Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders

REVIEW

Hylan G-F 20: Review of its Safety and Efficacy in the Management of Joint Pain in Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is a chronic degenerative joint disease that is a clinically and economically important disease. The increased prevalence of OA with aging, coupled to the demographics of aging populations, make OA a high priority health care problem. Viscosupplementation (VS) is a well-established treatment option in knee OA that is included in the professional guidelines for treatment of this joint disease, and could potentially provide a useful alternative in treating such patients with painful OA. Theoretically VS is an approach that should apply to all synovial joints.

Objectives: The aim of this review is to assess the efficacy and safety of viscosupplementation with Hylan GF-20 (Synvisc®) in the management of joint pain in osteoarthritis.

Methods: The following databases were searched: Medline, Database of Abstract on Reviews and Effectiveness, Cochrane Database of Systematic Reviews. Furthermore, the lists of references of retrieved publications were manually checked for additional references. The search terms Review, Viscosupplementation, Osteoarthritis, Hyaluronic acid, Hyaluronan, Sodium Hyaluronate, Hylan GF-20, Synvisc, intra-articular injection were used to identify all studies relating to the use of Synvisc® viscosupplementation therapy in OA.

Results: Hylan GF-20 is a safe and effective treatment for decreasing pain and improving function in patients suffering from knee and hip OA but new evidences are emerging for its use in other joints.

Keywords: review, viscosupplementation, osteoarthritis, hyaluronic acid, hyaluronan, sodium hyaluronate, synvisc®, hylan GF-20, intra-articular injection

Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2010:3 55–68

This article is available from http://www.la-press.com.

Introduction

Osteoarthritis is a chronic degenerative joint multifactorial disease. The disease process of osteoarthritis is characterised by the progressive destruction of the articular cartilage, leading to joint space narrowing, subchondral sclerosis, subchondral cyst, synovial inflammation and marginal osteophyte formation.[1] The progression of osteoarthritis leads to exposure of subchondral bone at a weight-bearing site at which the bone will then be subjected to abrasion and further damage. The primary role of synovial fluid is protective, by means of limiting axial forces on the articular surface and decreasing friction between joint surfaces. Hyaluronan is entirely responsible for the elastoviscosity of synovial fluid. Because of its hyaluronan content, synovial fluid can behave as either a predominantly viscous fluid or a elastic fluid.[2] Hyaluronan is also responsible for protecting the collagen fibrils and cells of articular surfaces, synovial tissue, capsule and ligaments from mechanical damage.[3] In osteoarthritis, the synovial fluid is more abundant and less viscous.[4]Hyaluronan becomes depolymerized, its concentration and molecular weight are decreased, resulting in a decrease in elastoviscosity. These changes increase the susceptibility of cartilage to injury.[2,5,6] Osteoarthritic synovial fluid functions primarily as a viscous rather than elastic fluid through the entire range of joint movement, which reduces its protective effect on cartilaginous, fibrous, and cellular structures. As articular cartilage is progressively damaged, the net rate of proteoglycan synthesis ultimately falls and the cartilage thins, resulting in a decrease in the load-bearing capacity.[7] Administration of exogenus Hyaluronan (HA) preparations addresses this problem by replacing the low viscoelastic synovial fluid with solutions of higher viscosity.[8] There are also substantial data that exogenously provided HA may also improve pain and function by non-mechanical, biologically based mechanisms within the synovial and articular environment.[9] Current treatment options for OA include the use of simple analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) corticosteroid injection, weight reduction and surgical treatment. Prior to surgical treatment of OA, which is expensive and not risk-free, all other treatment options should be fully considered. VS with IA HA was approved by Food and Drug Administration (FDA) in 1997. VS is a well-established treatment option in knee OA and is included in the professional guidelines for treatment of the disease in this joint.[10,11] Theoretically VS is an approach that should apply to all synovial joints. A number of recent studies have attempted to evaluate its efficacy in joints other than the knee. The primary symptom of OA is pain that is seen as entirely linked with function, with physical movements triggering pain, while pain, in turn, causes limitations in physical function. To cope, patients will avoid certain movements and activities that they know will cause pain, and will engage in adaptive behavior to moderate the pain experience, such as organizing their homes to limit the need for movements or positions that are more likely to be painful.[12] There are five injectable forms of HA approved by the United States FDA including Hyalgan®, Supartz®, Orthovisc®, Synvisc®, and Euflexxa®. Each of these HA products differ in their origin, method of production, molecular weight, dosing instructions, biologic characteristics, and possibly clinical outcomes. Hylan G-F 20 (Synvisc® Genzyme Corporation, Cambridge MA U.S.A.) is one of the VS products approved for marketing in Canada since 1992 and the United States since 1997 after public review of the data by a Food and Drug Administration (FDA) advisory panel.[13] Hylan GF-20 is a high-molecular weight HA derivate composed of two hylan polymers within a buffered physiological NaCl solution. The phenomenon of cross-linking (the first cross linking using formaldehyde and the second cross-linking forming sulfonyl-bis-ethyl cross-links between the hydroxyl groups of polymer chains) leads to the main characteristic of the product by the formation of a mixture of two different hylan polymers: hylan A (80%), which is a soluble high MW molecule (MW of 6.000.000 Da), hylan B (20%), which is an insoluble gel.[14] The rheological properties of two forms of hylan are different from each other and both are significantly different from unmodified hyaluronan; the cross-linking also allows a longer residence time into the joint than that of linear HA products, in particular for hylan B, whose insolubility delays its removal from the joint. The IA residence time of hylan GF-20 has been studies in animal models.[14] In rabbits, the estimated half-life is 40 h and that of linear HA does not exceed 24 h. Hylan GF-20 is non-immunogenic, non-inflammatory, and des not cause foreigh-body reaction. The

objective of this review is to assess the efficacy and safety of VS with Hylan GF-20 (Synvisc®) intra-articular injections in the management of joint pain in osteoarthritis of the knee, hip, ankle, shoulder, temporomandibular and thumb joint.

