-modifying therapy but also a treatment which may significantly decrease the rate of deterioration of joint structure. In this review we report data relative to knee and hip treatment. The ongoing studies continue to further our understanding of the fundamental mechanisms that likely underlie the therapeutic benefits of this treatment but, despite recent progress, many unresolved issues require further study. Large scale double blind controlled studies must be carried out to confirm these promising data and produce meaningful guidelines.

Keywords: osteoarthritis, hyaluronan, intra-articular injections, ultrasound-guided, visco-supplementation

Introduction

Osteoarthritis is one of the leading causes of disability in the elderly. The changes in the lubricating properties of synovial fluid lead to significant pain and loss of function. Viscosupplementation, the injection of hyaluronic acid (HA) into the joints, improves the biochemical properties of synovial fluid into osteoarthritis joints. The clinical effect is pain relief and disease modifying activity (Balazs and Denlinger 1993; Pelletier and Martel-Pelletier 1993).

Although there are many nonsurgical therapies available for the treatment of pain associated with osteoarthritis (OA), their long-term use and safety have not been systematically followed. Intra-articular (IA) hyaluronan therapy has been used in the treatment of symptoms associated with OA of the knee with a very favorable safety profile (Pagnano and Westrich 2005). In this connection, the physiological and pharmacological characteristics of HA have recently been reviewed. The high concentration of HA in spinal fluid (SF) is essential for normal joint function. The altered properties of the synovial fluid in OA, the decrease in molecular size and concentration of HA leads to reduced rheologic properties, which affect the lubrication and protection mechanism of action of IA hyaluronan and is probably more complex than previously thought (Maneiro et al 2004).

The hypothesis that HA could bind to specific receptors is now widely accepted. The cluster determinant 44 (CD44), the intracellular adhesion molecule-1 (ICAM-1) and the receptor for hyaluronate-mediated motility (RHAMM) expressed in many cells, are some of those implicated in the process (Hodge-Dufour et al 1997; Siegelman et al 1999). The binding of HA with its specific receptors has been reported to trigger various intracellular signal events such as cytokine release and stimulation of cell cycle proteins. The consequences of these interactions is to stimulate cell functional activities such as cell migration and proliferation (Cao et al 2004).

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More than ten years have passed since the original explanation by Balazs and Denlinger (1993) that the favorable effects of IA HA therapy in OA was related only to the restoration of SF rheological properties (Goldberg and Buckwalter 2005). Many subsequent studies have supported that IA HA therapy is a symptom-modifying approach that has been found to be safe and effective for reducing pain due to OA of the knee and furthermore may also significantly decrease the rate of deterioration of joint structure. This statement stems from different evidences. First of all, the complex biochemical effects of HAs in the synovium and extracellular matrix of the articular cartilage, including interactions between exogenously administered HA and articular cartilage, subchondral bone, matrix proteoglycans, and collagens. In the second place, the effects of HA administration in animal models of OA, including total or partial meniscectomy and anterior cruciate ligament transectomy. Thirdly, the results of clinical trials using one HA, Hyalgan (sodium hyaluronate, molecular weight 500–730 kDa) that evaluated structural outcomes, such as joint-space width, chondrocyte density and vitality, and arthroscopic evaluation of chondropathy. Localized severe acute inflammatory reactions reported with repeated treatment in some patients are not a class effect but may be linked to physicochemical characteristics of hylan-based treatment (Arrich et al 2005; Pagnano and Westrich 2005; Goldberg and Buckwalter 2005).

Studies on the effects of HAs of different molecular weight (MW) on specific receptors have shown that the results can vary depending on the size of the HA molecules used. For example low MH HA fragments generated during joint inflammation may promote chemokine gene expression by macrophages. Ohkawara and colleagues (2000) noticed that HA preparation of MW 0.2×10^6 Da was more effective in maintaining the survival of blood eosinophils than HA with an MW of 3×10^6 – 6×10^6 Da, proposing that the effect derived from the increased expression of granulocyte macrophage colony-stimulating factor after CD44 activation (Ohkawara et al 2000).

Different HA products

Presently, there are several different HA products available for injection. However, the source of hyaluronic acid varies. Some products are extracted from rooster combs but a contraindication to treatment would be an allergy to eggs or chicken.

Hyaluronic acid is available in a variety of products with different molecular weight ranging from 500 KD to more than 90 millions D (Table 1). Hylans are cross-linked hyaluronic acids, which gives them a higher molecular weight and increased elastoviscous properties.

HA products in the intra-articular treatment of knee OA

The first studies on the use of HA in human knee OA were carried out in the 1970s by Rydell and Balasz (1971) and Peyron and Balasz (1974). In 1974, Peyron injected 1, 2, or 3 ml of HA (Healon) in 23 knees and obtained positive responses in pain and function in 74% of patients. The treatment with two injections of 2 ml HA each appeared to have the best outcome.

Recent papers have reviewed clinical trials published in the last years using different HA preparation and the results of these trials are summarized in Table 2.

