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Three Weekly Intra-Articular Injections of Hylan G-F 20 vs Arthrocentesis in Patients with Chronic Idiopathic Knee Osteoarthritis: A Multicenter, Evaluator- and Patient-Blinded, Randomized Controlled Trial

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ABSTRACT

Background: Knee osteoarthritis is a leading cause of disability worldwide. Symptoms can vary over time, leading to episodes of worsened symptoms known as flares. Intra-articular injection of hyaluronic acid has demonstrated long-term symptomatic relief in the broader knee osteoarthritis population, although its use in the flare population has not been extensively examined.

Objective: To assess the efficacy and safety of 3 once-weekly intra-articular injections of hylan G-F 20 (as single and repeat courses) in patients with chronic knee osteoarthritis, including a subpopulation that experienced flare.

Methods: Prospective randomized controlled, evaluator- and patient-blinded, multicenter trial with 2 phases: hylan G-F 20 vs arthrocentesis only (control) and 2 courses vs single-course hylan G-F 20. Primary outcomes were visual analog scale (0–100 mm) pain scores. Secondary outcomes included safety and synovial fluid analysis.

Results: Ninety-four patients (104 knees) were enrolled in Phase I, with 31 knees representing flare patients. Seventy-six patients (82 knees) were enrolled in Phase II. Long-term follow-up was 26 to 34 weeks. In flare patients, hylan G-F 20 showed significantly more improvement than the controls for all primary outcomes except pain at night ($P = 0.063$). Both 1 and 2 courses of hylan G-F 20 showed significant improvements from baseline for primary outcomes with no differences in efficacy between groups in the intention-to-treat population at the end of Phase II. Two courses of hylan G-F 20 showed better improvement in pain with motion ($P = 0.0471$) at long-term follow-up. No general side effects were reported, and local reactions (pain/swelling of the injected joint) resolved within 1 to 2 weeks. Hylan G-F 20 was also associated with reduced effusion volume and protein concentration.

Conclusions: Hylan G-F 20 significantly improves pain scores vs arthrocentesis in flare patients with no safety concerns. A repeat course of hylan G-F 20 was found to be well tolerated and efficacious.

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Introduction

Osteoarthritis is a chronic degenerative condition characterized by the loss of joint cartilage and is among the leading causes of pain, disability, and lower quality of life worldwide.[1–3] The most commonly affected joint is the knee.[2,4] Globally, hip and knee osteoarthritis (KOA) combined were ranked as the 11th highest contributor to global disability and 38th highest in disability-adjusted life years of 291 conditions.[5] The lifetime risk of symptomatic KOA has been estimated to be 44.7%, which is increased in individuals with a history of knee injury and increasing body mass index.[6] Because increasing age is also associated with an increased risk of KOA, it is expected that the prevalence of KOA will continue to rise with the greater life expectancy of the general pop-

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ulation and increasing prevalence of greater body mass index and obesity.[2,4,5,7–9] KOA is also associated with a substantial socioeconomic burden; currently, it is estimated that KOA has an annual total cost of more than $27 billion.[2,10]

Symptoms of KOA can vary over time, with periods of stability followed by temporary episodes of increased pain, stiffness, and swelling; these transient episodes of worsened symptoms are generally known as flares, although there has been a range of definitions of flare used in the literature.[11–14] About 25% to 30% of patients with KOA experience these fluctuations in their symptoms, and the occurrence of KOA flares has been estimated at 2.4 episodes per person per year.[11,15,16] The duration of a flare is unpredictable because it can last minutes, hours, days, or even weeks.[12,17] Patients experiencing a KOA flare will often seek medical care because these episodes significantly influence their daily activities, sleep, and concentration; however, currently, little is known about managing KOA flares, likely due to the lack of available research on this topic.[11,17–20]

The prevalence of total knee replacement surgery, which should be delayed as long as possible and reserved for those with end-stage disease, is also on the rise, and there has been a shift toward operating on patients at younger ages.[2,21] Intra-articular (IA) injection of hyaluronic acid (HA) has become a nonoperative option for patients who have failed first-line pharmacological therapy, do not have a surgical indication, or do not want to undergo invasive procedures or surgery.[1,22–24] IA HA may also delay the need for total knee replacement surgery.[23,25,26] Proposed mechanism of actions of exogenous HA, a molecule found naturally within the knee joint, include viscosupplementation of the joint (ie, lubrication and shock absorption), the production of endogenous HA, and subchondral, anti-inflammatory, and analgesic effects.[23,25,27] For patients with a flare, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or opioids may be used as pharmacologic options to manage their symptoms; however, their beneficial effects are usually only short-term or may be inappropriate for some patients, and each of these therapies is associated with certain adverse events (AEs).[11,24,25,28–36] NSAIDs are associated with an increased risk of cardiovascular and gastrointestinal events.[29,34,37–40] Long-term use of corticosteroids can cause nerve damage and thinning of cartilage.[31,33,35] Opioid therapy can lead to addiction and AEs following their use, including nausea, vomiting, constipation, urinary retention, and respiratory depression.[41–43] HA has demonstrated more favorable long-term symptomatic relief in the broader KOA patient population, although its use in the flare population has not been extensively examined.[23,25,28,32]

Several HA therapies are available and vary in their characteristics, such as molecular weight and cross-linkage.[1,27] Prior research has shown that higher molecular weight and crosslinked HAs are associated with improved patient outcomes relative to lower molecular weight and non-crosslinked products.[1,44,45] For example, hylan G-F 20 (Synvisc; Sanofi, Bridgewater, New Jersey) is a high molecular weight (6000 kilodaltons), crosslinked HA product that is injected into the knee once weekly for 3 consecutive weeks (a single injection regimen, Synvisc-One [Sanofi], is also available).[46,47] This study aimed to assess the efficacy and safety of 3 once-weekly IA injections of hylan G-F 20 (as a single course and repeat courses) in patients with chronic KOA, including a subpopulation who experienced flare during a 4-week no-treatment period.

