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REVIEW

Treatment of osteoarthritis knee pain: update on use of intra-articular hylan G-F 20

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Background: Osteoarthritis is a public health concern, particularly in modern society, and is the leading osteoarticular pathology in developed countries. The increased prevalence of osteoarthritis with aging, coupled with the aging of populations, makes osteoarthritis a high priority health care problem. Viscosupplementation is a well established treatment option in knee osteoarthritis that is included in the professional guidelines for treatment of this joint disease.

Objective: This review assessed the efficacy and safety of viscosupplementation with hylan G-F 20 (Synvisc®) in the management of joint pain in knee osteoarthritis.

Methods: Three databases were searched, ie, Medline (1970–2010), the Database of Abstract on Reviews and Effectiveness, and the Cochrane Database of Systematic Reviews. Reference lists of relevant articles were examined for additional references.

Results: Eighteen studies were identified (six European, five Turkish, three US, two Canadian, one Swiss and one English), which reported efficacy of viscosupplementation in a total of 3689 patients undergoing viscosupplementation treatment with Synvisc for knee osteoarthritis compared with low molecular weight viscosupplementation, high molecular weight viscosupplementation, medium molecular weight viscosupplementation, placebo, corticosteroids, nonsteroidal anti-inflammatory drugs, and physical therapy.

Conclusion: Synvisc viscosupplementation in the treatment of knee osteoarthritis is a safe and effective therapeutic option that could also reduce the direct and indirect costs related to this disease.

Keywords: viscosupplementation, knee osteoarthritis, hyaluronic acid, hyaluronan, sodium hyaluronate, hylan G-F 20, intra-articular injection

Introduction

Osteoarthritis is a public health concern, and is the leading osteoarticular pathology in developed countries. In the US, osteoarthritis is the primary reason for medical consultations in persons older than 60 years of age. It has been estimated that 69.9 and 100 million people are affected by osteoarthritis in the US and Europe, respectively.[1,2] As a major cause of disability in the elderly, osteoarthritis is second only to cardiovascular disease. The increased prevalence of osteoarthritis with aging, coupled with the demographics of aging populations, makes osteoarthritis a high priority health care problem, and will probably worsen the socioeconomic impact of such pathologies.

Osteoarthritis is a chronic degenerative joint disease. The disease process is characterized by progressive destruction of the articular cartilage, leading to joint space narrowing, subchondral sclerosis, subchondral cysts, synovial inflammation, and

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marginal osteophyte formation.[3] Progression of osteoarthritis leads to exposure of subchondral bone at a weightbearing site at which the bone will then be subjected to abrasion and further damage. The primary role of synovial fluid is protective, by 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 a predominantly viscous fluid or as an elastic fluid.[4] Hyaluronan is also responsible for protecting the collagen fibrils and cells of articular surfaces, and the synovial tissue, capsule, and ligaments from mechanical damage.[5] In osteoarthritis, the synovial fluid is more abundant and less viscous.[6] Hyaluronan becomes depolymerized, and its concentration and molecular weight are decreased, resulting in a decrease in elastoviscosity. These changes increase the susceptibility of cartilage to injury.[4,7,8]

The recognition that synovial hyaluronan in osteoarthritis is abnormal led to the proposition that removal of pathologic osteoarthritis synovial fluid and replacement with products that restore the molecular weight and concentration of hyaluronan toward normal levels may have a beneficial therapeutic effect. This treatment approach has been termed viscosupplementation. Within the rheumatology and orthopedic communities there continue to be widely divergent opinions, ranging from skepticism to acceptance, on viscosupplementation as a mainstream symptom-modifying osteoarthritis therapy. There have been substantial data that exogenous hyaluronic acid may also improve pain and function by nonmechanical, biologically based mechanisms within the synovial and articular environment.[9]

Current treatment options for osteoarthritis include simple analgesics, nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injection, weight reduction, and surgical treatment. Viscosupplementation with intra-articular hyaluronic acid was approved by the Food and Drug Administration (FDA) in 1997. Viscosupplementation is a well established treatment option in knee osteoarthritis, and is included in the professional guidelines for treatment of the disease in this joint.[10,11] There are five injectable forms of hyaluronic acid approved by the FDA, including Hyalgan®, Supartz®, Orthovisc®, Synvisc®, and Euflexxa®. These hyaluronic acid products differ in their origin, method of production, molecular weight, dosing instructions, biologic characteristics, and possibly clinical outcomes.