Data support the benefit and safety of repeated treatment with IA HA. Many trials indicate that sodium hyaluronate (molecular weight [MW] 500–730 kDa) is well tolerated and as effective after multiple courses of treatment as it is after a single course (Pagnano and Westrich 2005). Other data state that viscosupplementation is an effective treatment for patients with knee OA who have ongoing pain or are unable to tolerate conservative treatment or joint replacement.

Viscosupplementation appears to have a slower onset of action than intra-articular steroids, but the effect seems to last longer (Wang et al 2004).

HA not only relieves the symptoms of OA but also modifies the structure of the diseased joint and the rate of

Table 1 Molecular weights of hyaluronic acid (HA) products

Trade name	Molecular weight	Source	Mg/ml
Hyalgan	500–730 KDa	HA extracted from rooster combs	20 mg/2 ml
Hyalubrix \cong	1500 KDa	Fermentative HA	30 mg/2 ml
Artz (Supartz)	800–1170 KDa	HA extracted from rooster combs	25 mg/2.5 ml
Synovial (Jointex)	800–1200 KDa HA	Fermentative HA	16 mg/ml
Synvisc	6000 KDa	HA extracted from rooster combs	16 mg/2 ml
Durolane	90 millions Da	Synthetic HA	20 mg/ 3 ml
Euflexxa	2.400–3.600 kDa	Fermentative HA	20 mg/2 ml

Table 2 Recent clinical trials using HA

Author / Year	N trials	Intervention	Conclusions
Lo et al 2004	22 selected trials	Hyalgan, Synvisc, Artzal, Suplasyn, BioHy, Orthovisc	Measurable effect when compared with placebo. Highest-molecular-weight HAs may be more. Heterogeneity of these studies limits definitive conclusions.
Aggarwal et al 2004	Five case series 13 RCTs	Synvisc low-molecular-weight HA	High-molecular-weight HAs effective. Conflicting results with low-molecular-weight. Slower onset of action than intra-articular steroids, but the effect last longer.
Wang et al 2004	Twenty blinded randomized controlled trials	Hyaluronic acid versus placebo	Therapeutic efficacy and safety
Axe et al 2005	Potential use in the treatment of inflammatory arthropathies (eg, acute joint trauma and fractures)	Hyaluronans	Trials limited in design and patient number. Moderate results. Controlled clinical trials are warranted.
Goldberg et al 2005	A review on a Medline search through June 2004	Hyalgan, Supartz, Synvisc	In addition to relieving the symptoms, HAs also modify the structure of the diseased joint and the rate of OA disease progression.
Arrich et al 2005	Twenty-two trials	Hyaluronic acid	The data available did not allow an appropriate assessment of any end point. Adverse events occurred slightly more often.
Bellamy et al 2005	Thirty-seven trials included comparisons of hyaluronan/hylan and placebo, nine trials included comparisons of intra-articular corticosteroids, and five trials included comparisons of (NSAIDs)	Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease), Duro-lane, Fermatron, Go-on, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum	The effects against 'placebo' controls generally supported the efficacy. Delayed effects on pain and function. Comparable efficacy against NSAIDs and longer-term benefits against IA corticosteroids. Few adverse events were reported.
Pagnano et al 2005	Databases were searched using the terms hyaluronan, sodium hyaluronate, hyaluronic acid, hylan, hylan G-F 20	Hyaluronan, sodium hyaluronate, hyaluronic acid, hylan, hylan G-F 20	Hyaluronans are safe and effective in the treatment of pain. Sodium hyaluronate decrease the rate of deterioration of joint structure

Abbreviations: IA, intra articular; RCT, randomized controlled trials; HA, hyaluronic acid; OA, osteoarthritis.

OA disease progression, at least early in the evolution of the disease process (Ohkawara et al 2000).

Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment at different post injection periods but especially at the 5 to 13 week post injection period with a dramatic effect on the reduction of NSAIDs monthly consumption.

However, there are few randomized head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products.

In some analyses, viscosupplements were comparable in efficacy to systemic forms of treatment, with more local reactions but fewer systemic adverse events. In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the

HA class of products in the treatment of knee OA (Lo et al 2003). In one systematic review, IA HA has not been proven clinically effective and may be associated with minimal and transient risk of adverse events (Arrich et al 2005).

At present no case of septic arthritis has been reported in any clinical trial. Most adverse events are minor and transient at the injection site. Painful post-injection reaction occurred in 1%–2% of patients, the pain did not last more than 72 hours. Systemic allergic reactions due to individual hypersensitivity were rarely recorded. Therefore viscosupplementation seems to be an efficacious and safe treatment.

The heterogeneity of these studies limits definitive conclusions on different treatment regimen with diverse molecular weight HA but in our opinion we think that the different HA products act with the same class effect (Axe and Shields 2005).