Methods

Eligibility criteria

The study's detailed inclusion and exclusion criteria are provided in **Appendix A** (see the online version at doi:10.1016/j.curtheres.2023.100707). Male and female adults (aged 18 years or older) with chronic idiopathic KOA were eligible for this study. Patients with grade I KOA or grade IV KOA in all 3 knee compartments were excluded.

Study design

This prospective, randomized, parallel, controlled, evaluator- and patient-blinded, 2-phase, multicenter study included patients with chronic idiopathic KOA who were taken off all NSAIDs and steroidal drugs for 4 weeks before treatment. Patients were enrolled from 6 participating investigational sites within the United States. The study design of the trial is provided in Figure 1.

No-treatment period and flare population

The 4-week washout was performed to identify patients whose pain worsened (ie, flare) while they were off NSAIDs. For this study, patients with flare were identified during this no-treatment period based on a patient's self-evaluation of pain on motion (walking) and pain at rest at Weeks 0 and 4. Patients whose pain level increased by 20 mm or more on the 0 to 100 mm visual analog scale (VAS) for either pain on motion or resting pain were considered flare patients. The flare population was enrolled as a subset of the intention-to-treat (ITT) population. After the no-treatment period, the rest of the study was conducted over 2 phases.

Treatment details

Patients randomized to the treatment group received 3 2-mL IA injections of hylan G-F 20 at weekly intervals, and patients randomized to the control group received arthrocentesis once weekly for 3 weeks. Hylan G-F 20 is a highly purified and chemically modified hyaluronan from an avian source containing a small amount of protein. Arthrocentesis involved the insertion of a needle attached to an empty sterile 2-mL glass syringe and was performed on all patients (treatment and control group) at each injection visit, before hylan G-F 20 administration in the treatment group, to remove any fluid in the joint.

Phase I (1 hylan G-F 20 treatment period)

Phase I, a controlled, randomized, evaluator- and patient-blinded investigation, was initiated after the 4-week no-treatment period where patients were assigned 1:1 to either the treatment (3 arthrocentesis followed by hylan G-F 20 injection [2 mL] 1 week apart) or control (3 arthrocentesis 1 week apart) via a computer-generated blocked randomization scheme. Sealed numbered envelopes with the assigned treatment group were given to the treating physician. The physician followed the sequentially numbered envelopes as patients who met the eligibility criteria entered the study. The physician was instructed not to open the envelope until just before the patient received treatment. Each knee was randomized separately and independently followed for patients with bilateral KOA. The physician was instructed to remove all fluid (normal volume or effusion) at the time of arthrocentesis (control) and before hylan G-F 20 was injected (treatment). Phase I took place over Weeks 4 to 10, with study follow-up visits at each injection visit (ie, Weeks 4–6) and every 2 weeks (ie, Weeks 8 and 10) after that.

Phase II (2-course hylan G-F 20 treatments)

Patients completing Phase I were eligible to participate in Phase II of the study. At the start of the second phase, patients in the treatment group were allowed to receive a repeat course of hylan G-F 20 at the same injection regimen as in phase I (ie, 3 once-weekly injections), and patients in the control group could receive their first course of hylan G-F 20 injections; patients could enter Phase II any time between Week 10 and Week 18. Phase II patients were observed for another 8 weeks after injection, meaning

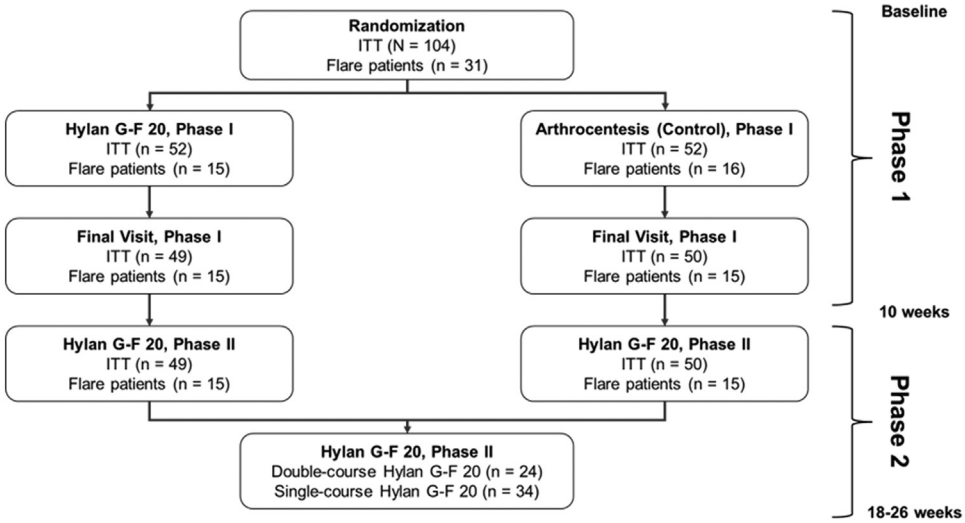

Figure 1. Study design of the 2-phase randomized controlled trial. ITT = intention-to-treat; n = number of knees.

that patients could be followed for 18 to 26 weeks throughout the study. In addition, patients were requested to participate in a long-term follow-up program that involved another study visit between 26 and 34 weeks. This study design permitted the safety evaluation of a second treatment following the first treatment.

Blinding

Patients and evaluators were blinded throughout the study; however, physicians administering the injections were not blinded. Blinding was assured by administering the IA injections behind a screen to obscure observation by the patient. The evaluation of patients was done by a member of the investigational staff who was not aware of the patients' treatment group assignment. No communication was permitted between the evaluator and the treating physician concerning any aspect of the study. Patient- and evaluator-blinding was maintained throughout both phases of the study because only the treating physician was aware that all patients in Phase II would receive hylan G-F 20.

Outcomes

Efficacy

The primary efficacy outcomes were patient-reported pain measures:

- Pain at rest (VAS),
- Pain with motion (VAS),
- Pain while walking (VAS),
- Pain at night waking patient (VAS),
- Overall arthritis pain assessment (VAS), and
- Categorical grading (>50% improvement on VAS).

Improvements in VAS pain outcomes were compared with a minimal clinically important improvement of 20 mm.[48–51] Patients were given diaries and asked to track pain status and medications at baseline and subsequent visits.

