

Intra-articular injections of hylan G-F 20 in patients with symptomatic hip osteoarthritis: An open-label, multicentre, pilot study

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Abstract

Objective

To obtain prospective data on feasibility and safety of intra-articular injections of hylan G-F20 in patients with symptomatic hip osteoarthritis (OA).

Methods

Fifty-seven patients with primary hip OA, Kellgren-Lawrence grade II-III, aged ≥ 40 and walking pain 50-90 mm on a visual analogue scale (VAS) were enrolled in an open-label, multicentre pilot trial. Hylan G-F20 (2 ml) was injected intra-articularly (IA) in the hip under fluoroscopy at D0, and follow-up visits were performed at D7-30-60-90. The possibility of a second injection at D30-60 or 90 was considered if the reported pain level was equivalent to baseline. Adverse events, walking pain (VAS), WOMAC index, patient and physician's global assessment were recorded at each visit.

Results

Twenty-five patients received 1 injection and 32 received 2 injections. Transient hip pain was reported following 10.1% of injections, but no patient withdrew from the study because of this. Two mild synovial fluid aseptic effusions occurred after the first injection. No systemic device-related adverse event was reported. Walking pain decreased from 69.3 mm at entry to 39.5 mm at the end point ($p < 0.0001$). All other outcome measures decreased significantly.

Conclusion

Viscosupplementation with hylan G-F20 is feasible, easy to perform and well-tolerated in hip OA. A double-blind, controlled study should be performed to confirm data on its efficacy.

Key words

Hyaluronic acid, hip osteoarthritis, and osteoarthritis treatment.

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Introduction

Osteoarthritis (OA) is the most prevalent joint disorder in adults aged 50 years and older, and is a major source of pain and disability (1). Non-steroidal anti-inflammatory drugs (NSAIDs) are the most used treatments to decrease pain and improve function but are frequently a cause of serious adverse events. Viscosupplementation is a local therapeutic approach whose goal is to decrease pain and to improve joint mobility by injecting intra-articularly (IA) viscoelastic solutions of hyaluronan or its derivatives (2). Indeed, one element contributing to the pathophysiology of OA may be loss of the viscoelastic properties of the synovial fluid during the course of the disease (3, 4). This diminished viscoelasticity of the synovial fluid may alter the transmission of mechanical force to the cartilage, increasing its susceptibility to mechanical damage. The loss of viscoelasticity of the synovial fluid in OA is due to a decrease in the molecular weight and concentration of hyaluronan, a glycosaminoglycan which is responsible for the lubricating and shock absorption properties of the synovial fluid (4).

Hylan G-F20 is a high molecular weight, cross-linked derivative of hyaluronan, an extract of cockscomb (2). Its mechanism of action could involve a combination of factors, including the restoration of synovial fluid rheology, anti-nociceptive effects and the normalization of endogenous hyaluronan synthesis. However, other mechanisms of actions have been suggested (5). The clinical benefit, which persists well beyond the intra-articular residence time of the product, is suggested to be due to the re-establishment of joint homeostasis (2). Clinical trials of HA therapy are complicated by the large placebo response to IA injection and this has confounded some studies (5), but most placebo-controlled studies report a significant additional effect of viscosupplementation. Whatever the precise pathophysiological mechanisms involved, the safety and efficacy of viscosupplementation with hylan G-F 20 for the treatment of knee OA have been widely evaluated in clinical trials

(6-10). Hylan G-F 20 is classified as a medical device and was approved for the treatment of pain in OA of the knee in many countries since 1992. Hyaluronic acid injections have been recently recommended by expert panels as an effective symptomatic slow acting treatment in the management of patients with knee OA (11, 12).

The hip is another very frequent site of OA. The prevalence of hip OA ranges from 7 - 25% in subjects over 55 in the white European population (1,13,14). Guidelines for the medical management of the disease have been proposed (11,15). They include non-pharmacological means (patients' education, weight loss, physiotherapy) and pharmacological treatment with analgesic, NSAIDs and corticosteroid injections. Nevertheless, as in knee OA, the use and efficacy of corticosteroids remains debatable due to lack of proper testing. Hylan G-F 20 has not yet been assessed in prospective clinical trials for symptomatic OA of the hip. This open-label trial was designed to assess dosage and safety and to help design a subsequent controlled study.

Patients and methods

Patients with primary hip OA (16) were recruited in a multicentre (3 centres), prospective, open-label, pilot trial whose aim was to obtain data on the feasibility and safety of IA injections of hylan G-F 20 in the hip joint. Analgesics (except for paracetamol) and NSAIDs were stopped 2 to 8 days prior to injection. The study protocol and the patients' informed consent form were submitted to and approved by the ethics committee of Lyon A.