Hylan G-F 20 (Synvisc) is one of the viscosupplementation products approved for marketing in Canada since 1992 and in the US since 1997 after public review of the data by an FDA advisory panel.[12] Hylan G-F 20 is a high molecular weight hyaluronic acid derivate composed of two hylan polymers within a buffered physiologic 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, ie, hylan A (80%), a soluble high molecular weight molecule (6,000,000 Da) and hylan B (20%), an insoluble gel.[13] The rheologic properties of the two forms of hylan differ from each other and both are significantly different from unmodified hyaluronan. The cross-linking also allows a longer residence time in the joint than that of linear hyaluronic acid products, in particular for hylan B, the insolubility of which delays its removal from the joint. This review assesses the efficacy and safety of viscosupplementation with hylan G-F 20 in the management of joint pain in knee osteoarthritis.

Materials and methods

Literature search

The literature search was limited to original studies, including male and/or female patients with a diagnosis of knee osteoarthritis treated with hylan G-F 20. The diagnosis of osteoarthritis was made on the basis of detailed clinical and radiographic information. Studies comparing different types of hyaluronic acid with placebo and other treatments (nonsteroidal anti-inflammatory drugs, corticosteroids, exercise therapy) were included. The outcome measures for analysis were the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score, patient global assessment, clinical observer global assessment, patient-rated knee osteoarthritis pain assessment, patient and physician global assessment, pain at rest, at night, and on walking, 15 m walking time, use of rescue medications, Lequesne index, SF-36 score, reduction of activity while performing daily tasks, improvement of the most painful knee movement, Hospital for Special Surgery knee score, Oxford knee score, and EuroQol EQ-5D scores. The minimum criterion for inclusion of a trial in the review was the adequate reporting of at least one of these outcome variables. Information regarding other outcome measures and adverse events was extracted and analyzed when feasible.

Search strategy

The following databases were searched: Medline (1970–2010), the Database of Abstract on Reviews and Effectiveness,

and the Cochrane Database of Systematic Reviews. The search terms "review", "viscosupplementation", "knee osteoarthritis", "hyaluronic acid", "hyaluronan", "sodium hyaluronate", "Synvisc", "hylan G-F 20", and "intra-articular injection" were used to identify all studies relating to the use of viscosupplementation therapy for knee osteoarthritis. Furthermore, the lists of references of retrieved publications were manually checked for additional references.

Results

Eighteen studies were identified (six European, five Turkish, three US, two Canadian, one Swiss, and one English) which reported the efficacy of viscosupplementation with Synvisc for knee osteoarthritis compared with low molecular weight viscosupplementation, high molecular weight viscosupplementation, medium molecular weight viscosupplementation, placebo, corticosteroids, nonsteroidal anti-inflammatory drugs, and physical therapy in a total of 3217 patients (see Table 1).

Efficacy

Hylan G-F 20 versus placebo

Data in the literature show that hylan G-F 20 is an effective and safe method for relieving pain and increasing mobility in patients with chronic idiopathic osteoarthritis of the knee. There are three randomized, placebo-controlled trials showing the efficacy of three intra-articular injections of hylan G-F 20 compared with placebo at eight,[14] 12,[15] and 26[16] weeks. Cubukçu et al[14] performed a prospective, randomized, placebo-controlled trial, in which hyaluronic acid or saline was injected intra-articularly in 30 patients with clinical and radiologic knee osteoarthritis. Thirty patients were randomly assigned to either an active treatment group (n = 20) in which patients received three weekly intra-articular 2 mL injections of hylan G-F 20 solution (10 mg/mL, total of 30 knees) or a control group (n = 10) in which patients received three intra-articular injections of 2 mL saline at weekly intervals (total of 10 knees). For both groups, the injections were performed under sterile conditions by a physician using a medial approach. Patients were evaluated prior to the injections and at weeks 1, 2, 3, and 8 post-treatment. The outcome measures were pain at rest, at night, and on walking (using a visual analog scale [VAS]), WOMAC score, 15 m walking time, need for paracetamol, and patient assessment. Post-treatment WOMAC parameters, 15 m walking time, and patient assessment were statistically different compared with baseline in the hyaluronic acid group. These parameters remained unchanged in the placebo group. There were also statistically significant differences between the two groups in all of these parameters ($P < 0.05$) except for WOMAC-B and 15 m walking time. Rest pain decreased starting from week 3 and continuing to week 8. Night pain, pain on walking, and need for paracetamol in the hyaluronic acid group was significantly lower than in the placebo group at week 8 ($P < 0.05$). The patients in the hyaluronic acid group had a greater reduction in WOMAC pain score beginning in week 3, and the improvement continued through to week 8 ($P < 0.05$ compared with the placebo group). The difference between the groups in WOMAC-C functional impairment score was statistically significant at week 8 ($P < 0.05$). Furthermore, the need for paracetamol in the hyaluronic acid group was significantly lower than in the placebo group at week 8 ($P < 0.05$), and this result confirms that hyaluronic acid has an analgesic effect in the early period and modulates pain perception in patients with knee osteoarthritis.