Safety

At each study visit, patients were evaluated and questioned regarding current or between-treatment AEs. All AEs were recorded, which included the investigator's assessment of the relationship of the AE to the test device, whether or not remedial treatment was required, whether or not there were sequelae, the nature of such sequelae, and whether or not treatment discontinuation was required. AEs considered serious or life-threatening by the investigator were to be reported immediately to the study sponsor.

Synovial fluid analysis

Synovial fluid was collected to measure volume, hyaluronan and protein concentration, average hyaluronan molecular weight, hyaluronan molecular weight distribution, and rheology. For this study, effusion was defined as fluid in the joint greater than normal volume (ie, >2 mL).

Statistical methods

Statistical analyses were conducted for the ITT population using the last observation carried forward approach. The unit of analysis was each knee to account for patients with bilateral KOA who received hylan G-F 20 in 1 knee and control treatment in the other. The least squares mean change from baseline VAS scores were calculated and used to compare group outcomes. Data for continuous outcomes are presented as the mean (SEM). Within-group improvements from baseline in VAS scores were analyzed using a paired t test. Between-group improvements from baseline in VAS scores were compared using a 1-way ANOVA. Finally, categorical outcomes were analyzed using χ^2 analysis. Two-tailed tests with an alpha level of 0.05 were used for all statistical analyses.

Sample size

The planned sample size of the study was based on the assumption that at least 80% of the active treatment group, compared with 50% of patients in the control group, would experience a 25% improvement. This calculation was based on an alpha level of 0.05 and a power level of 0.80. Thus, the required sample size was 45 patients per group (or 90 patients total).

Ethics

Each patient's written informed consent was obtained before enrolment. The study was conducted in the United States under IDE #G890108 according to Good Clinical Practice guidelines and was approved by the institutional review board of each participating investigational site.

Table 1
Patient characteristics of the intention-to-treat population.

Parameter	Phase I			Phase II		
	Hylan G-F 20	Bilateral* single/double	Control	Hylan G-F 20	Bilateral* single/double	Control
Sex†						
Male	18 (38)	0 (0)	13 (30)	14 (40)	0 (0)	11 (29)
Female	29 (62)	4 (100)	30 (70)	21 (60)	3 (100)	27 (71)
Age, y						
Mean (SEM)	62 (2)	61 (6)	67 (2)	63 (2)	66 (5)	67 (2)
Median	63	63	67	65	69	67
Range	38-89	47-72	42-87	38-89	57-72	46-87
Height, in						
Mean (SEM)	67 (1)	65 (1)	65 (1)	67 (1)	65 (2)	65 (1)
Median	66	65	65	66	64	65
Range	58-74	63-68	54-75	59-74	54-75	63-68
Weight, lb						
Mean (SEM)	196 (7)	203 (13)	182 (6)	194 (8)	209 (26)	182 (7)
Median	195	212	180	194	216	178
Range	105-400	165-224	110-290	105-400	162-250	110-290
Race†						
White	42 (89)	4 (100)	36 (84)	32 (91)	3 (100)	32 (84)
Black	4 (9)	0 (0)	7 (16)	2 (6)	0 (0)	6 (16)
Other	1 (2)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)

* Indicates only those patients who received hylan G-F 20 in 1 knee and control in the other. All other bilaterally treated patients received hylan G-F 20 or control in both knees and have been included in the appropriate treatment groups in the analysis.
† Values are presented as n (%).

Table 2
Joint characteristics of the intention-to-treat population.

Parameter	Phase I		Phase II	
	Hylan G-F 20	Control	Hylan G-F 20	Control
Disease duration				
Years*	9 (1)	8 (1)	8 (1)	8 (1)
<1 year†	3 (6)	5 (10)	2 (5)	5 (11)
1-5 years†	20 (38)	21 (40)	16 (42)	15 (39)
>5 years†	29 (56)	26 (50)	20 (53)	24 (55)
OA grade by compartment†				
Medial				
I	7 (13)	5 (10)	3 (8)	3 (7)
II	17 (33)	18 (35)	16 (42)	16 (36)
III	23 (44)	21 (40)	17 (45)	18 (41)
IV	5 (10)	8 (15)	2 (5)	7 (16)
Lateral				
I	18 (35)	21 (43)	14 (38)	16 (39)
II	25 (49)	19 (39)	17 (46)	17 (41)
III	6 (12)	8 (16)	5 (13)	7 (17)
IV	2 (4)	1 (2)	1 (3)	1 (2)
Patellofemoral				
I	9 (17)	13 (25)	8 (21)	10 (23)
II	30 (58)	23 (44)	22 (58)	18 (41)
III	12 (23)	10 (19)	8 (21)	10 (23)
IV	1 (2)	6 (12)	0 (0)	6 (14)

OA = osteoarthritis.
* Values are presented as mean (SEM).
† Values are presented as n (%).

Results

Patient demographics

Between September 1990 and December 1992, 94 patients (104 knees) were enrolled in Phase I and included in the ITT analysis, which included 31 knees (15 hylan G-F 20 and 16 controls) from the flare population. Seventy-six patients (82 knees) were enrolled in Phase II and included in the ITT analysis, in which 38 knees received a second course of hylan G-F 20 and 44 received their first course of hylan G-F 20. Patient and joint characteristics of the ITT population are provided in Table 1 and Table 2, respectively.

Of the 104 patient knees in the ITT population, 99 completed Phase I. A total of 5 patients withdrew from the study prematurely (2 hylan G-F 20 and 3 controls). The 2 patients who withdrew from the hylan G-F 20 group had a total knee replacement. Of those who withdrew from the control group, 1 developed severe pain in other joints, 1 did not like the treatment, and 1 patient received steroids to treat herpes zoster. Of the 82 knees that entered Phase II, 58 (24 2-courses of hylan G-F 20; 34 1-course of hylan G-F 20) completed the final evaluation of this phase. Reasons for withdrawal from Phase II are provided in **Appendix B** (see the online version at doi:10.1016/j.curtheres.2023.100707).

There were no significant differences in demographic parameters other than the predominance of female vs male patients ($P < 0.0001$) and White vs Black/Other patients ($P = 0.0001$).