Inclusion/exclusion criteria

Inclusion criteria: Ambulatory patients of both sexes, aged 40 years or more, with a primary OA of the hip diagnosed clinically more than 1 year ago and with Kellgren-Lawrence X-ray grade II or III (17), a walking pain score of 50 to 90 mm on a 100 mm VAS, persistent pain for more than 30 days and no joint replacement planned within the next 6-month period. If a wash-out period was necessary, walking pain must have increased by at least 10 mm on the VAS

between the screening visit and the day of injection.

Exclusion criteria: Bilateral symptomatic hip OA, Kellgren-Lawrence grade I or IV, evidence of rapid destructive coxarthrosis (18), major dysplasia or congenital abnormality of the target hip, presence of inflammatory arthropathy or other diseases which may affect joints (e.g. rheumatoid arthritis, chondrocalcinosis, metabolic bone disease, psoriasis, gout, and active infection), any musculoskeletal or vascular condition that would impede measurement of efficacy at the target hip, women who were pregnant or nursing, or women of childbearing potential who were not using a medically acceptable mean of birth control, prior viscosupplementation therapy of the hip, patients with related hypersensitivities to avian protein or any components of hyaluronan-based injection devices, systemic corticosteroids or IA injection within the last 3 months, previous surgery in the target hip, contra-lateral hip arthroplasty or arthroscopy in either hip within 6 months before screening, surgery scheduled during the period of the study, any severe chronic disorders (e.g. cardiovascular, neurological, metabolic, infectious, psychiatric, kidney or skin diseases) and oral or parenteral anticoagulant therapy.

Study design

At the screening visit, the patient's written informed consent was obtained and the inclusion/exclusion criteria were checked. A standard antero-posterior radiograph of the target hip, taken within 3 months before screening, was obtained for assessment of the Kellgren-Lawrence grade, joint space narrowing grade (19) and patterns of femoral-head migration within the acetabulum. Patients were given a full clinical examination. Patients taking NSAIDs had to undergo a 2- to 8-day wash-out period depending on the half-life of the given NSAID before being administered the hylan G-F 20 injection. The screening and baseline visits were performed on the same day if no wash-out period was required.

Follow-up visits were performed at day

7, 30, 60 and 90. At baseline and on each further visit, pain and function were assessed using visual analogue scales (walking pain as assessed by the patient, global assessment of the patient and physician) and the French validated version of the WOMAC index (20). Adverse events were also collected for a safety analysis. In the event that the first injection did not provide sufficient improvement (such that the patient reported pain equivalent to baseline levels), it was possible for a second injection to be administered by the same physician at day 30. If the first injection was efficacious but walking pain returned to its initial value during the follow-up period, a second injection was to be given at day 30, 60, or 90, depending upon the time the failure occurred. In the case of a second injection, the follow-up visits were again at days 7, 30, 60 and 90 after the injection in order that all patients would be evaluated 90 days after the last administration of hylan G-F 20. During the course of the study paracetamol (0.5 to 3 g/day) was the only analgesic allowed. NSAIDs, aspirin at doses above 325 mg/day and corticosteroids were prohibited. Oral symptomatic slow-acting drugs for OA (chondroitin sulphate, glucosamine sulphate, diacerhein and avocado-soja unsaponifiables) were authorized if they were being taken at a stable dose for more than 3 months prior to inclusion in the study. Additionally, these medications could not be initiated or changed during the course of the study.

Technique of injection

Viscosupplementation therapy consisted of an IA injection of 2 ml of hylan G-F20 in the target hip. Injections were performed in a hospital day care clinic under fluoroscopy by experienced rheumatologists. In two centres injections were performed using an anterior approach, while a lateral approach was performed at the third centre. A strict aseptic administration technique was followed. Arthrocentesis was carefully performed prior to each injection to remove any effusion. If synovial fluid was obtained, the injection was then directly performed. In all other cases

the intra-articular positioning of the needle was assured by injecting a minimal (0.1 to 1 ml) dose of sodium and meglumine ioxaglate (Hexabrix 320 arthro™) before the hylan G-F 20 injection. Injection of local anaesthetics into the joint space was prohibited. After the injection, patients returned home with the standard precaution following any IA injection (rest at home until the next morning) being given.