Inclusion Criteria

The following databases were searched: Medline, Database of Abstract on Reviews and Effectiveness, Cochrane Database of Systematic Reviews. Furthermore, the lists of references of retrieved publications were manually checked for additional references. The search terms Review, Viscosupplementation, Osteoarthritis, Hyaluronic acid, Hyaluronan, Sodium Hyaluronate, Hylan GF-20, Synvisc, intra-articular injection were used to identify all studies relating to the use of Synvisc® viscosupplementation therapy in OA. The search of the literature performed in this study were limited to published original studies including patients with a diagnosis of knee, hip, ankle, shoulder, basal joint and temporomandibular OA, made based on detailed clinical and radiographic information. All studies using Hylan GF-20 in treatment of OA in human were included. Studies comparing Hylan GF-20 with different types of HA, treatments such as placebo, NSAIDs, corticosteroid injections, supportive measures and other active treatments, were included. Furthermore, respect the studies using Hylan GF-20 in treatment of knee OA we calculated the percentage of pain reduction from baseline to end of follow-up (Table 1 and Table 2).

Results

Clinical data in knee Oa

Hylan GF-20 vs. Placebo

Data in literature shows that Hylan GF-20 is effective and safe in relieving pain and increasing mobility in patients with chronic idiopatic OA of the knee. There are 3 randomized placebo controlled trials which shows efficacy of 3 IA injection of hylan GF-20 compared to placebo at 8,[15] 12[16] and 26[17] weeks. Only one transient local AE that not required treatment was reported by Scale et al[16] systemic reaction such as itching and calf cramps were reported by Wobig et al[17] in three hylan GF-20-treated patients but none of these required treatment or study discontinuation. Another RCT, performed by Chevalier et al[18] shows that IA injection of another formulation of hylan GF-20 with a volume of 6 mL syringe (SynviscOne®) as unique injection is safe and efficacious at 26 weeks. The efficacy and safety of a single 6 mL injection of hylan GF-20 was reported also by Conrozier et al[19] that performed a prospective, randomized trial comparing different therapeutic regimens of hylan GF-20. This study suggests that a single 6 mL injection of hylan G-F 20 may be as efficacious, and as well tolerated, as 3 × 2 mL one week apart. Two RCT compare the efficacy and safety of three products (Hylan GF-20, Artzal[20] or Orthovisc[21]) versus placebo. In the first one[20] the IA injections produced a significant improvement on all outcome measures after 26 weeks in all the groups. In direct comparison against placebo for weeks 0–52, neither hyaluronan treatment showed a significantly longer duration of clinical benefit than placebo. However, when data for the two hyaluronan-treated groups were pooled, treatment with hyaluronan had a significantly longer duration of benefit compared with placebo ($P = 0.047$). No difference in AE between two groups were recordered. In the second trial,[21] at the end of 6 months follow-up, the outcome measures were significantly better than baseline for both of the HA groups and remained significant until the end of 6 months. All groups expressed improvement with physician global assessment scores after the first injection; this improvement reached statistical significance at the third injection in favour of HA group and lasted until the end of 3 months. Although the placebo group seemed worse, this difference was not statistically significant.

Hylan vs. other HA derivated

Differences of efficacy related to the molecular weight and other characteristics of hyaluronans are under discussion. Several RCT evaluated efficacy of Synvisc compared with low molecular weight Hyaluronan (Table 2). Juni et al[22] assessed the comparative efficacy and safety of three viscosupplements: hylan GF-20, a medium MW HA from avian sources (Orthovisc®) and a medium MW HA derived from bacterial sources (Ostenil®). 660 patients were randomly assigned to receive 1 cycle of 3 IA injection of these 3 preparations. They concluded that no evidence was found for a difference in efficacy between hylan GF-20 and HA. Two AEs, 1 episode

Table 1. Overview of RCT concerning viscosupplementation with Hylan GF-20 in treatment of knee osteoarthritis.