The limits of this study were its small number of patients and short observation period that may not be enough to draw strong conclusions on the clinical and qualitative effects of intra-articular hyaluronic acid injections on the articular cartilage. Multicenter studies using larger patient groups and longer observation periods are warranted to determine the reproducibility of these results and the effect of hyaluronic acid on the quality of articular cartilage.

In a double-blind, randomized, placebo-controlled trial with a six-month follow-up, performed by Scale et al,[15] 80 patients affected by knee osteoarthritis Grade II–IV according to Larsen score were randomly assigned to treatment with either 2.0 mL of hylan (treatment) or 2.0 mL of buffered saline solution (control) injected into the joint two (study 1) or three times (study 2) daily. In study 1, 25 patients were treated with hylan and 25 with buffered saline solution two weeks apart (n = 50). In study 2, 15 patients were treated with hylan and 15 with buffered saline solution three weeks apart (n = 30). Patients were evaluated before each injection, and at weeks 4, 8, and 12 in the first study and at weeks 8 and 12 in the second study after the first injection. A long-term follow-up evaluation was conducted at six months by telephone interview. The outcome measures were weightbearing pain and night pain (evaluated by VAS), reduction of activity while performing daily tasks, ie, joint mobility (VAS), improvement in the most painful knee movement (VAS), and global evaluation of efficacy (VAS). The results of this study clearly show that hylan viscosupplementation significantly reduces all outcome measures related to pain and increases the utility and mobility of the joint. Improvement was demonstrated for all outcome measures during the entire 26-week follow-up

Table 1 Overview of randomized controlled trials concerning viscosupplementation with hylan G-F 20 in treatment of knee osteoarthritis

Author	Year	Patients (n)	Products	Outcome measures	Injections (n)	Interval	Follow-up	*P* value
Scale et al[15]	1994	80	Synvisc Placebo	WBP-NP (VAS) RAPDT (VAS) IMPKM (VAS)	2 3	2 w 1 w	3 m 6 m	<0.05 <0.05 <0.05
Wobig et al[16]	1998	110	Synvisc Placebo	WBP (VAS) NP (VAS) IMPKM (VAS)	3	1 w	6 m	0.001 <0.005 <0.0001
Çubukçu et al[14]	2005	30	Synvisc Placebo	RP-NP-WP (VAS) WOMAC A, B, C	3	1 w	2 m	< 0.05 (WB, $P > 0.05$) < 0.05 (WOMA C B, > 0.05)
Chevalier et al[19]	2010	253	SynviscOne Placebo	WOMAC A	1	–	6 m	0.047
Karlsson et al[20]	2002	210	Synvisc Artzal Placebo	WBP Lequesne WOMAC	3	1 w	6 m 12 m	Neg
Kotevoglu et al[21]	2006	59	Synvisc Orthovisc Placebo	WOMAC A, B, C PGA PhGA	3	1 w	6 m	Neg
Juni et al[22]	2007	660	Synvisc Orthovisc Ostenil	WOMAC A	3 (second cycle)	1 w	6 m	Neg
Karatosun et al[23]	2005	92	Synvisc Orthovisc	HSS	3	1 w	12 m	Neg
Raman et al[24]	2008	392	Synvisc Hyalgan	VAS Pain WOMAC A, B, C	3 5	1 w	12 m	0.04 0.007 Neg 0.004
Wobig et al[25]	1999	70	Synvisc LMW	WBP IMPKM	3	1 w	12 m	<0.05 <0.05
Raynauld et al[27]	2002	255	AC + Synvisc AC	WOMAC Patient global assessment SF-36 HUI3	3	1	12 m	0.0001 <0.0001 <0.0001 <0.0001
Atamaz et al[31]	2006	80	Synvisc or Orthovisc PTA	SP (VAS) WOMAC pain and function	3 + 1	1 w + 6 m twice a week for 3 weeks	9 m 12 m	<0.05 (PTA) <0.05 (O) <0.05 (S) <0.05 (S) <0.05 (S)
Adams et al[32]	1995	102	NSAID Hylan G-F 20 Hylan G-F 20 + NSAID	WBP NP RP RA	3	1 w	3 m 6 m	Neg Neg 0.05 (hylan) Neg <0.05 (H + N vs N) <0.05 (H + N vs N, vs H) <0.05 (H + N vs N, vs H) <0.05 (H + N vs N)
Kahan et al[33]	2002	506	Hylan G-F 20 Conventional treatment	Lequesne WOMAC SF12 WP Medical costs	3	1	9 m	<0.0001 <0.0001 <0.0001 <0.0001 Neg

(*Continued*)

Table 1 (*Continued*)