Statistics

In the absence of a control group in this pilot study, analysis was mainly descriptive. The results were obtained using intent-to-treat analysis for safety, and per-protocol analysis for pain and function changes. Full details of all adverse events were listed. For qualitative values, the number and percentage of patients for each modality were calculated. For quantitative data, the mean and standard deviation were provided. Changes between baseline and each visit in pain and function parameters (pain, WOMAC, patient and physician's global assessment) were evaluated using Student's paired t-test for each assessment. Patients who completed the study were evaluated 90 days after the last administration of the device (end-point). In those who dropped out, the endpoint data were those corresponding to the last patient visit available irrespective of the number of injections or the follow-up stage.

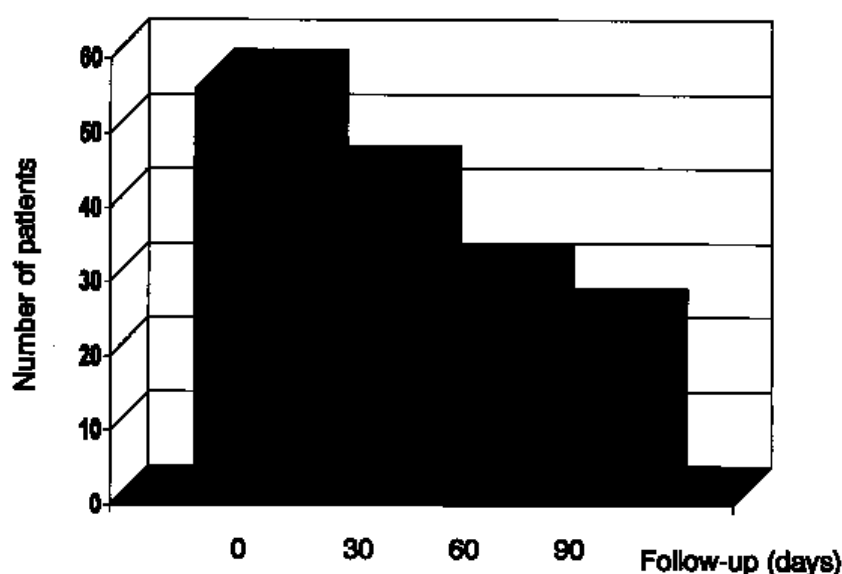
Results

A total of 89 injections were performed in 57 patients: 25 patients received 1 injection and 32 received 2 injections. One patient subsequently diagnosed with aseptic osteonecrosis of the hip was analysed for safety only. Patient characteristics are summarized in Table I. The mean age at entry and mean disease duration were respectively 59.8 and 5.1 years. Topography of the joint space narrowing was superolateral, superointermediate, superomedial and inferior in respectively 53.6%, 12.5%, 12.5% and 21.4% of the cases.

The second injection was performed at month 1, 2 and 3 respectively in 13, 13 and 6 patients (Fig. 1). The mean time between the two injections was 53 days.

Table I. Characteristics of the 56 per protocol patients treated with hylan G-F 20 intra-articular injection for hip osteoarthritis.

Age (mean \pm SD)	59.8 \pm 9.5 (range 42-79)
Disease duration (mean \pm SD)	5.9 \pm 8.0 years
Body mass index (mean \pm SD)	25.6 \pm 4.3
Walking pain on VAS (mean \pm SD)	69.3 \pm 11.9 mm
Gender	
Male	N= 23
Female	N= 33
Kellgren-Lawrence	
Grade II	N= 25
Grade III	N= 31
OA treatment intake at entry	
NSAIDs	N= 10
Analgesics	N= 33
SYSADOA	N= 23

**Fig. 1.** Over time, the number of patients treated by hylan G-F 20 intra-articular injection for hip osteoarthritis who did not receive a second injection.

Anterior and lateral routes of injection were used respectively in 64 and 25 cases. The mean injected amount of sodium and meglumine ioxaglate was 0.4 ml (range 0.1-1ml).

Safety

Among the 57 patients enrolled in the trial, 8 did not complete the study: 3 for lack of efficacy, 2 for non-related adverse events (1 sciatica, 1 femoral nerve radicular pain), and 2 were lost to follow-up. Eleven target hip adverse events possibly related to the treatment were reported in 8 patients (following 9 injections) though none of these caused withdrawal from the study. Seven patients (8 injections) experienced

transient hip pain that appeared within 24 hours after the injection and either resolved spontaneously (3 cases) or with non-NSAID analgesics (5 cases) within 0.5 to 27 days (median 3 days). Two mild synovial fluid (SF) aseptic effusions (demonstrated by SF aspiration at the time of the second injection) occurred after the first injection. In one patient, the volume of SF collected was too small to be analyzed (0.1 ml). SF was yellow, clear and of high viscosity. This woman did not experience any improvement after the first or after the second injection, but did not report pain associated with this effusion. In the second patient a 2 ml SF effusion was removed and analysed by a local

laboratory which found: Fluid: yellow, clear; Viscosity: fair; RBC 86 units/mm³; WBC: 116 units/mm³; Granulocytes 25%; Lymphocytes 0%; Monocytes 70%; and Undifferentiated cells 5%).

