

# Effectiveness and utility of hyaluronic acid in osteoarthritis

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## Summary

**Osteoarthritis (OA) is a chronic degenerative joint disease characterized by pain and progressive functional limitation. Viscosupplementation with intra-articular hyaluronic acid is a treatment option in knee OA that is included in the professional guidelines for treatment of this joint disease, but potentially should apply to all synovial joints in order to reduce pain and improve joint lubrication. Exogenous HA can enhance chondrocyte HA synthesis, prevent the degradation of cartilage and promote its regeneration. Moreover it can reduce the production of proinflammatory mediators and matrix metalloproteinases involved in OA pathogenesis. This mini review highlights the evidence of hyaluronic acid in reducing osteoarthritis symptoms and structural damage, as well as its ability to delay prosthetic surgery. Viscosupplementation should be considered as a long-term therapy.**

*KEY WORDS: hyaluronic acid; osteoarthritis management; viscosupplementation; intra-articular hyaluronic acid.*

## Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive damage of articular cartilage and underlying bone. It is a common rheumatic disease that affects both genders and the majority of older people, but also younger subjects with consequent loss of workdays (1). The most important symptom is pain, accompanied by morning stiffness, usually of short duration, accentuated by movements and reduced by rest. Moreover joint damage causes a progressive functional limitation (2). As part of the overall management of patients with osteoarthritis it is important to use a therapeutic strategy including physical therapy and rehabilitation, non-steroidal anti-inflammatory drugs, analgesics, chondroprotecting agents and intra-articular treatment with infiltrative substances such as steroids and hyaluronates (3). Viscosupplementation (VS) with intra-artic-

ular hyaluronic acid (IA-HA) is a well-established treatment option in knee OA and is included in the professional guidelines for treatment of the disease in this joint but it should apply theoretically to all synovial joints in order to reduce pain, improve joint function and contrast joint damage (4).

## HA mechanism of action

HA is a non-sulfated glycosaminoglycan consisting of alternately repeating D-glucuronic acid and N-acetylglucosamine units. HA exists naturally in various animal tissues, including rooster combs, shark skin, bovine eyeballs, bovine nasal cartilage, rabbit brain and heart and in various human tissues, including the umbilical cord, serum, vitreous body, dermis, epidermis, thoracic lymph, urine and synovial fluid (SF). However, the highest amounts of HA in the human body are found in the ECM of soft connective tissues (5). HA could bind to specific receptors expressed in many cells, such as the cluster determinant 44 (CD44), the intracellular adhesion molecule-1 (ICAM-1) and the receptor for hyaluronate-mediated motility (RHAMM) (6, 7). This binding triggers 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 (8). In osteoarthritic joints synovial fluid contains a lower concentration of HA than in healthy joints, so intra-articular therapy with exogenous HA can restore its viscoelastic properties. *In vivo* and *in vitro* studies have shown various physiological effects of exogenous HA that may contrast the mechanisms involved in osteoarthritis pathogenesis. Indeed, exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans, prevent the degradation of cartilage and promote its regeneration. Moreover it can reduce the production of proinflammatory mediators and matrix metalloproteinases, and reduce nerve impulses and nerve sensitivity associated with OA pain (9).

## Symptoms effectiveness

Globally, data indicate that intra-articular hyaluronan preparations provide OA pain relief that is comparable to or greater than that observed with conventional treatment, NSAID medications, intra-articular corticosteroids, arthroscopic lavage, physical therapy and exercise (10). Also placebo effectively relieved pain, and improved patient function and stiffness in particular when placebo has been given as an injection of saline (11) but it does not have the ability to determine structural benefits. Moreover several clinical trials have shown that HA is more active than saline in reducing arthritic pain in osteoarthritis of the knee with significant improvements in pain and physical function (12-16) and an excellent tolerability profile with a low incidence of complica-

tions at local level and absence of systemic effects (17, 18). A recent systematic review showed that Hylan GF-20 is a safe and effective treatment for decreasing pain and improving function in patients suffering from knee but also hip OA. Moreover new evidences are emerging for its use in other joints (19). In patients with osteoarthritis non-steroidal anti-inflammatory drugs (NSAIDs) consumption in order to reduce pain is often inappropriate and strictly related to both high gastrointestinal and cardiovascular morbidity and increasing mortality rate. Instead HA intra-articular treatment is well tolerated and is associated with a low incidence of adverse effects. A multicentric, open and retrospective study, that enrolled more than two thousand patients, has investigated if NSAID consumption may be reduced by the use of ultrasound-guided intra-articular injection of several hyaluronic acid (HA) products in hip joint administered in patients affected by symptomatic hip OA. The consumption of NSAIDs was reduced of 48.2% at the third month when compared with baseline values. This sparing effect increased at 12th and 24th month with a reduction respectively of 50% and 61% in comparison to baseline values. These data point out that intraarticular hyaluronan preparations provide OA pain relief and reduce NSAIDs consumption in a large cohort of patients for a long period of follow-up (20).