Author	Year	Patients (n)	Products	Outcome measures	Injections (n)	Interval	Follow-up	*P* value
Caborn et al[34]	2004	218	Hylan G-F 20 Triamcinolone hexacetonide	WOMAC A1 WOMAC total score Patient and investigator assessments (VAS)	3 1	1 w	6 m	0.007 0.001 0.0001 <0.0300
Leopold et al[35]	2003	100	Hylan G-F 20 Betamethasone Sodium phosphate	Knee society clinical rating scale WOMAC VAS pain	3 1 (±1)	1 w	6 m	Neg Neg Neg

Abbreviations: WBP, weight-bearing pain; NP, night pain; RAPDT, reduction of activity while performing daily tasks (joint mobility); IMPKM, improvement in most painful knee movement; RM, rescue medication; WP, walking pain; HSS, Hospital for Special Surgery knee rating index; PGA, patient global assessment; PhG, physician global assessment; PTA, physical therapy agents; RP, pain at rest; SP, spontaneous pain; RA restriction activity; PFW, pain during a 50-foot walk; AC, appropriate care. HUI3, Health Utilities Index Mark 3; vs, versus; w, weeks; VAS, visual analog scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index.

period. Patients in the control group also demonstrated some improvement, but it was much less and of shorter duration than that seen with hylan treatment. The placebo effect in osteoarthritis treatment has been re-evaluated in a recent meta-analysis showing that it induces significant pain relief, especially when given by intra-articular injections.[17] Patients receiving hylan injections showed significantly greater improvement than those in the control group at all follow-up time points ($P < 0.05$). Three hylan injections were significantly more effective than two injections, produced successful treatment outcomes in 70%–80% of patients, and the beneficial effect of treatment persisted throughout the entire six-month study period. Treatment with two hylan injections, however, was effective for all ($P < 0.05$) but one outcome parameter, ie, global assessment of treatment by the investigator, which showed no significant difference compared with control treatment at weeks 8 and 12 after the first injection.

Wobig et al[16] performed a randomized, controlled trial with a 26-week follow-up in 110 patients affected by knee osteoarthritis. Three intra-articular injections of hylan G-F 20 2 mL were administered one week apart to 57 patients with knee osteoarthritis. The control group (n = 60) received 2 mL of buffered saline solution at the same time points. The differences between the two treatment groups were statistical significant for all the outcome measures (pain at rest during the night, weightbearing pain, and treatment success) in favor of the hylan group after the first injection ($P < 0.01$–0.0001 for assessments). The pain-reducing effect of hylan remained evident until week 26, with 39%–71% of patients assessed as being symptom-free, and few of these patients required rescue medication (only 6%). In contrast, most patients in the placebo group were symptomatic at week 26, with significantly fewer being assessed as symptom-free (13%–45%) and the majority having required rescue medication (53%, n = 32).

Another prospective, randomized trial performed by Conrozier et al[18] demonstrated the efficacy and safety of a single 6 mL injection of hylan G-F 20, in a comparison of different dosing regimens in the treatment of knee osteoarthritis. 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 injections given one week apart. The efficacy and safety of a single 6 mL injection of hylan G-F 20 was afterwards observed in a randomized, controlled trial performed by Chevalier et al,[19] in which they observed that intra-articular injection of hylan G-F 20 with a volume of 6 mL by syringe (SynviscOne®) is safe and efficacious at 26 weeks for knee osteoarthritis (n = 253) when compared with intra-articular injection of placebo 6 mL. The treatment effect using hylan G-F 20 was significantly superior to placebo for the primary endpoint, ie, change in WOMAC-A (pain) over 26 weeks ($P = 0.047$). Some, but not all, of the secondary endpoints, including WOMAC-A1 (walking pain), patient global assessment, and clinical observer global assessment completed by a blinded evaluator showed statistically significant differences between the two groups and favoring hylan G-F 20 treatment ($P = 0.022$, $P = 0.005$, and $P = 0.025$, respectively).

On the other hand, two randomized, controlled trials comparing the efficacy and safety of three products (hylan G-F 20, Artzal®[20] and Orthovisc[21]) versus placebo showed no statistical difference between the treatment groups. In the first study, performed by Karlsson et al,[20] the intra-articular injections produced a significant improvement in 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. However, when data for the two hyaluronan-treated groups were pooled, treatment with hyaluronan had a significantly longer duration of benefit compared with placebo ($P = 0.047$). In the second trial, performed by Kotevoglu et al,[21] the outcome measures were significantly better than baseline at six-month follow-up for both the hyaluronic acid groups. All groups showed improvement on physician global assessment scores after the first injection. This improvement reached statistical significance at the third injection in favor of the hyaluronic acid group ($P < 0.05$) and lasted until the end of three months. Although the placebo group seemed worse, the difference was not statistically significant.

Hylan versus other hyaluronic acid derivates

Differences in efficacy related to molecular weight and other characteristics of hyaluronan were considered. Several randomized, controlled trials evaluated the efficacy of Synvisc compared with low molecular weight hyaluronan.