There was no report of infectious IA adverse events. There were no severe systemic reactions. One patient experienced mild and transient pruritus that did not require treatment. One patient reported moderate and transient muscular cramps that did not require treatment.

Pain and function

In the absence of a control group, analysis was only descriptive. Walking pain decreased significantly from 69.3 mm on VAS at entry to 39.5 mm at the end point ($p < 0.0001$). All other outcome measures decreased significantly between baseline and the end-point as shown in Table II (all $p < 0.0001$). Walking pain decreased at day 7 following the first injection (-27.3 mm, range -86 to $+12$) even in patients who required a second injection (median -24.5 mm, range -60 to $+12$). At the end-point, 29 patients (51.7%) had a 50% or more improvement in walking pain. Eighteen patients (32.1%) experienced a 75% or more improvement in walking pain on VAS. Three patients reported a worsening of pain ($> 10\%$ on VAS) during the course of the study. The decrease in walking pain and disability (Table III) was much better in patients who required one injection only (walking pain at end point 27.5 mm \pm 26.5) than in those who needed 2 injections (walking pain at end point 49.2 mm \pm 28.6), regardless of the time between the first and second injections (Fig. 2).

No predictive factor for pain changes was identified by the multivariate analysis. No difference in adverse events was detected between the patients injected using the anterior and lateral approaches.

Discussion

To the authors' knowledge, this is the first multicentre prospective study published regarding viscosupplementation by high molecular weight hyaluronan

Table II. Variation in the outcome measures between baseline and the end-point in patients treated with hylan G-F 20 intra-articular injection(s) for hip osteoarthritis.

Outcome Measure	Baseline mm (SD)	End-point mm (SD)	Mean change mm (SD) [%]	p* (ES)
Walking pain	69.3 (11.9)	39.5 (29.5)	-29.8 (28.7) [-43%]	<0.0001 (2.5)
WOMAC A	53.7 (17.2)	34.9 (27.1)	-15.2 (23.0) [-28.3%]	<0.0001 (0.88)
WOMAC B	54.2 (23.2)	34.6 (27.2)	-15.9 (25.8) [-29.3%]	<0.0001 (0.68)
WOMAC C	50.8 (20.3)	34.4 (26.9)	-13.1 (22.6) [-25.8%]	<0.0001 (0.64)
WOMAC aggregate	157.2 (53.5)	104.0 (79.7)	-44.2 (65.6) [-28.1%]	<0.0001 (0.83)
Patient's global assessment	66.1 (12.4)	41.0 (28.5)	-25.1 (29.3) [-38%]	<0.0001 (2.02)
Physician's global assessment	62.8 (9.4)	36.3 (24.5)	-26.5 (24.7) [-42.2%]	<0.0001 (2.95)

SD: standard deviation; ES: Effect-size. * Student t-test

Table III. Variation in the outcome measures between baseline and the end-point in 25 patients treated with a single hylan G-F 20 intra-articular injection for hip osteoarthritis.

Outcome Measure	Baseline mm (SD)	End-point mm (SD)	Mean change mm (SD) [%]	p* (ES)
Walking pain	67.1 (11.4)	27.5 (26.5)	-39.6 (24.2) [-59%]	<0.0001 (2.63)
WOMAC A	51.1 (16.3)	27.0 (25.4)	-22.8 (22.9) [-44.6%]	<0.0001 (1.40)
WOMAC B	54.8 (21.4)	29.0 (27.2)	-24.5 (25.8) [-44.7%]	<0.0001 (1.14)
WOMAC C	47.3 (19.5)	26.2 (23.1)	-19.5 (23.1) [-41.2%]	<0.0001 (1.0)
WOMAC aggregate	153.3 (49.7)	82.1 (74.5)	-66.8 (65.9) [-43.6%]	<0.0001 (1.34)
Patient's assessment	66.1 (11.8)	31.4 (24.9)	-34.7 (26.7) [-52.5%]	<0.0001 (2.94)
Physician's assessment	61.7 (8.5)	30.8 (24.0)	-30.9 (23.6) [-50.1%]	<0.0001 (3.63)

SD: standard deviation; ES: Effect-size. * Student t-test

in hip OA. There are a large number of published reports on viscosupplementation in knee OA using up to 5 injections of a hyaluronan or 3 injections of a cross-linked HA such as hylan G-F 20. Although the hip joint can be injected, in practical terms injection of the hip is more difficult to perform than knee injection since it requires the use of more resources (21), frequently within the hospital. It also exposes the patient to small doses of radiation if fluoroscopy is used.