Study	Year	Trial	Patients	Products	Outcome measures	IA Inj	Interval	Pain reduction %	Follow up	Statistic results
Scale (16)	1994	RCT	80	Synvisc Placebo	WBP -NP (VAS) RAPDT (VAS) IMPKM (VAS)	2/3	1 w	S: 60, 50, 45% P: 20, 10, 10%	12 w	$P < 0.05$ $P < 0.05$ $P < 0.05$
Wobig (17)	1998	RCT	110	Synvisc Placebo	WBP (VAS) NP (VAS) RAPDT (VAS) IMPKM (VAS)	3	1 w	S: 40, 24, 37, 36% P: 15, -, 16, 8%	26 w	$P = 0.001$ $P < 0.005$ $P < 0.0001$
Çubukçu (15)	2005	RCT	30	Synvisc Placebo	RP-NP-WP (VAS) WOMAC A, B, C	3	1 w	S: 24, 22, 31% 31, 35, 14% P: 10, 10, 14% 15, 10, 0.5%	8 w	$P < 0.05$ $P < 0.05$
Chevalier (18)	2010	RCT	253	SynviscOne Placebo	WOMAC A	1	–	S: 36% P: 29%	26 w	$P = 0.047$
Karlsson (20)	2002	RCT	210	Synvisc Artzal Placebo	WBP LEQUESNE WOMAC	3	1 w	S: 20%, 20%, 11.3% A: 20%, 20%, 16.8% P: 20%, 20%, 16.8%	26 w 52 w	Neg
Kotevoglu (21)	2006	RCT	59	Synvisc Orthovisc Placebo	WOMAC A, B, C PGA PhGA	3	1 w	S: 35, 34, 25%, 35%, 20% Or: 35, 32, 20%, 30%, 35% P: 35, 10, 10%, 20%, 20%	6 m	Neg

Abbreviations: WBP, weight-bearing pain; NP, night pain; RAPDT, reduction of activity while performing daily task (joint mobility); IMPKM, improvement in most painful knee movement; RM, rescue medication; WP, walking pain; S, synvisc; P, placebo; A, artzal; Or, orthovisc.

Table 2. Overview of RCT concerning viscosupplementation with Hylan GF-20 vs. LMW HA in treatment of knee osteoarthritis.

Study	Year	Trial	Patient	Products	Outcome measures	IA Inj	Interval	Pain reduction %	Follow up	Statistic results
Juni (22)	2007	RCT	660	Synvisc Orthovisc Ostenil	WOMAC A	3 (second cycle)	1 w	S: 10% Or: 10% Os: 10%	6 months	Neg
Raman (24)	2008	RCT	392	Synvisc Hyalgan	VAS Pain WOMAC A, B, C	3 5	1 w	S: 36%, 34%, -, 21% H: 9%, 3%, -, 14%	12 m	$P = 0.04$ $P = 0.007$ Neg $P = 0.004$
Keratosan (23)	2005	RCT	92	Synvisc Orthovisc	HHS	3	1 w	S: 57% O: 47%	12 m	Neg
Wobig (25)	1999	RCT	70	Synvisc LMW	WBP IMPKM	3	1 w	S: 39%, 67% L: 27%, 51%	12 m	$P < 0.05$ $P < 0.05$
Atamaz (26)	2006	RCT	80	Synvisc or Orthovisc PTA	SP (VAS) WOMAC pain and function	3 + 1	1 w + 6 m twice a week for 3 weeks	S: 33, 20% O: 18, 30% PTA: 42, 20% S: 20, 20, 20 O: 10, 13, 4 PTA: 34,+10, 11	9 m 12 m	$P < 0.05$ (PTA) $P < 0.05$ (O) $P < 0.05$ (S) $P < 0.05$ (S) $P < 0.05$ (S)

Abbreviations: HHS, hospital for special surgery; WBP, weight-bearing pain; IMPKM, improvement in most painful knee movement; PGA, patient global assessment; PhGA, physician global assessment; PTA, physical therapy agents; RP, pain at rest; SP, spontaneous pain; S, synvisc; Or, orthovisc; Os, ostenil; H, hyalgan.

of septic arthritis after avian HA injection, and 1 episode of anaphylactic shock after hylan injection, were judged to be probably related to the treatment. Keratosan et al[23] compared the long-term effects of three intra-articular injections of Synvisc® or Orthovisc® in patients with severe OA of the knee. In this trial both HA preparation shows a reduction in pain and improved function during a period of 52 weeks without statistically significant differences. At the opposite, Raman et al[24] demonstrated a significant superiority of Hylan GF-20 over Hyalgan®. Hylan acted more rapidly and with a more lasting effect of HA. No statisically significant difference in AE related to the treatment were reported. Other trials compared the effects of three intra-articular injections of high and low MW HA in patients with knee OA. Wobig et al[25] showed a significantly better results on all primary outcome measures in the hylan group compared with those who received LMW HA. Atamaz et al[26] compared the effects of physical therapy agents like infrared, short-wave diathermy pulsed patterns and interferential therapy (PTA) versus Orthovisc® and Hylan GF-20. The results of this study support the PTA to be useful, safe and well-tolerated treatment, as well as hyaluronan therapy, but PTA includes some disadvantages: it is time wasting and its availability is conditioned on coming to the rehabilitation center during consecutive 15 days. Moreover Compared with HA, hylan seems to be a more appropriate agent with its high molecular weight for some of the symptoms such as pain. Data obtained from these trials are conflicting. The conclusions of the Cochrane meta-analysis presented seem to be in favour of a higher efficacy both on pain and function of Hylan G-F 20 to any form of systemic intervention or intra-articular corticosteroids.[27–29]

Hylan vs. conventional terapies

Raynault et al[30] conducted a prospective, randomized, pragmatic 12-month, healt outcome study in 255 patients randomized to either appropriate care (AC), alone or AC plus VS with hylan GF-20 (AC+H). The AC+H group was superior to the AC group for all primary and secondary outcome measures. These differences were all statistically significant and exceeded the 20% differences between groups set by the investigators as the minimum clinically important difference. As OA is a chronic

condition, the efficacy of repeated treatments is an important consideration. Several trials have studied patients receiving up to eight course of VS and, overall, found that efficacy levels are maintained with repeated treatment.[31,32] Paker et al[33] in a RCT 6-months follow-up, assessed and compared the efficacy of TENS and IA Hylan GF- 20 in 60 patients with symptomatic knee OA. TENS was applied for 3 weeks in the first group, and in the second group, hylan GF-20 was injected once a week for 3 weeks. The results of this study showed that these therapies used in combination may alleviate symptoms in patients with OA.