Efficacy

Phase I

Flare population. At the end of Phase I, hylan G-F 20 patients in the flare population improved significantly more than control patients for all primary efficacy outcomes except pain at night (Figure 2 and **Supplemental Table 1** [see the online version at doi:10.1016/j.curtheres.2023.100707]). For pain at night, the hylan G-F 20 group improved twice as much as controls, but the P value was 0.063. Notably, pain at night was significantly lower for hylan G-F 20-treated patients at baseline than controls ($P = 0.020$).

Additionally, a significantly greater proportion of patients in the hylan G-F 20 group achieved >50% improvement on all primary efficacy variables except pain while walking and overall arthritic pain (Figure 3 and **Supplemental Table 2** [see the online version at doi:10.1016/j.curtheres.2023.100707]).

ITT population. The ITT population, which included the nonflare population, did not demonstrate significant differences between hylan G-F 20 and controls in the primary efficacy outcomes by the end of Phase I (Figure 4 and **Supplemental Table 3** [see the online version at doi:10.1016/j.curtheres.2023.100707]), although the improvement of most measures was greater in the hylan G-F 20 group than in the control group.

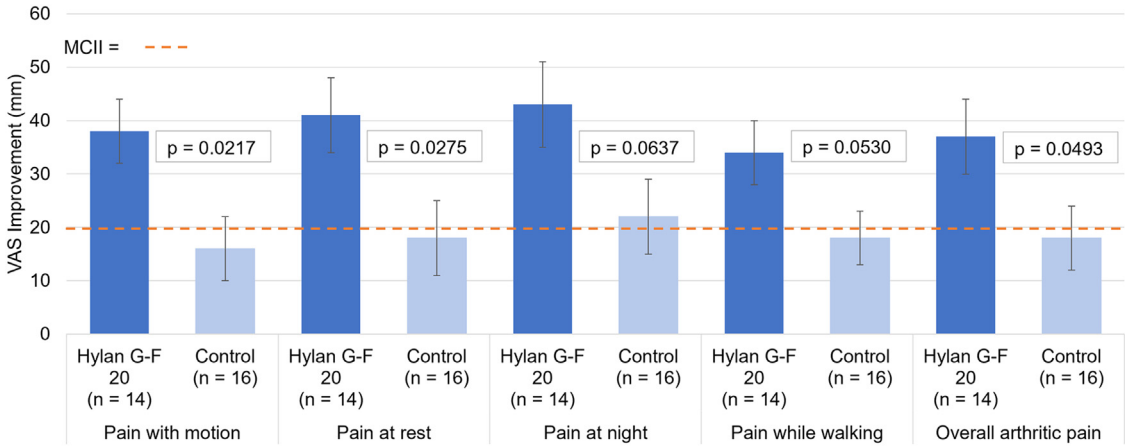

Figure 2. Mean (SE) improvement from baseline to 10 weeks in primary efficacy outcomes for the flare population (Phase I). MCII = minimal clinically important improvement; VAS = visual analog scale.

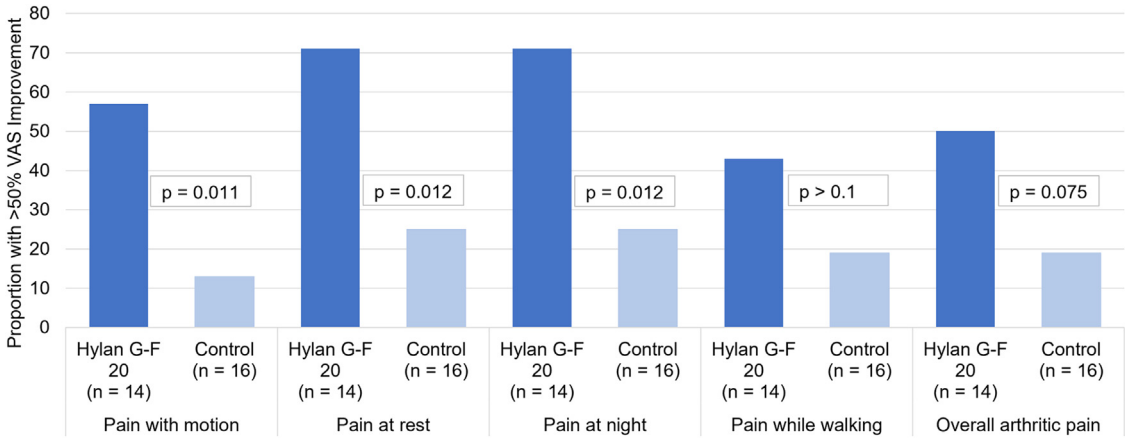

Figure 3. Proportion of patients with >50% improvement on the primary efficacy outcomes for the flare population (Phase I). VAS = visual analog scale.

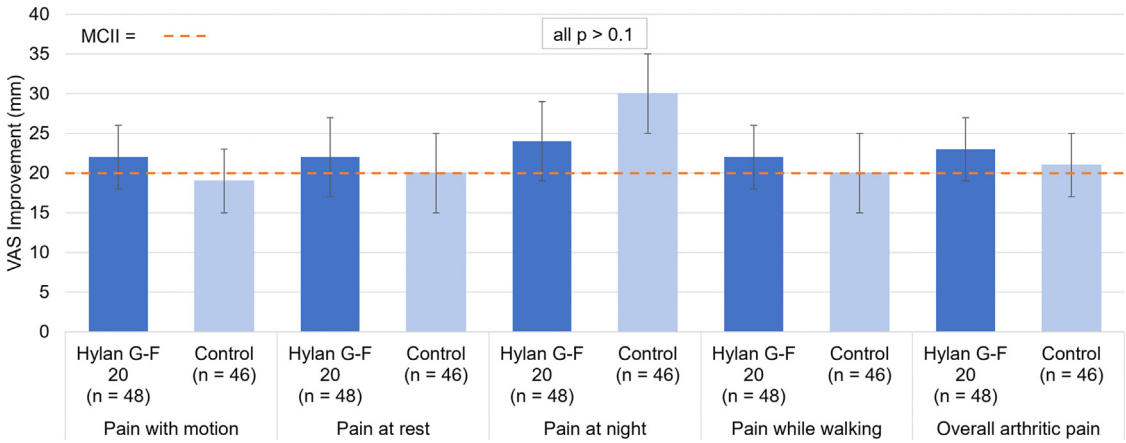

Figure 4. Mean (SE) improvement from baseline to 10 weeks in primary efficacy outcomes for the intention-to-trea population (Phase I). MCII = minimal clinically important improvement; VAS = visual analog scale.