Juni et al[22] assessed the comparative efficacy and safety of three viscosupplements, ie, hylan G-F 20, a medium molecular weight hyaluronic acid from avian sources (Orthovisc), and a medium molecular weight hyaluronic acid derived from bacterial sources (Ostenil®). In total, 660 patients were randomly assigned to receive one cycle of three intra-articular injections of these three preparations. They found no evidence of a difference in efficacy between hylan G-F 20 and hyaluronic acid. The limits of this trial were the decision to assess the primary outcome measure at a single six-month follow-up, because it is now recognized that differences should be tested for throughout the observation period. Furthermore, the authors did not provide information on the level of pain at baseline, but it is obvious that patients with end-stage disease were included in this trial, as were patients with knee osteoarthritis Grade III and IV. Karatosun et al[23] compared the long-term effects of three intra-articular injections of Synvisc or Orthovisc in 92 patients with severe osteoarthritis of the knee. In this trial, both hyaluronic acid preparations showed an improvement in Hospital for Special Surgery knee scores from 71 ± 11.6 to 86.7 ± 11.6 (high molecular weight group) and from 66.7 ± 11 to 86.6 ± 9.1 (low molecular weight group) at the end of the trial ($P < 0.01$). There were no statistically significant differences between the groups, and both groups improved in all parameters at the final follow-up ($P = 0.000$).

In contrast, Raman et al[24] demonstrated significant superiority of hylan G-F 20 over Hyalgan. Although the positive results were in favor of hylan, that seems to act more rapidly and with a more lasting hyaluronic acid effect, this trial had some limitations. The methodology was poor in the absence of a prestatistical analysis for the number of patients to be included, an absence of standard deviations in the results, and its monocentric follow-up. In addition, the number of injections (three versus five) in each of the groups is a source of treatment bias. Furthermore, the investigators did not include two placebo injections in the hylan G-F 20 group and, as a result, the patients were not blinded to their treatment. The effectiveness of viscosupplementation treatment could not be proven in this trial due to the lack of a third placebo control group.

Wobig et al[25] performed a 12-week, prospective, randomized, double-masked, comparative multicenter study in which 70 patients were injected intra-articularly with 2 mL of either hylan G-F 20 or low molecular weight hyaluronic acid at weeks 0, 1, and 2. At week 12, knees treated with hylan G-F 20 showed a greater mean improvement in weightbearing pain than those treated with low molecular weight hyaluronic acid, with a statistically significant difference ($P < 0.05$). Furthermore, mean scores for the improvement measures, ie, overall improvement in osteoarthritis pain as assessed by patients and evaluators and improvement in the most painful knee movement, were statistically better in the hylan G-F 20 group than in the low molecular weight hyaluronic acid group ($P < 0.05$).

Kirchner and Marshall[26] performed a prospective, multicenter, randomized, double-blind trial in which 321 patients were centrally randomized to receive either Euflexxa (biological hyaluronic acid, Ferring Pharmaceuticals, Inc., Suffern, NY, USA molecular weight 2.4–3.6 million Da) or Synvisc (cross-linking hyaluronic acid, Genzyme Corporation, Cambridge, MA, USA molecular weight 6,000,000 Da). Both products were administered as a course of three 2 mL injections, administered weekly. Both groups experienced statistically significant and clinically important improvements from baseline in the primary endpoint ($P < 0.0001$), without any statistical difference between the two groups. The proportion of patients whose VAS score for the average of the five WOMAC pain questions was <20% (defined previously as "symptom-free" patients) was compared for the two treatment groups in a post hoc analysis. At the study endpoint,

more patients in the biological hyaluronic acid group were symptom-free than were patients in the cross-linking hyaluronic acid group, with a statistically significant difference ($P = 0.038$). With respect to the trial's secondary outcome measures, statistically significant differences favoring the biological hyaluronic acid group were found for patient global assessments ($P = 0.03$) and the percentage of patients requiring paracetamol as rescue medication ($P = 0.013$). Statistically significant and clinically important differences in safety outcomes were also found in the trial. The incidence of joint effusion was significantly higher in the cross-linking hyaluronic acid group ($P = 0.0015$), with 15 episodes in 13 patients compared with one episode reported in one patient for the biological hyaluronic acid group. The results of this trial provide evidence that biological hyaluronic acid can reduce pain and improve function in patients with knee osteoarthritis, without the iatrogenic local reactions associated with cross-linking intra-articular hyaluronic acid products. The absence of an adequately powered, placebo-controlled.

Hylan versus conventional therapies

Raynauld et al[27] conducted a prospective, randomized, open-label, 12-month follow-up study in 255 patients randomized to either appropriate care alone or appropriate care + visco-supplementation with three intra-articular injections of hylan G-F 20 administered one week apart (appropriate care + hylan G-F 20). The appropriate care + hylan G-F 20 group was superior to the appropriate care alone 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.