### Structural effects

HA is a useful tool in OA treatment, with a potential structure-modifying activity. The structural effects of HA given as 5 weekly injections (20 mg/2 ml once a week for 5 weeks), were evaluated by microarthroscopy and morphological analysis of biopsy samples taken at baseline and after 6 months in an open clinical trial on 40 patients with knee osteoarthritis. At 6 months, the microarthroscopic evaluation indicated that the majority of the patients (60%) showed no changes compared to baseline, while 32.5% of the patients showed improvement in the grading and/or extension of cartilage lesions and 7.5% showed a worsened condition. These changes were accompanied by a statistically significant reduction in the synovial inflammation. At 6 months, compared to baseline, a statistically significant reconstitution of the superficial amorphous layer of the cartilage, an improvement in the chondrocyte density and vitality, and a statistically significant reduction in synovial inflammation accompanied by a significant increase in the synovial repair process were observed (21). Similar data were obtained in a prospective, controlled study of 1-year duration in which 36 patients with painful knee osteoarthritis were enrolled. After randomization, either conventional therapy or three cycles (every 3 months) of three intra-articular injections of Hyalgan (once a week) were given. Then patients were arthroscopically evaluated for severity of chondropathy and cartilage deterioration was observed in both control and HA groups, but was significantly less in the HA group (22). In another study, synovial membranes from patients with knee OA were examined by arthroscopy and by light and electron microscopy before and 6 months after local injection of HA (2 ml of 500-730.000 MW hyaluronan, 10 mg/ml in saline, one injection per week for 5 weeks) or MP (1 ml of methylprednisoloneacetate, 40 mg/ml, one injection per week for 3 weeks). Arthroscopy revealed a significant decrease of tissue inflammation after both treatments which tended to decrease the numbers of macrophages, lymphocytes, mast cells and

adipocytes, and to decrease oedema and to increase the number of fibroblasts and the amount of collagen throughout the thickness of the synovial tissue (23). Instead, a similar study showed that six months after hyaluronan treatment thickness of the superficial amorphous layer, chondrocyte density and territorial matrix appearance were significantly higher with HA compared with baseline but also with intra-articular steroid treatment (24).

### Viscosupplementation and joint progression

Treatment with repeated cycles of IA-HA is suggested to delay surgical interventions in knee and hip osteoarthritis. This aspect was investigated in some studies. In a prospective cohort study with 54-month follow-up period, involving 183 patients who received at least a single course of 3-weekly injections of IA-HA (500-730 Kilodalton, Hyalgan), patients who responded well to this treatment were recommended to repeat the administration of a 3-weekly injections every 6-12 months based on their symptoms. The incidence of TKR (total-knee-replacement) was only 28.4% with a mean time to TKR of 15.4 months (25). Moreover in a retrospective case series review the incidence and time to TKR were determined from October 1997 to November 2003 in patients treated with 1 or more courses of intra-articular hylan G-F 20 injections (3 weekly injections per course) who were TKR candidates. The incidence of TKR in hylan G-F 20-treated knees (1,187 knees; 863 patients) was 19% (n=225 knees). The median time to TKR in these patients was 638 days (1.8 years) and survival analysis showed that 75% of knees had not a TKR by 1,370 days (3.8 years) (26). In another study 120 patients candidate for a total hip arthroplasty received viscosupplementation and 51% of these patients did not undergo total hip arthroplasty at 3 years after viscosupplementation (27). In addition in a retrospective pilot study 224 patients with symptomatic hip OA and treated with hylan G-F 20 were analyzed. Eighty-four patients (37.5%) progressed to THR, 206 patients (92.0%) achieved 12 months survival, 170 patients (75.9%) achieved 24 months survival, and 69 patients (30.8%) achieved 5 years survival. Mean survival time was 36 months (28). Similar data were obtained in a retrospective study in patients suffering from hip OA treated with ultrasound-guided intra-articular injections of HyalOne (Hyalubrix 60 Italian brand name). At 24 months, 159 out of 176 (90%) patients did not undergo THR. At 48 months, 82% (N = 144) of the study population treated with intra-articular hyaluronic acid avoided THR. In the group of 93 patients considered candidates for THR only 17 had undergone THR, with survival results of 82% at 24 months. At 48 months, this percentage reduced to 66% in this group (29).

### Viscosupplementation as long-term therapy

In consideration of its clinical and structural effectiveness and its tolerability, therapy with hyaluronic acid can be regarded as a long term therapy. In particular AMELIA (Osteo Arthritis Modifying Effects of Long-term Intra-articular Adant) study (30) showed the benefit of treatment with more than one course of hyaluronan. AMELIA was a multicentre, randomised, patient and evaluator-blinded, controlled study in 306 patients with knee osteoarthritis, and was designed to compare against placebo the efficacy and safety of repeated injections of hyaluronic acid (HA) over 40 months. Pa-

tients received four cycles of five intra-articular HA or placebo injections with a follow-up of 6 months after the first and second cycles, and 1 year after the third and fourth cycles. At the 40-month visit significantly more patients responded to HA compared with placebo and the number of responders to HA increased through the study, whereas those to placebo did not change. Significant differences were found in favor of HA for pain, function and patient global assessment. The results of AMELIA offer important evidence that repeated cycles of intra-articular injections of HA not only are safe and improve knee osteoarthritis symptoms during the in-between cycle period but also exert a marked carry-over effect for at least 1 year after the last cycle.

## Conclusion

Intra-articular hyaluronic acid is an useful therapeutic tool in the management of patients with osteoarthritis. Literature data seem to indicate its ability to reduce pain and improve joint function. Moreover, considering its high tolerability, its ability to contrast the structural joint damage and to delay the use of prosthetic surgery, it can be seen as a safe and effective long-term therapy.

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