Phase II

ITT population. At the end of Phase II (ie, the follow-up visit 6 weeks after the last hylan G-F 20 injection in Phase II), both the single-course and 2-course hylan G-F 20 groups showed significant improvements from baseline in the primary efficacy outcomes ($P <$ 0.05 for all). Although no significant differences were observed between groups (Figure 5 and **Supplemental Table 4** [see the online version at doi:10.1016/j.curtheres.2023.100707]). Improvements in the VAS across all efficacy outcomes ranged from 23 to 43 mm. VAS improvements were significantly greater when the same group of patients was treated with hylan G-F 20 in Phase II vs when they were treated with arthrocentesis in Phase I. Pain reductions follow-

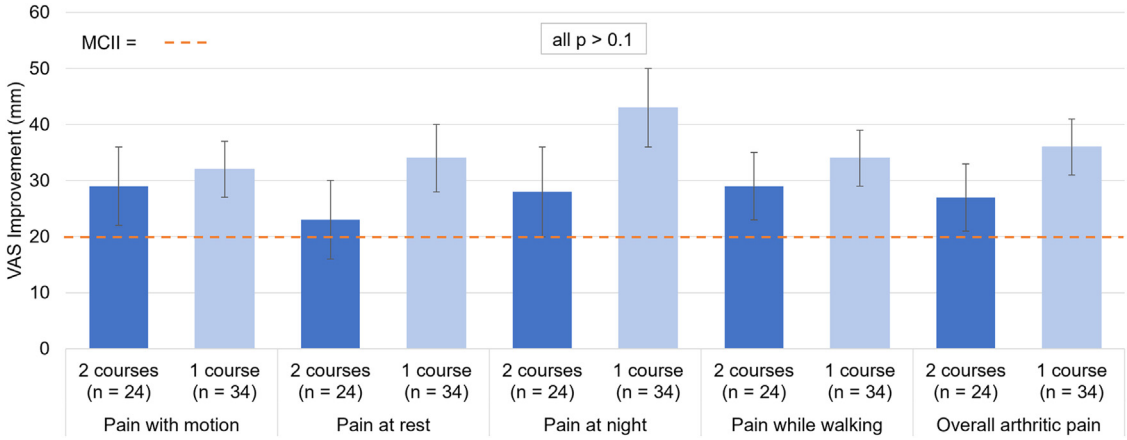

Figure 5. Mean (SE) improvement from baseline to 18 to 26 weeks in primary efficacy outcomes for the intention-to-treat population (Phase II). MCII = minimal clinically important improvement; VAS = visual analog scale.

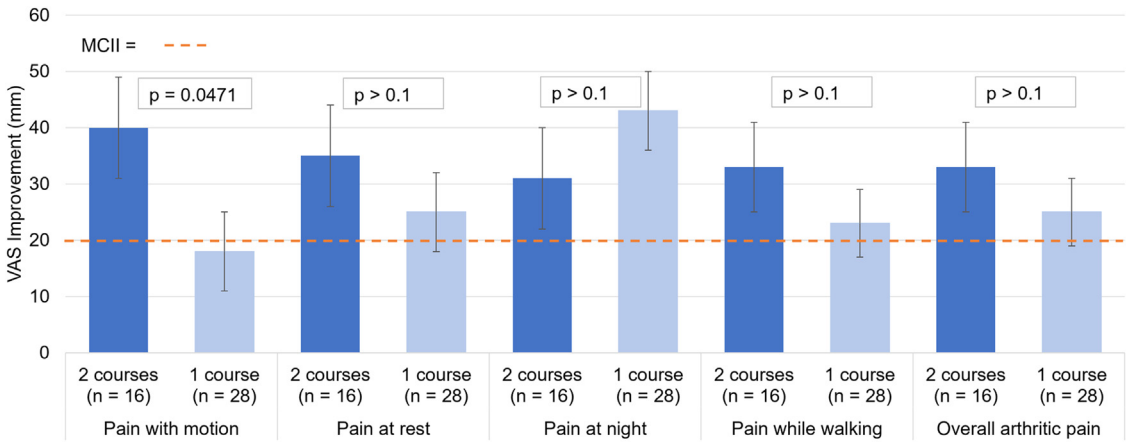

Figure 6. Mean (SE) improvement from baseline to 26 to 34 weeks in primary efficacy outcomes for the intention-to-treat population (long-term follow-up). MCII = minimal clinically important improvement; VAS = visual analog scale.

ing arthrocentesis peaked after 2 weeks and regressed back toward baseline values at subsequent visits, whereas pain scores following hylan G-F 20 injections continued to decrease beyond 2 weeks.

Long-term follow-up

Among patients who returned for the long-term follow-up visit (ie, between 26 and 34 weeks), repeat treatment with hylan G-F 20 (ie, a course of 3 injections twice) was found to more than double the improvement in pain with motion compared with a single course of hylan G-F 20 (40 vs 18 mm, respectively; $P = 0.0471$). This was significant (Figure 6 and **Supplemental Table 5** [in the online version at doi:10.1016/j.curtheres.2023.100707]). The average pain scores were found to decrease further with the second course of therapy, and the additive improvement was significant for the primary efficacy variables. Significantly more patients in the 2-course hylan G-F 20 treatment groups improved by more than 50%.