Because osteoarthritis is a chronic condition, the efficacy of repeated treatments is an important consideration. Several trials have studied patients receiving up to eight courses of viscosupplementation and, overall, found that efficacy levels are maintained with repeated treatment.[28,29] Paker et al,[30] in a randomized controlled trial with a six-month follow-up, compared the efficacy of transcutaneous electrical nerve stimulation with that of intra-articular hylan G-F 20 in 60 patients with symptomatic knee osteoarthritis. In the first group, transcutaneous electrical nerve stimulation was applied for three weeks; in the second group hylan G-F 20 was injected once a week for three weeks. The results of this study showed that these therapies used in combination may alleviate symptoms in patients with osteoarthritis. Atamaz et al[31] compared the effects of physical therapy agents, including infrared, short-wave diathermy pulsed patterns and interferential therapy, versus Orthovisc and Hylan G-F 20. The results of this study support these physical therapy agents, as well as hyaluronan therapy, to be useful, safe, and well tolerated treatments. Moreover, compared with hyaluronic acid, hylan seems to be a more appropriate agent for some of the symptoms, such as pain.

Hylan G-F 20 has been compared with continuous intake of nonsteroidal anti-inflammatory drugs in two controlled, randomized, multicenter trials. Adams et al[32] compared hylan G-F 20 viscosupplementation with continuous nonsteroidal anti-inflammatory drug therapy. Hylan G-F 20 was at least as effective for pain during motion as nonsteroidal anti-inflammatory drug therapy at 12 weeks, but was significantly better than nonsteroidal anti-inflammatory drug therapy alone at 26 weeks ($P < 0.05$). A second, prospective, randomized trial performed by Kahan et al[33] compared the pharmacoeconomic benefits accrued over nine months in 506 patients given hylan G-F 20 or conventional treatment. This study confirmed that Synvisc viscosupplementation is more effective than conventional treatment, at no additional cost.

Results from randomized, controlled trials[34,35] comparing hylan G-F 20 with intra-articular corticosteroids in a total of 318 patients showed controversial results. Caborn et al[34] reported a 26-week, single-blind, randomized, controlled trial comparing three weekly injections of hylan G-F 20 2 mL with one intra-articular injection of triamcinolone hexacetonide 40 mg (2 mL of a 20 mg/mL suspension) in 218 patients with knee osteoarthritis. Treatment with hylan G-F 20 showed a longer duration of effect than triamcinolone hexacetonide. These data support the preferential use of hylan G-F 20 over triamcinolone hexacetonide for treatment of chronic osteoarthritis knee pain. Leopold et al[35] performed a randomized, controlled trial comparing three weekly injections of hylan G-F 20 2 mL with one intra-articular injection of betamethasone sodium phosphate-betamethasone acetate 2 mL mixed in 4 mL of bupivacaine and 4 mL of lidocaine. No differences were detected between the two groups with respect to pain relief or function at six-month follow-up. In general, patients treated with hylan G-F 20 experienced a greater sustained improvement over time than those treated with intra-articular corticosteroids. Intra-articular corticosteroid injection seems to be more effective at the beginning because of its faster action, but hyaluronic acid is better in terms of the duration of pain relief. Furthermore, a review of studies evaluating the use of corticosteroid

injections shows a lack of consensus regarding dosing and the time course of administration. Among these reviews, we also observed that confusion often arises regarding dosing when making a direct correlation between equivalence 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 with chronic use, large doses, and errant injection.

Safety

Viscosupplementation with hylan G-F 20 in the treatment of knee osteoarthritis seemed to be safe in these studies. The majority of adverse events were transient pain, stiffness, swelling, or joint effusion in the treated knee that resolved within a few days without sequelae. The study performed by Kirchner and Marshall[26] showed a higher incidence of postinjection effusion in the cross-linking hyaluronic acid group, which provides a safety advantage for biological hyaluronic acid. These data suggest that biological hyaluronic acid has an improved benefit-risk profile compared with cross-linking hyaluronic acid. Only one case of anaphylactic shock and one case of pseudosepsis were recorded in the studies performed by Juni et al[22] and by Raman et al[24] respectively. A literature search detected two case series reporting eight cases of granulomatous inflammation after three intra-articular injections of hylan G-F 20.[36,37] In these case reports, the granulomatous inflammation seems to have been caused by the injected viscosupplementation material. Histologic analysis demonstrated foreign body granulomatous inflammation surrounding acellular material in a palisading fashion. It is not known whether the pathologic agent responsible was 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 pathologic response to a viscosupplementation product, which should raise clinical awareness of this potential complication. The precise role of hylan G-F 20 viscosupplementation in the pathogenesis of granulomatous inflammation in treated joints is not yet clear. At present, the low incidence of side effects and the safety of hylan G-F 20 make it particularly suitable for elderly patients who cannot tolerate nonsteroidal anti-inflammatory drugs and corticosteroids, or patients in whom these agents are contraindicated. Viscosupplementation can also be used concomitantly with other therapies commonly used by elderly patients. However, we must mention the Reichenbach meta-analysis that, in view of the likely lack of superior effectiveness of hylan over hyaluronic acid and the increased risk of local adverse events associated with hylan, discouraged the use of intra-articular hylan in patients with knee osteoarthritis.[38]