Therefore the aim of this initial study

was to evaluate the tolerability of IA injections of hylan G-F20 in patients with symptomatic hip OA. Our data suggest that hylan G-F 20 injected IA under fluoroscopy in the hip is safe and well tolerated. Treatment-related adverse events were mostly localized at the target hip (11.2% of the injections) and none caused patients to withdraw from the study. This frequency is similar to the one reported in the treatment of knee OA (7, 9). In addition for injection of the hip there is the possibility of reactions to the contrast media. An

alternative to fluoroscopy would be sonography (22, 23) and this might address some of the reservations concerning repeated fluoroscopy and the use of radiation. This method may not be available as routine in many centres. Whichever method is used, the additional costs of injecting the hip (versus the knee) need to be considered. This has to be viewed alongside the risks and benefits. Viscosupplementation poses no greater risk than use of corticosteroids and may present greater benefits. The 8 patients (14%) who experienced transient hip pain recovered within a median of 3 days, either spontaneously or after NSAID treatment, as described for the treatment of local pain associated with hylan GF 20 injections for knee OA. Two synovial fluid aseptic effusions occurred after the first injection (2.2%), one of which was asymptomatic. In the patient whose SF was analyzed, white blood cells were slightly increased and were predominantly monocytes, as frequently found in crystal induced arthropathy. There was no report of infectious adverse event or serious systemic reactions. The two discontinuations of follow-up for non-related adverse events concerned one case of sciatica and another of femoral nerve radicular pain, which is not unusual considering the high frequency of low back pain and spine OA in patients with hip OA. In the absence of a control group, the true efficacy of the treatment cannot be proved, even if the present data suggest that hylan G-F 20 may be an effective treatment of hip OA. The present data showed that a second injection did not increase the risk of an adverse event. The number of injections needed to obtain optimal clinical response should be investigated further.

In summary, this prospective, open-label pilot clinical study provides valuable initial information about the use of hylan G-F 20 in patients with symptomatic hip OA:

- It showed that it is easily feasible to inject hylan G-F 20 under fluoroscopy for verification of the IA space, by injecting a very low amount of contrast liquid to avoid dilution of the device. However, this

PAIN (VAS mm)

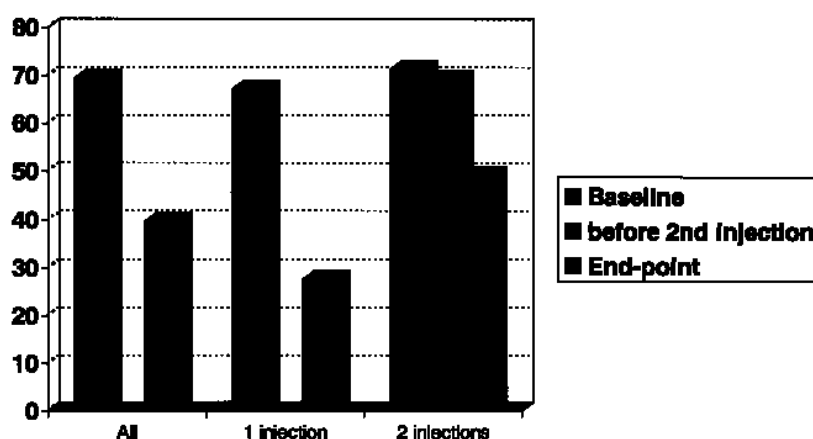


Fig. 2. Variation of walking pain in VAS in patients who required one or two injections of hylan G-F 20 for hip osteoarthritis.

technique should be administered by experienced physicians, under strict aseptic conditions, ideally in a hospital, outpatient setting;

- It showed that there are no major safety concerns associated with a single injection of 2 ml hylan G-F 20, nor following a second injection if required.
- It suggested a symptomatic effect, as seen by improvement between baseline and the endpoint in pain and function, which needs to be demonstrated by double-blind, controlled studies.

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