Hylan vs. oral NSAIDs

Hylan GF-20 has been compared with continuous intake of NSAIDs in two controlled randomized multi-centre trials (Table 3). Adams et al[34] compared VS with Hylan GF-20 with continuous NSAID therapy. Hylan GF-20 was at least as effective for pain during motion as NSAID therapy at 12 weeks but was significantly better than NSAID therapy at 26 weeks ($P < 0.05$). In a second prospective randomized trial, performed by Kahan et al[35] was compared the medioeconomic beneficts over 9 months in 506 patients given Hylan GF-20 or conventional treatment. This study confirms that Synvisc® VS is more effective than conventional treatment, at no additional cost.

Hylan vs. CCS

Results from randomized controlled trials[36,37] comparing Hylan GF-20 to intra-articular corticosteroids, including a total of 318 patients, showed controversial results (Table 4). Caborn et al[36] reported a 26-week, single-blind RCT comparing three weekly injections of Hylan G-F 20 to one IA injection of triamcinolone hexacetonide in 218 patients with knee OA. Treatment with Hylan G-F 20 showed a longer duration of effect than triamcinolone hexacetonide. Both treatments were well tolerated with 10% of patients in each group reporting an adverse event that resulted in withdrawal from the trial. These data support the preferential use of HG-F 20 over TH for treatment of chronic OA knee pain. Leopold et al[37] performed a randomized controlled trial comparing three weekly injections of Hylan G-F 20 to one IA injection of betamethasone sodium phosphate in which no differences were detected between the two groups with respect to pain relief or function at six months of follow-up. In general patients treated with Hylan GF-20 experienced a grater improvement sustained over time than those treated with intra-articular corticosteroids. IA corticosteroids injections seems to be more effective at the beginning but HA is better in terms of the duration of pain relief. Furthermore, a review of studies evaluating the use of corticosteroid injections show a lack of consensus regarding their dosing and time course of administration.

Table 3. RCT concerning viscosupplementation treatment vs. NSAIS.

Study	Year	Trial	Patients	Products	Outcome measures	IA Inj	Interval	Follow up	Statistic results
Adams (34)	1995	RCT	102	NSAID Hylan GF-20 Hylan GF-20+NSAID	WBP NP RP RA	3	1 w	12–26 w	Neg Neg $P = 0.05$ (Hylan) Neg $P < 0.05$ (H+N vs. N) $P < 0.05$ (H+N vs. N, vs. H) $P < 0.05$ (H+N vs. N, vs. H) $P < 0.05$ (H+N vs. N)
Kahan (35)	2002	RCT	506	Hylan GF-20 conventional treatment	Lequesne WOMAC SF12 WP Medical Costs	3	1	9 m	$P < 0.0001$ $P < 0.0001$ $P < 0.0001$ $P < 0.0001$ Neg

Abbreviations: WBP, weight-bearing pain; NP, night pain; RP, pain at rest; RA, restriction activity; PFW, pain during a 50 foot walk; WP, walking pain.

Table 4. RCT concerning viscosupplementation treatment vs. corticosteroids.

Study	Year	Trial	Patients	Products	Outcome measures	IA Inj	Interval	Follow up	Statistic results
Caborn (36)	2004	RCT	218	Hylan GF-20 Triamcinolone hexacetonide	WOMAC A1 WOMAC Total score patient and investigator assessments (VAS)	3 1	1 w	26 w	$P = 0.007$ $P = 0.001$ $P = 0.0001$ $P < 0.0300$
Leopold (37)	2003	RCT	100	Hylan GF-20 Betamethasone sodium phosphate	Knee Society clinical rating scale WOMAC VAS pain	3 1 (±1)	1 w	6 m	Neg Neg Neg

Among these reviews, we also observed that confusion often arises regarding dosing when making a direct correlation between equivalences and relative potency of corticosteroids. This lack of uniform injection guidelines is important because deleterious consequences, both systemic and local, can result from corticosteroid injections, especially from chronic use, large doses, and errant injection.

Clinical Data in Others Joints than Knee

Theoretically viscosupplementation is an approach that should apply to all synovial joints. Starting from 2006 Synvisc® is also approved in European countries for ankle and shoulder OA. Off-label use in degenerative arthritis of temporo-mandibular and carpo-metacarpal joint of the thumb seems to be increasing and a number of recent studies have attempted to evaluate its efficacy in joints other than the knee and the hip.

Clinical data in hip OA

Conrozier et al[38,39] in two pilot study without control group, suggest that Hylan GF-20 could be a symptomatic treatment for hip OA, particularly in less severe radiological cases. The percentage of "responder" patients according to the OMERACT OARSI criteria gives an indication of the potential benefit of this treatment as more than 50% of patients fulfilled the response criteria 90 days after the fluoroscopic guided injection. Transient hip pain was reported following 10.1% of injections, but no patients withdrew from the study because of this. Two mild synovial fluid aseptic effusions occurred after the first injection.