Prosthesis delay and cost-effectiveness

Total knee replacement (TKR) is considered a last resort for treatment of osteoarthritis knee pain in appropriate patients when other therapies fail. While TKR is an effective option for osteoarthritis pain relief for many patients, it is not medically desirable for some patients (advanced age, heart disease, diabetes, pulmonary disease, obesity, or generalized medical debilitation) and is not preferred by others. Additionally, complications of surgery have been reported, including infection,[39] pulmonary embolism, nerve damage, thromboses, urinary complications,[40] fat embolism,[41] patellar fracture,[42] heterotopic ossification,[43] stiffness,[44] and vascular injuries.[40,45] It may also be desirable to delay TKR in younger patients because of the risk of need for hardware revision, loosening from the bone, pain from overuse, or to delay or avoid the procedure altogether in older patients or patients with comorbidity who may have an increased risk of complications with surgery. Prior to surgical treatment of osteoarthritis, which is expensive and not risk-free, all other treatment options should be fully considered. In a retrospective study performed by Waddel et al,[46] a total of 1187 knees (863 patients) with osteoarthritis Grade IV were treated with hylan G-F 20. The majority of knees during the observation time did not require TKR. In total, 225 knees underwent TKR. Within age categories, the incidence of TKR was highest for patients aged 60–69 years, which was more than double the percentage of patients aged <50 or $^{3}80$ years who had a TKR. This retrospective study showed that the use of one or more courses of hylan G-F 20 in orthopedic practice can delay the need for surgery in patients who are candidates for TKR (knee osteoarthritis Grade IV according to Kellgren-Laurence). The incidence of TKR in the population of TKR candidates studied here was low, and for knees that underwent TKR, use of hylan G-F 20 had the ability to delay surgery for approximately 1.8 years. In others, the median time of hylan G-F 20 treatment and patient follow-up without having a TKR was 2.2 years. Previously reported data also show that hylan G-F 20 can delay the need for TKR in patient populations with predominantly advanced osteoarthritis. In an open-label, multicenter trial, osteoarthritis knee pain in 86% of patients (n = 60) with advanced

osteoarthritis (75% Grade IV) receiving hylan G-F20 therapy (up to four courses) improved sufficiently to delay TKR at week 12 of the study. At the end of the 30-month observation period, a total of 59% of treated patients were able to delay TKR.[47] Another preliminary case-control study (110 TKR patients; 1151 patients without TKR), performed by Waddel et al,[48] shows that the probability of progression to TKR in a population of predominantly advanced osteoarthritis (83% Grade IV) knee patients was reduced with hylan G-F 20 therapy.

Given that TKR is the primary cost driver in the treatment for osteoarthritis of the knee, cost savings to any plan would be a function of delaying or avoiding the number of TKR in insured patients.[49] With its ability to delay TKR, use of hylan G-F 20 therapy has the potential to reduce costs for knee osteoarthritis treatment, including both initial and revision surgery. A theoretic managed care model with a large Medicare population developed to evaluate the potential savings associated with incorporating hylan G-F 20 into the standard treatment regimen for osteoarthritis knee pain demonstrated cost savings. In this hypothetical cohort of 100,000 patients (3835 with mild, moderate, or severe osteoarthritis of the knee) followed for three years, significant cost savings were predicted from the use of hylan G-F 20. These cost savings were primarily due to the predicted 808 TKRs that could be avoided with hylan G-F 20 therapy. Over this three-year period, total cost savings of $8,810,771 was reported for the plan, with a total cost savings of $4706 per patient receiving hylan G-F 20.[49]

Furthermore, use of viscosupplementation in knee osteoarthritis seems to reduce the use of nonsteroidal anti-inflammatory drugs and corticosteroids drastically, with consequent reduction of the adverse events related to these drugs,[28] such as gastrointestinal injury, and the direct and indirect costs. In these days of pharmacoeconomic evaluation of therapy options, it is appropriate to consider this therapy in the primary management of knee osteoarthritis.