Safety

Across both phases of this trial, 391 hylan G-F 20 injections were administered to 96 knees of 88 patients (patients with bilateral KOA could receive up to 9 injections) and were followed up for 34 weeks. The time lag (from 4 to 12 weeks) between repeated treatments also enables the evaluation of any potential danger due to accumulation of residual hylan G-F 20 or any sensitization phenomena. Most patients received 3 (49%) or 6 (41%) injections. No general side effects or general systemic AEs were reported after 1 to 9 repeat injections. After hylan G-F 20 injection, local reactions occurred in 14 patients and were all described as pain or swelling of the injected joint, usually occurring 24 hours postinjection, which slowly disappeared within 1 to 2 weeks. Of the 14 AEs, 1 was related, 2 were unrelated, and 6 were not likely related to hylan G-F 20; the remaining 5 had an unknown relationship. Five patients discontinued therapy due to AEs in the injected joint, and the remaining 9 patients completed the 3-injection therapy without any further events. Seven AEs required analgesics, 6 required arthrocentesis to remove excess fluid, and 1 patient experienced a torn meniscus and surgery was recommended. All patients experiencing local AEs recovered, and there were no sequelae. In the control group, 1 general AE occurred during Phase I, described as dizziness, which resolved without needing treatment or sequelae.

Synovial fluid analysis

In patients who had effusion at baseline, those randomized to hylan G-F 20 showed a significantly greater reduction in effusion volume compared with controls (improvement: 2.8 vs 0.09 mL; $P = 0.024$) (Figure 7 and **Supplemental Table 6** [see the online version at doi:10.1016/j.curtheres.2023.100707]). In patients who did not have effusion at baseline, none of those randomized to hylan G-F 20 developed effusion after treatment, whereas 18% of the control patients developed effusion by the first arthrocentesis of Phase II ($P = 0.048$).

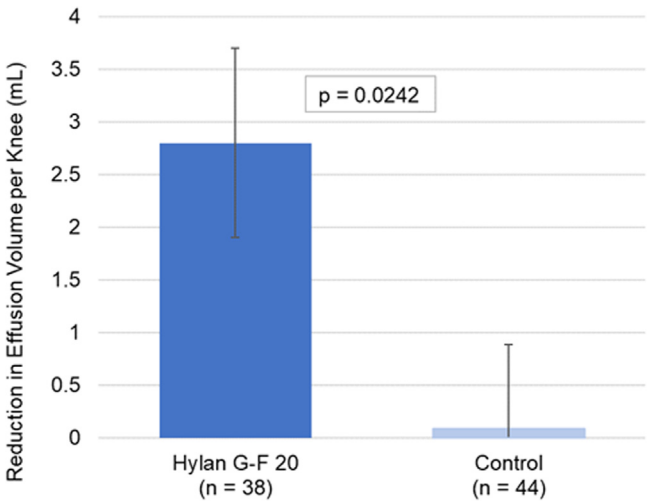

Figure 7. Mean (SE) improvement from pretreatment to posttreatment in synovial effusion volume.

Protein concentration of the synovial effusion also showed benefits due to treatment with hylan G-F 20. At the end of Phase I, protein concentration (SD) was slightly greater for the controls (25.4 [2.5] mg/mL vs 23.9 [2.1 mg/mL]). By Phase II, the controls' protein concentration (SD) had increased, whereas that of hylan G-F 20 patients decreased (29.4 [1.6] mg/mL vs 23.6 [1.9] mg/mL). This difference was significant ($P = 0.04$).

Discussion

To our knowledge, this was the first study conducted (from 1990 to 1992) that compared the efficacy and safety of HA injections and arthrocentesis in patients with KOA. Phase I of this randomized, evaluator- and patient-blinded, controlled trial demonstrated that hylan G-F 20-treated flare patients had significantly more favorable clinical improvement than the controls in all primary efficacy outcomes except pain at night ($P = 0.0637$). However, the VAS pain scores at night significantly differed between groups at baseline ($P = 0.0200$), where controls had significantly higher baseline values than those in the hylan G-F 20 group (83 vs 67 mm, respectively). Categorical analysis of the primary efficacy outcomes (patients with >50% improvement on VAS) also revealed a greater treatment response with hylan G-F 20 relative to controls in the flare population. AEs following hylan G-F 20 injections were localized to the injected joint (ie, pain and swelling), and only 1 AE was considered related to hylan G-F 20 by the investigator. In all of the reported AEs, no symptoms indicating a local or generalized hypersensitivity for hylan G-F 20 were observed. All patients experiencing local AEs recovered within 1 to 2 weeks, and there were no sequelae. These results demonstrate that viscosupplementation with hylan G-F 20 provides effective pain relief and is well tolerated when anti-inflammatory medications are ineffective or discontinued in the flare population. Additionally, relative to an minimal clinically important improvement of 20 mm on the VAS, mean improvements across all pain scores following hylan G-F 20 were also clinically significant; average pain reductions among patients in the flare population with arthrocentesis only were not clinically meaningful, except for pain at night.

Although there were no significant differences in the primary efficacy outcomes between hylan G-F 20 and controls in the ITT population, the analysis revealed that arthrocentesis-only patients started to show increased pain scores after the 2-week visit. In contrast, hylan G-F 20 patients continued to show decreasing scores. The short duration of Phase I of this trial (ie, 10 weeks) may explain why the comparative effects between treatment groups in the ITT population were not significant. Prior research has shown that viscosupplementation with HA has a delayed therapeutic effect, and its peak effectiveness may not occur until 3 months (ie, 12 to 13 weeks) postinjection.[52–55] Additionally, patients first treated with arthrocentesis only showed significant improvements following hylan G-F 20 injections. These findings suggest that the injection procedure (ie, joint aspiration) provides symptomatic relief in patients with KOA, but viscosupplementation with hylan G-F 20 offers an additive therapeutic effect. Such conclusions have been drawn in prior studies that examined the placebo effect associated with IA injections.[1,48,56,57] A repeat course of hylan G-F 20 was also shown to be well tolerated and efficacious in Phase II of this study. The average pain scores decreased further following the second course of hylan G-F 20 therapy and were significant relative to baseline at the study's final follow-up (26–34 weeks), demonstrating the long-term benefits of viscosupplementation with hylan G-F 20.