In three prospective open label study 1-year, 3-months and 6-moths follow-up, performed respectively by Vad et al[40] Caglar Yagci et al[41] and Brocq et al[42] was showed that IA injections of Hylan GF-20 under fluoroscopic guidance is a viable option for treatment of mild to moderate OA of the hip joint. No complications related to the injection[40,41] and a self-limited exacerbation of pain during the first few days in three patients were observed.[42] In the study of Vad et al 40 twenty-two patients who had failed to find pain relief from conservative methods were injected with 2 mL of Hylan GF-20 at 2, 3, and 4 weeks and a fluoroscopic lavage with 100 mL of normal saline was performed at week 1. All patients had standard hip exercise regimen after the injection. At 1-year follow-up, the AAOS (American Academy of Orthopaedic Surgeons) Lower Limb Core Scale score improved from a pre-injection mean of 44.2 to a follow-up mean of 86.1 ($P = 0.05$). The mean visual numeric pain score improved from a pre-injection mean of 8.7 (range, 6.4–10) to a follow-up mean of 2.3 (range, 0–7.2). The overall success rate was 84%. In patients with mild to moderate OA, the mean pain score decreased from a pre-injection value of 7.8 to a follow-up value of 1.7. The success rate was 90.5% in that subgroup. In patients with severe OA, the mean pain score decreased from a pre-injection value of 9.1 to a follow-up value of 3.8. The success rate was 50% in that subgroup. Caglar et al[41] established that, after three weekly hip injections with Hylan GF-20, at the 30th and 90th days of treatment, VAS, Lequesne hip

OA severity index, and 15-meter walking period were statistically significantly lower than the corresponding values before treatment. This decrease continued after the 30th day and was consistent with the reduced need of analgesics at the 1st and 3rd months. Brocq et al[42] performed one or two Hylan GF-20 injections each to 22 patients with OA of the hip under fluoroscopic guidance and defined the treatment response as a 50% decrease in the Lequesne score at day 30. The response rate was 50% (11/22) after the first injection. Patients who failed to respond to the first injection received a second one on day 30. The cumulative response rate was found to be 13/22, and short-term safety was reported as satisfactory. Migliore et al[43–48] published 6 original articles concerning the ultrasound guided IA injection of Hylan GF-20 in the treatment of symptomatic hip OA. In five prospective open uncontrolled studies with a follow-up of 3,[43] 6,[45] 12[44,47] and 18 months,[46] Migliore et al found that after injections of Hylan GF-20 2 mL into the hip joint, the Lequesne/Womac index, VAS pain score and NSAID consumption showed a statistically significant reduction comparing to the baseline. The first 12-months post-marketing study[44] assessed the safety and efficacy of Hylan GF-20 in a large cohort of 220 patients with symptomatic hip OA. Patients received a single 2 mL injection of Hylan GF-20, under ultrasound guidance,with optional-additional injection at 3 month interval during follow-up if symptomatically appropriate. Patients were followed up for 12 months. Outcome measures were: Lequesne Index, patient evaluation of pain in target hip during the last week (VAS), NSAID intake, patient and physician global assessment of the target hip (VAS).

The treatment provides a statistically significant improvement in all the outcome measures ($P < 0.05$). These clinical improvement occurred as soon as the third month after treatment and were maintained for up to 12 months. NSAID intake reduced significantly after treatment and maintained significant to end of the study. Treatment was well tolerated despite the high mean age of the cohort and the co-morbidities of some patients. No AEs were recorded. Only mild and transient local adverse event were observed. Rennesson-Rey et al[49] performed an open-label, prospective trial, 6-months follow-up, to evaluate the influence of a joint effusion on the clinical response to a single injection of Hylan GF-20, fluoroscopic guided, in 55 patients affected by hip OA. The conclusion of the Authors was that the presence of a joint effusion is associated with worse pain and functional impairment at baseline but has no influence on the clinical response to Hylan GF-20 in patients with hip osteoarthritis. No AEs were recorded. Tikiz et al[50] performed a RCT in which the efficacy of IA injections of a LMW HA (Ostenil®) versus Hylan G-F 20 (Synvisc®) in 43 patients with hip OA was compared. The IA injections, performed under fluoroscopic guidance, produced a significant reduction in pain VAS, WOMAC and Lequesne index scores without significant differences in outcome between the two products. In the study of Van den Bekerom et al[51] 120 patients, candidate for surgical treatment with a total hip arthroplasty, received VS with one of three hyaluronate formulations: Adant® (Group 1) LMW, Synocrom® (Group 2) LMW and Synvisc® (Group 3) HMW. Patients were assessed 6 weeks after each infiltration, performed under fluoroscopic guidance. VAS and Harris Hip Score (HHS) increased significantly in groups 1 and 2 compared to baseline, but no statistical significant difference was noted between the groups. The Synvisc® group never reached statistical significance in HHS and VAS during walk test after treatment, possibility due to the small number of patients (n = 15) in this group. The results of this trial should be considered in the light of the limitations of the design study, that is a non placebo controlled non randomized prospective study.