Predictors of clinical response

A recent Cochrane review[50] concluded that hyaluronic acid showed superior efficacy compared with placebo for improvement in pain and function of knee osteoarthritis. However, there are few data identifying patients most likely to respond. Several studies have attempted to identify clinical and imaging predictors of response to intra-articular hyaluronan. Early radiographic grade,[51–53] presence and absence of effusion,[51,54] and high baseline functional index[55] have been found to predict better response. The quality of the relevant trials has been variable, with conflicting results. Data from a large retrospective Canadian study[51] showed radiographic grade of the knee to be a predictor of response, with significantly higher response rates in those with Grade I–II osteoarthritis than in those with end-stage disease. While other studies have reported a similar outcome,[52] a recent retrospective review of 155 patients with knee osteoarthritis who had received hylan G-F 20 found that radiologic grade did not have a marked influence on treatment outcomes.[54] This study also reported improved outcomes in study recruits with moderate knee effusions compared with those having none. This contradicts findings from the large Canadian study,[51] where the efficacy of intra-articular hylan was reduced in patients presenting with effusion.

Anandacoomarasamy et al[56] performed a prospective pilot study to evaluate synovial fluid, and clinical and imaging predictors of clinical response in 32 patients with mild to moderate knee osteoarthritis receiving intra-articular hylan G-F 20 injections. Synovial fluid and clinical and radiographic parameters were assessed. Patella and tibial cartilage volume and cartilage defect scores were measured at baseline and at six months using magnetic resonance imaging. The primary outcome measure was the relationship between synovial fluid measures at baseline and at three months, and the likelihood of clinical response as defined by the Osteoarthritis Research Society International (OARSI)-Outcome Measures in Rheumatology Clinical Trials (OMERACT) responder criteria for osteoarthritis ("high improvement" in pain and function at three and six months, ie, $\geq$50% improvement in pain or function, and absolute change $\geq$20 NU on the Western Ontario and McMaster University Osteoarthritis Index questionnaire). Secondary outcomes included magnetic resonance imaging outcomes (change in cartilage volume and cartilage defect scores) at baseline and six months. Clinical outcomes measured included change in self-reported WOMAC scores, VAS pain score, patient global score, and physician global score. Fifteen patients achieved "high improvement". High baseline synovial fluid hyaluronic acid concentration was a statistically significant predictor of clinical response, with an odds ratio of 6.04 ($P < 0.02$). A baseline hyaluronic acid concentration value $>$ 2 mg/mL provided the greatest tradeoff between sensitivity and specificity, with values of 60% and 77%, respectively, a likelihood ratio of 2.55, and an odds ratio of 4.88. Baseline clinical and radiographic measures did not predict clinical response in this cohort with mild to moderate osteoarthritis, and no change was noted in cartilage volumes

or cartilage defect scores over six months. Baseline synovial fluid hyaluronic acid concentration seems to predict clinical response in patients receiving intra-articular hylan. This result could have implications for the selection of patients who are likely to respond to this therapy.

Conclusion

Current treatment options for osteoarthritis include simple analgesics, nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injection, weight reduction, and/or surgical treatment. Despite the increasing morbidity of pain and functional impairment, standard therapies for osteoarthritis have not progressed over the past few years. Standard therapies include corticosteroids or nonsteroidal anti-inflammatory drugs, 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 with intra-articular corticosteroids, which have 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 for which corticosteroids are contraindicated. Several studies have shown a significantly reduced nonsteroidal anti-inflammatory drug intake in knee osteoarthritis after hylan G-F 20 treatment, which was maintained significant for a long time. Moreover, to evidence improvement in pain management, the benefits of a reduction in the direct and indirect costs related to chronic nonsteroidal anti-inflammatory drug use or to the prosthesis delay are obvious. Furthermore, according to OARSI-OMERACT criteria, TKR must be considered after conservative treatment failure.[57] Within this context, a correct evaluation of the role of hylan G-F 20 in the overall management of osteoarthritis 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. In these days of pharmacoeconomic evaluation of therapy options, it is appropriate to consider this opportunity in the overall management of hip osteoarthritis. Data obtained from trials reported in the literature are conflicting. There are some limits in the interpretation of these trials concerning their different and sometimes poor methodology, their different outcome measures, scoring systems, statistical analysis, and interpretation of results. The conclusions of the Cochrane meta-analysis seem to be in favor of higher efficacy of hylan G-F 20, both on pain and function, than any other form of systemic intervention or intra-articular corticosteroids.[50,58] Because osteoarthritis is a chronic condition, the efficacy of repeated treatments is an important consideration. Several trials have studied patients receiving repeated courses of hylan G-F 20 and, overall, found that efficacy levels are maintained with repeated treatment in knee osteoarthritis. At present, the low incidence of side effects and the safety of hylan G-F20 make it particularly suitable for elderly patients who cannot tolerate nonsteroidal anti-inflammatory drugs and corticosteroids or in whom these agents are contraindicated. Viscosupplementation can also be used concomitantly with other therapies commonly used by elderly patients.

Disclosures

The authors declare no conflicts of interest.

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