This study also showed that hylan G-F 20 reduces effusion volume and protein concentration relative to arthrocentesis. Additionally, hylan G-F 20 decreased the formation of effusion in patients who already had effusion at the beginning of the study and significantly prevented the formation of effusion in patients who did not have effusion at the beginning of the study. These observations suggest that viscosupplementation with hylan G-F 20 may help restore the normal physiology of the joint by restoring the rheological homeostasis of the joint. It is also an important finding that in this study, there was no difference in the pain-attenuating effect of hylan G-F 20 in patients with effusion compared with patients without effusion.

It is known that patients with chronic idiopathic osteoarthritis experience periods with moderate to severe pain (flare) in the earlier stage. As the disease progresses with time and with increasing cartilage degeneration, the painful episodes become more frequent, and the patient has fewer and shorter periods of remission of pain. However, the optimal management of flare patients has not yet been established.[20] Traditionally, these patients have been treated with other pharmacological agents such as NSAIDs or corticosteroids, and a flare may have been considered a contraindication to viscosupplementation.[11,24,25,30] The results of this study demonstrated that hylan G-F 20 injections could provide another therapeutic option for this group, especially given the short-term benefits and AEs associated with the other therapies.[28,29,31–35] There were no AEs of general or systemic nature in this study that could be attributed to hylan G-F 20 therapy. Only 1 of the local AEs was considered related to hylan G-F 20 injection by the investigator, and that reaction did not indicate a local or generalized hypersensitivity. All other 13 AEs were considered to be unrelated to treatment with hylan G-F 20 or of unknown origin. This is an important finding because cyclic flare in pain is common in patients with early-stage KOA; some patients might not respond to anti-inflammatory and analgesic medications or become nonadherent. Clinical trial evidence on the flare population is limited, especially regarding the use of HA in this population, which may be part of the reason why viscosupplementation has not been endorsed for flare patients historically.[11,17,18] Another issue with research on the flare population is that the occurrence of a flare is still not fully understood, and there is currently no consensus on its definition, limiting comparability between trials examining this patient population.[12,20]

The results of this study are consistent with prior research on hylan G-F 20 and repeat courses of viscosupplementation injections. A 2005 publication by Raynauld et al[58] also showed significantly greater pain reductions for both single-course and repeat-course hylan G-F 20 groups relative to controls, with no significant difference between the hylan G-F 20 groups, at 12 months. Simi-

larly, Chevalier et al[46] demonstrated that a single injection of hylan G-F 20 was safe and effective relative to a placebo injection over 26 weeks and confirmed the safety of repeat hylan G-F 20 injections. Lastly, a systematic review by Altman et al[59] concluded that repeat courses of IA HA maintained or further improved pain reduction while introducing no increased safety risk. Additionally, expert committees have recently published guidance on retreatment with HA. In 2017, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis was the first group of experts to recommend repeat HA injections in KOA patients who had benefited from a previous treatment cycle after the recurrence of symptoms.[60] In 2021, the European experts on osteoarthritis supported this recommendation and recommended retreating patients with a high risk of KOA progression, young patients, and those participating in a professional sport.[61,62] Such guidance from stakeholders with expertise in treating KOA confirms that a repeat course of viscosupplementation is a safe and effective strategy for managing these patients in real-life practice. This study adds valuable data to the KOA evidence base, as the literature on this specific topic (ie, repeat HA injections) is scarce.[63]

A strength of this study was that it was a randomized, patient- and evaluator-blinded controlled trial. Blinding is needed in clinical trials to ensure validity and limit bias in assessing subjective outcomes.[64,65] The study also included a 4-week washout period to prevent the effects of any prior therapies from carrying over into the investigational period and to identify those flare patients whose pain increased over this period. The VAS was used to evaluate efficacy in this trial, which is a valid, dependable, and frequently used tool to measure pain in clinical trials.[66–68]

A limitation of this study was that the physician who administered the injections was not blinded to treatment allocation; however, pain measures were patient-reported, the synovial fluid analysis involved objective outcomes, and safety was evaluated by a separate individual who was blinded to treatment allocation, reducing the potential for bias with regard to blinding. Patients with bilateral KOA were also included in this study, and because each knee was randomized to treatment, a patient could have 1 knee assigned to each treatment group. This may lead to confounding results, although the occurrence of such cases were few in this study (4 patients had bilateral disease and had 1 knee randomized to each group). Another limitation was that the flare population represented a subgroup of the ITT population. Thus, the trial was not adequately powered to analyze patients with flare. Additionally, Phase I was limited by the short-term evaluation of efficacy and, consequently, the extended no-treatment period.

This study was originally conducted 30 years ago. Among the main reasons this trial's results were not published earlier is that the trial was conducted in parallel to several other clinical trials on hylan G-F 20.[69–71] It was in the investigator's best interest then to prioritize publishing the other trial results that were considered more generalizable to this patient population. Specifically, this trial focuses primarily on a subpopulation of flare patients, whereas the other trials aimed to evaluate the efficacy and safety of hylan G-F 20 in all chronic KOA patients. Additionally, this trial used arthrocentesis as a comparator, whereas the other trials used IA saline, previously a more common and well-accepted comparator in KOA research. Another limitation of this study is that it does not include a Consolidated Standards of Reporting Trials (CONSORT) patient flow diagram. CONSORT encompasses various initiatives developed by the CONSORT Group to mitigate issues that may arise from inadequate reporting of randomized clinical trials. The 2010 CONSORT statement describes the standard practice for conducting and reporting on any randomized clinical trial.[72] The reason the CONSORT flow diagram could not be presented in the article is related to the age of the study. Specifically, the original CONSORT statement, which included a 32-item checklist and a flow diagram, was not published until 1994,[73] 2 years after the completion of this trial. It was not considered standard practice at the time of the trial to report on important enrollment metrics that are today's gold standard of reporting. Likewise, it should be noted that some aspects of trial methodology have evolved in this area since then (eg, use of IA saline injections for comparisons), although recent analyses confirmed the therapeutic effect of IA saline placebo.[48,56,74,75] However, this trial provides data on the use of hylan G-F 20 in a flare population, data on patients who received repeat hylan G-F 20 injections, data on effusion volume, and data on synovial fluid analysis, which have so far not been well reported. This study is also consistent with prior research on the use of hylan G-F 20 in KOA.[46,69–71] Additionally, all research should be available in the published literature regardless of their findings and when they were conducted. These results can still inform treatment decisions because study trial designs and the clinical practice of treating patients with KOA have not drastically changed since the end of this trial. The current study also provides a scientific rationale to conduct further research in this area (eg, use of HA in patients with flare, patients with knee effusion, and the clinical value of repeat HA injections).