Clinical data in ankle OA

Luciani et al[52] performed a prospective clinical trial with an 18-months follow-up in which 3 three weekly IA injections Hylan GF-20 2 mL was performed without any instrumental guidance in 21 patients affected by ankle OA. The primary outcome measure was the ankle osteoarthritis score (AOS), that includes nine items on a pain sub scale (AOS-A) and nine items on a disability sub scale (AOS-B) and VAS scale. Regarding pain (AOS-A) the improvement was statistically significant at the 12 and 18 month follow-up if compared with baseline ($P < 0.05$). Regarding disability (AOS-B) the improvement reached significance at the 6-month follow-up and over time until the 18-month follow-up ($P < 0.001$). Also for pain assessed with VAS scale, a similar trend was observed, with a step decrease over the first 6 months ($P < 0.0005$).

This reduction remained significant at the 18-month follow-up. In the prospective multicenter open study of Witteveen et al[53] 55 patients with symptomatic ankle OA, were treated with IA injection of Hylan GF-20 2 mL, without any instrumental guidance, plus an optional second injection if pain remained at baseline level after 1, 2 or 3 months, with 6–9-months follow-up period. The primary efficacy endpoint was the change from baseline in the patient-completed Study Ankle OA Pain VAS Score at 3 months. There was a statistically significant decrease in the mean score of the patient-completed Study Ankle OA Pain VAS from 68.0 mm at baseline to 33.8 mm at month 3 ($P < 0.001$). 31 patients received one intra-articular injection, and they had a mean change in VAS Score of –42.5 mm ($P < 0.001$); 24 patient who received two injections had a mean change in VAS Score of –23.5 mm ($P < 0.001$). The secondary efficacy endpoints were the change from baseline in: the total Ankle OA scale score, the patients' global OA Assessment VAS score, the physicians' global OA Assessment VAS score, the health related quality of life (SF-36). For all these endpoints, after the last injection, patients showed statistically significant improvement. Carpenter et al[54] performed a clinical trial, 13-months follow-up, in which the efficacy of ankle arthroscopy alone (AAA) versus ankle arthroscopy combined with weekly IA injection of Hylan GF-20 2 mL (AA+H) during the first three postoperative weeks, was compared in 26 patients affected by ankle OA. Injection was blindly performed and without any instrumental guide. For the AAA group, the median and interquartile range for the pre-intervention pain score was 8 (7.5, 9.5), whereas that for the post-intervention score was 3 (2, 3.5), and this difference was statistically significant ($P = 0.002$). For the AA+H group, the median and interquartile range for the pre-intervention pain score was 9 (8, 9), and that for the post-intervention pain score was 1 (0, 2), and this difference was highly statistically significant ($P = 0.0009$).The median and interquartile range for the post-intervention pain score for the AAA group was 3 (2, 3.5); whereas that for the AA+H group was 1 (0, 2), and this difference was statistically significant ($P = 0.0002$). The median and interquartile range for the reduction in pain for the AAA group was 5.5 (5, 6); whereas that for the AA+H group was 7.5 (6, 9), and this difference was statistically significant ($P = 0.0014$). Both treatment groups experienced statistically significantly decreased pain following the intervention, and patients receiving three IA injections of Hylan G-F 20 following ankle arthroscopy improved statistically significantly more than arthroscopy group as a sole therapy. None of the totality of patients displayed any type of local or systemic adverse events.

Clinical data in shoulder OA

Noel et al[55] performed an open-label, prospective, multicenter study in 33 patients with shoulder OA and an intact rotator cuff, to evaluate the feasibility, safety, and symptomatic efficacy of one or two IA Hylan GF-20 performed under fluoroscopic guidance. All the outcome measures (VAS pain score change between the baseline visit and 3 months after the last injection, VAS pain score differences between the last injection and each of the subsequent visits, the VAS pain score change between baseline and study completion, changes in shoulder stiffness and function as evaluated using the WOOS score, changes in the SF36 quality-of-life score, and the patient and physician 100 mm VAS scale scores for shoulder osteoarthritis related discomfort) showed significantly decrease at 3 months after the last injection. 33 patients received a first injection. A second injection was performed in 16 patients, after 1 ($n = 7$), 2 ($n = 4$), or 3 ($n = 5$) months. The VAS pain score decreased significantly, from 61.2 mm at baseline to 37.1 mm 3 months after the last injection ($P < 0.001$). The mean WOOS score was 45.7% at baseline, 61.7% after 7 days ($P < 0.001$), 63.1% after 3 months ($P < 0.001$), and 62.4% ($P = 0.008$) after 6 months. The mean SF-36 score was 38.6 points at baseline, 40.7 points after 3 months ($P = 0.069$), and 43.3 points after 6 months ($P = 0.007$). The mean patient VAS discomfort score decreased from 55.7 at baseline to 36.3 mm after 3 months ($P < 0.001$), and the mean physician VAS discomfort score decreased from 59.6 mm at baseline to 35.7 mm after 3 months ($P < 0.001$). In the overall population, the proportion of responders was greatest after 2 months (20/29, 60.6%) and decreased slightly thereafter (54.5% after 3 months and 51.6% after 6 months). The response rates were higher in the subgroup of patients who required a single injection (better immediate response): 70.6% after 3 months and 64.7% after 6 months, compared to 37.5 and

35.7% in the subgroup of patients who required two injections.No AEs were reported during the study. Only eight patients reported local adverse events. Also a case-series study, performed by Silverstein et al[56] evaluating the effects of 3 IA weekly injections of Hylan GF-20 2 mL in 30 patients with symptomatic glenohumeral OA who had failed 6 months of conservative treatment, showed a significant improvement in VAS pain, UCLA score and Simple Shoulder Test (SST) at the 6-month follow-up. The mean VAS score showed a significant reduction from baseline to 1, 3, and 6 months after treatment ($P = 0.01$).