Furthermore preliminary data indicate a potential use for hyaluronans in the treatment of inflammatory arthropathies (eg, acute joint trauma and fractures) that require long periods of immobilization, and in tissue engineering for chondral defects. Although the trials that have investigated the use of hyaluronan therapy for the management of traumatic and degenerative musculoskeletal disorders seen in sports medicine have limitations in design and patient number, the results have been promising and suggest that larger controlled clinical trials are warranted (Peyron and Balasz 1974).

HA products in the intra-articular treatment of hip OA

Few data exists in literature about the viscosupplementation of hip OA in spite of it is the second most common site of the disease after the knee (Pelletier and Martel-Pelletier 1993; Pagnano and Westrich 2005). One of the limiting factors for this practice might be related to the injection procedure. The intra-articular injection of the hip is not as easy as for the knee, mainly for anatomical features of the joint and the proximity of "sensitive" structures such as the femoral artery and nerves. Even though hip injection may be performed "blindly", failure rate is nevertheless significant (Jones et al 1993) and when using a slow absorbing viscosupplement like hyaluronan, the potential local complications may jeopardize the therapeutic benefit (Jackson et al 2002). For such reasons, it has been suggested to perform intra-articular injection of the hip under radiological or ultrasound control. Although several ultrasound guidance techniques were available (Qvistgaard et al 2001), we developed a personal one using an antero-superior approach (Migliore et al 2003).

Since no single or double blind randomized controlled trials have yet been published, we analyzed all the available trials on MEDLINE to assess viscosupplementation for the treatment of hip OA (Table 3).

The efficacy data underlines significant improvement in pain and function as has been shown in the knee OA studies despite the small size of the sample. The short period of observation has not seen a change in the natural history of the disease. In order to confirm these promising data, large scale double blind controlled studies must be carried out.

Conclusions

The ongoing studies continue to further our understanding of the fundamental mechanisms that likely underlie the therapeutic benefits of this treatment. The meta-analysis in progress are further establishing a role for viscosupplementation in ameliorating the symptoms of knee and hip osteoarthritis. At the moment it is clear that viscosupplementation is more efficacious in the initial and intermediate stages of OA more than at an advanced stages and that this therapy is exceptionally safe compared with other OA treatments.

Despite recent progress, many unresolved issues require further study. These include determining the cost-effectiveness of viscosupplementation, exploring the therapeutic effectiveness and safety, clearly defining the relation between molecular weight and the clinical effectiveness of the various hyaluronan products, establishing optimal dosing regimens, evaluating efficacy in different OA populations, determining how to best incorporate viscosupplementation into the evolving OA treatments algorithms, exploring the potential for treatment of OA joints other than the knee, as already shown for the hip, and assessing potential synergistic or additive effects with other modalities such NSAIDs and SYSADOA.

It is encouraging that hyaluronan-based therapy is proving to be safe and effective for many patients with symptomatic hip and knee OA despite the fact that many unresolved issues requiring further study remain. If hyaluronan derivatives are eventually proven to have clear

Table 3 Viscosupplementation studies for the treatment of hip osteoarthritis

Author year	HA	Nr of pts.	Outcome measures	Months of follow-up	Nr.of injections
Brigantini 1994	Hyalgan	44	P/GA/NSAIDs	6	3-5
Brocq 2002	Synvisc	22	LI	1-6	1-2
Conrozier 2003	Synvisc	57	P/W/GA	3-6	1-2
Vad 2003	Synvisc	22	P/AAOS/LLCSS	12	3
Migliore 2003	Hyalgan	28	P/LI/NSAIDs	NG	1-3
Caglar-Yagci 2005	Synvisc	14	P/LI/15 mWT	3	3
Berg 2004	Durolane	31	W/GA	3	1
Migliore 2005	Synvisc	26	P/LI/NSAIDs	12	1-2
Tikiz 2005	Synvisc vs Ostenil	25 vs 18	P/W/LI	6	3
Migliore 2006	Synvisc	36	P/W/NSAIDs	18	1-2

Abbreviations: P, pain; GA, global assessment; 15 mWT, 15-meter walking time; NSAIDs, NSAIDs consumption; LI, Lequesne index; W, Womac index; AAOS, American Academy of Orthopaedic Surgeons; LLCSS, Lower Limb Core Scale Score.

disease-modifying effects, it may then be reasonable to consider their use early in cartilage injury or disease, before the onset of symptomatic OA.

Additional well-designed randomized controlled trials with high methodological quality are needed to resolve the continued uncertainty about the therapeutic effects of different types of hyaluronic acid products on osteoarthritis in various clinical situations and patient populations (Wang et al 2004).

At the moment the Arthritis Foundation believes that while more studies are needed to determine the long-term results of such treatments, HA provides an option for people with knee OA who have not responded well to drug treatments or exercise and physical therapy. It also may be appropriate for those who may be at increased risk for upper gastrointestinal (GI) complications, such as patients who: are over 65 years old; are taking oral corticosteroids and/or anticoagulants; have a history of peptic ulcer disease or upper GI bleeding; are smokers; and consume high volumes of alcohol. HA also may be considered in patients with kidney failure.

Disclosure

The authors report no conflicts of interest.

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