The mean modified UCLA scores improved from baseline at 1, 3, and 6 months after treatment with a statistically significance ($P < 0.001$). When the changes in individual scores were analyzed compared with baseline, pain (2.3-point improvement) and function (1.8-point improvement) were found to be both statistically ($P < 0.001$) and clinically significant. At baseline, the mean SST score was 5.7 of 12 "yes" responses. Mean "yes" responses significantly increased at 1 ($P = 0.012$), 3 ($P = 0.001$), and 6 months ($P = 0.001$) after the third injection. When the SST score was evaluated in patients with a clinically significant improvement in VAS (≥20 points), the score improved from 5.7 at baseline to 8.7 of 12 "yes" responses at 6 months. In those for whom the VAS improvement was < 20 points, the SST increased for 5.7 at baseline to 6.4 at 6 months. The number of patients who could sleep comfortably without any interference from their arthritic shoulder significantly increased ($P \leq 0.001$) from baseline (n = 4) to the 1, 3, and 6-month visits. These data support the beneficial role of Hylan GF-20 in some symptomatic patients with glenohumeral osteoarthritis.

Clinical data in TMJ OA

The case-series of Yustin et al[57] was one of the first that reported the use of 1 mL of hylan GF-20 by IA injection to manage TMJ OA and their patient functioned well and felt comfortable for 4 months after 3 Injections. Møystad et al[58] performed a RCT to compare the bone changes in the TMJ, assessed on computed tomography (CT) examinations, before and after 2 IA TMJ injections of hylan GF-20 or Celestone Chronodose, in patients with TMJ OA. Thirty-six patients were radiographically re-examined with high resolution CT after 6 months. There were no statistically significant differences between the 2 study groups with regard to any of the variables and to the averaged score of any of the Osteoarthritic signs. This study shows that both progression and regression of radiographic bones changes might occur in the TMJ after injection of Hylan GF-20 or corticosteroid after a short-term observation of 6 months. Yeung et al[59] showed a statistically significant reduction of pain intensity and improvement in the maximum mouth opening parameter, after 2 IA injection of Hylan GF-20 2 mL in 27 patients with a MRI-confirmed diagnosis of non-reducing displacement of the TMJ disc who does not respond to conservative treatment. No AE were registered. Yeung et al[60] performed also a preliminary report to establish a protocol for image-guided minimally invasive surgical access to the TMJ. Axial MRI of the TMJ was obtained and loaded into an intra-operative navigation system to guide joint space injection. With the assistance of an intra-operative navigational system, the TMJ MRI images were visualized in 3 dimensions and enabled guiding a needle into the superior and inferior joint spaces for therapeutic injection. The treatment outcome for both patients was satisfactory with improvement in pain score and mandible motion.

Clinical data in thumb OA

Heyworth et al[61] compared IA hylan, corticosteroid, and placebo injections with regard to pain relief, strength, symptom improvement, and metrics of manual function in sixty patients with 1st CMC OA. The Hylan group received 2 IA injections of Hylan GF-20 1 mL one week apart; the steroid group 1 mL placebo injection of normal saline and a 1 mL of sodium betamethasone sodium phosphate–betamethasone acetate (Celestone Soluspan) 1 week later; the placebo group two IA injection of normal saline 1 mL one week apart. No statistically significant differences were observed among the three products for most of the outcome measures at any of the follow-up time points. However, based on the durable relief of pain, improved grip strength, and the long-term improvement in symptoms compared with pre-injection values, Authors suggest that hylan injections should be considered in the management of basal joint arthritis of the thumb. Figen Ayhan F. et al[62] performed a RCT to evaluate the efficacy of

Hylan GF-20 on pain, function, and pinch strength for 6 months follow-up period in 33 patients with bilateral thumb base OA (1st CMC OA). A total of 1 mL of Hylan G-F20 was injected to one trapezio-metacarpal joint and 1 mL saline injection was made to contra-lateral joint. Statistically significant improvements were detected in function ($P = 0.02$) , VAS pain ($P = 0.02$), and pinch strength ($P = 0.002$) at the 24th week in the Hylan GF-20 group. However, only VAS pain scores decreased temporarily in control hands at the 6th week. Mandl et al[63] performed a prospective open-label study to investigates if 3 repeated injections of Hylan GF-20 1 mL would relieve pain and improve function in patients with CMC OA. At 26 weeks, mean VAS pain and DASH scores had improved significantly. Both the DASH and VAS for pain were significantly improved over baseline at 26 weeks. A DASH change of 10–14 is considered clinically meaningful. At 26 weeks the mean change in DASH was 12.6, (SD 17.2) and the mean change in VAS for pain was 15.2 mm, (SD 29.5). VAS scores for pain at 26 weeks were moderately correlated with patient satisfaction (Spearman r = 0.52, P-value < 0.01), but were not correlated with hand strength, as measured by opposition and key grip. Although DASH scores at 26 weeks were significantly correlated with hand strength at 26 weeks, DASH scores showed no correlation with patient satisfaction. Adverse events potentially related to the injections included three episodes of post-injection pain and swelling, and one case of pseudogout.

Discussion

Despite the increasing morbidity of pain and functional impairment, standard therapies for OA have not progressed over the past few years. Standard therapies currently include the use of corticosteroids or NSAID despite evidence of increased frequency and severity of adverse effects and associated morbidity, particularly in elderly patients. Hylan G-F 20 is comparable in efficacy to IA corticosteroid that has a faster onset of action but a shorter duration of action than Hylan. In addition, repeated use of hylan is safer than corticosteroids in patients with comorbidity such as corticosteroids are contraindicated. Several studies have shown a significantly reduced NSAIDs intake in both hip and knee OA after Hylan GF-20 treatment; it was maintained significant for a long time. Moreover to evidence the improvement in pain management, the benefits of a reduction in the direct and indirect costs related to chronic NSAIDs use are obvious. In these days of heath economic evaluation of therapy options it is appropriate to consider this opportunity in the overall management of hip OA. Within this context, a correct evaluation of the role of Hylan GF-20 in the overall management of OA seems appropriate and in particular it seems to be a safe and effective treatment for decreasing pain and improving function in patients suffering from osteoarthritis. As OA is a chronic condition, the efficacy of repeated treatments is an important consideration. Several trials have studied patients receiving repeated courses of Hylan GF-20 and, overall, found that efficacy levels are maintained with repeated treatment both in knee and hip OA.[15–19,24–51]

The range of reduction in symptoms and pain seems to fluctuate in the various studies that evaluate the efficacy of Hylan GF-20 vs. LWM or vs. placebo in knee OA between 30 and 20% depending on the study and endpoint. Whereas this range, is understandable that some of these RCTs showed no statistically significant difference. In addition to establish a statistically significant difference between two different hyaluronic acid the sample size should be very high and this would lead to cost too high. Several studies have shown a significantly reduced NSAIDs intake in both hip and knee OA after Hylan GF-20 treatment; it was maintained significant for a long time. Moreover to evidence the improvement in pain management, the benefits of a reduction in the direct and indirect costs related to chronic NSAIDs use are obvious. In these days of heath economic evaluation of therapy options it is appropriate to consider this opportunity in the overall management of hip OA.

The dose given is different for each joint. Is well known for knee and hip joint (3 weekly injections of 2 mL or one of 6 mL in knee OA and one injection of 2 mL every six months, repeatable till every three months if clinically necessary, in hip OA). On the contrary volume and scheduling for MCF, ankle and shoulder is not clearly defined. In these reported studies it ranges from 1 mL to 2 mL for MCF, which is a small joint and 2 mL for ankle and shoulder joint.

In the European package insert is reported that Hylan GF-20 used in the treatment of hip OA should be carry out under image-guidance (Fluoroscopy,

TC or US). The use of ultrasound guidance ensures the accurate placement of Hylan GF-20 in the articular space. The ultrasound guidance is faster and cheaper than X ray, which are used in fluoroscopy and CT, and does not required the use of contrast. Additionally, ultrasonography can be repeated without the problems associated with radiation load for both patient and operator. The use of US guidance may help to avoid the possible side effects of blind injections into difficult joint, especially for the hip. Direct evidence of the needle placement and direct evidence of the therapeutic fluid's placement inside the joint space guarantee the efficacy and safety of the treatment.

In recent years the use of Hylan GF-20 was extended to other joints offering new possibility in the treatment of OA. For instance shoulder OA is a common disorder resulting in pain, progressive loss of function, and diminished quality of life with limited treatment possibilities. The study of Noel[55] suggests that injections of Hylan GF-20 may constitute a valid option specifically in patients with primary shoulder OA and an intact cuff. Also temporomandibular joint may be affected by OA, and in this case too, Hylan GF-20 seems to show encouraging results. Data regarding use of Hylan GF-20 in hand and ankle OA appear to be promising. However further studies are necessary to clarify injecting volume, dosing regimen and outcome predictors.

The treatment with Hylan GF-20 is well tolerated in all joints without severe systemic AE. Only 2 case series reported 8 cases of granulomatous inflammation after three intra-articular injections of Hylan GF-20.[64,65] In these case reports the granulomatous inflammation seems to have been caused by the injected viscosupplementation material. Histological analysis demonstrated foreign-body granulomatous inflammation surrounding acellular material in a palisading fashion. Moreover, it is not known whether the pathological agent responsible is the hyaluronate derivative, a contaminant of the purification process, or a component of the carrier substance. Importantly, it appears that the synovial granulomatous inflammation documented in these studies represents a previously unreported pathological response to a viscosupplementation product, which should raise clinical awareness of this potential complication. Further studies will be needed to demonstrate the real role played by Hylan GF-20 viscosupplementation in granulomatous inflammation of the treated joints. At present, this low incidence of side effects and the safety of Hylan GF-20 make it particularly suitable in elderly patients who can't tolerate NSAID and corticosteroids or in whom they are contraindicated. VS can also be used concomitantly with other therapies commonly used by elderly patients.

Abbreviations

AC, Appropriate care; AE, Adverse events; Aes, Severe adverse events; CMC, Carpometacarpal; CT, Computed tomography; FDA, Food and Drug Administration; HA, Hyaluronic acid; IA, Intra-articular injection; LMW, Low molecular weight; MRI, Magnetic resonance imaging; MW, Molecular weight; NSAIDs, Non steroidal anti-inflammatory drugs; OA, Osteoarthritis; PTA, Physical therapy agents; RCT, Randomised controlled trial; TMJ, Temporomandibular joint; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; US, Ultrasonography; VAS, Visual analogue scale; VS, Viscosupplementation.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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