Conclusions

Hylan G-F 20 significantly improves pain scores compared with arthrocentesis in a flare population with no safety concerns. Hylan G-F 20 also results in significantly more favorable synovial fluid outcomes among all patients with KOA (ie, the ITT population), with a greater decrease of effusion volume relative to control patients treated with arthrocentesis only. In addition, a repeat course of hylan G-F 20 was found to be more efficacious in pain relief relative to a single course of treatment.

Declaration of Competing Interest

The authors have indicated that there is no conflict of interest regarding the content of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2023.100707.

References

1. Bhandari M, Bannuru RR, Babins EM, et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. *Ther Adv Musculoskelet Dis*. 2017;9(9):231–246.
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393(10182):1745–1759.
3. Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. *BMC Musculoskelet Disord*. 2019;20(1):493.

4. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. *Arthritis Rheumatol*. 2016;68(8):1869–1875.
5. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323–1330.
6. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum*. 2008;59(9):1207–1213.
7. Driban JB, Bannuru RR, Eaton CB, et al. The incidence and characteristics of accelerated knee osteoarthritis among women: the Chingford cohort. *BMC Musculoskelet Disord*. 2020;21(1):60.
8. OECD. *Elderly population (indicator)*; 2022 *https://data.oecd.org/pop/elderly-population.htm* PublishedAccessed May 1, 2022.
9. World Health Organization (WHO). *Ageing and health*; 2021 *https://www.who.int/news-room/fact-sheets/detail/ageing-and-health#:~:text=At%20this%20time%20the%20share,2050%20to%20reach%20426%20million* PublishedAccessed May 1, 2022.
10. Hohmann E. Editorial Commentary: Platelet-Rich Plasma and Hyaluronic Acid Injection for Knee Osteoarthritis Are Both Cost Effective. *Arthroscopy*. 2020;36(12):3079–3080.
11. Bowden JL, Kobayashi S, Hunter DJ, et al. Best-practice clinical management of flares in people with osteoarthritis: A scoping review of behavioral, lifestyle and adjunctive treatments. *Semin Arthritis Rheum*. 2021;51(4):749–760.
12. Cross M, Dubouis L, Mangin M, et al. Defining Flare in Osteoarthritis of the Hip and Knee: A Systematic Literature Review - OMERACT Virtual Special Interest Group. *J Rheumatol*. 2017;44(12):1920–1927.
13. Guillemin F, Ricatte C, Barcenilla-Wong A, et al. Developing a Preliminary Definition and Domains of Flare in Knee and Hip Osteoarthritis (OA): Consensus Building of the Flare-in-OA OMERACT Group. *J Rheumatol*. 2019;46(9):1188–1191.
14. Parry EL, Thomas MJ, Peat G. Defining acute flares in knee osteoarthritis: a systematic review. *BMJ Open*. 2018;8(7):e019804.
15. Fautrel B, Hilliquin P, Rozenberg S, et al. Impact of osteoarthritis: results of a nationwide survey of 10,000 patients consulting for OA. *Joint Bone Spine*. 2005;72(3):235–240.
16. Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of cohort data. *BMC Musculoskelet Disord*. 2017;18(1):80.
17. Parry E, Ogollah R, Peat G. 'Acute flare-ups' in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case-crossover analysis. *Osteoarthritis Cartilage*. 2019;27(8):1124–1128.
18. Murphy SL, Lyden AK, Kratz AL, et al. Characterizing Pain Flares From the Perspective of Individuals With Symptomatic Knee Osteoarthritis. *Arthritis Care Res (Hoboken)*. 2015;67(8):1103–1111.
19. Paskins Z, Sanders T, Hassell AB. What influences patients with Osteoarthritis to consult their GP about their symptoms? A narrative review. *BMC Family Practice*. 2013;14(1):195.
20. Thomas MJ, Guillemin F, Osteoarthritis Flares Neogi T. *Clin Geriatr Med*. 2022;38(2):239–257.
21. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am*. 2015;97(17):1386–1397.
22. Gilat R, Haunschild ED, Knapik DM, Evuarherhe Jr A, Parvaresh KC, Cole BJ. Hyaluronic acid and platelet-rich plasma for the management of knee osteoarthritis. *Int Orthop*. 2021;45(2):345–354.
23. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin Arthritis Rheum*. 2016;45(4 Suppl):S28–S33.
24. Yaftali NA, Weber K. Corticosteroids and Hyaluronic Acid Injections. *Clin Sports Med*. 2019;38(1):1–15.
25. Legré-Boyer V. Viscosupplementation: techniques, indications, results. *Orthop Traumatol Surg Res*. 2015;101(1 Suppl):S101–S108.
26. Maheu E, Bannuru RR, Herrero-Beaumont G, Allali F, Bard H, Migliore A. Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: Results of an extensive critical literature review. *Semin Arthritis Rheum*. 2019;48(4):563–572.
27. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC musculoskeletal disorders*. 2015;16 321-321.
28. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61(12):1704–1711.
29. Goldstein JL, Cryer B. Gastrointestinal injury associated with NSAID use: a case study and review of risk factors and preventative strategies. *Drug Healthc Patient Saf*. 2015;7:31–41.
30. Gossec L, Dougados M. Do intra-articular therapies work and who will benefit most? *Best Pract Res Clin Rheumatol*. 2006;20(1):131–144.
31. Hartmann K, Koenen M, Schauer S, et al. Molecular Actions of Glucocorticoids in Cartilage and Bone During Health, Disease, and Steroid Therapy. *Physiol Rev*. 2016;96(2):409–447.
32. He WW, Kuang MJ, Zhao J, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis. *Int J Surg*. 2017;39:95–103.
33. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. *Jama*. 2017;317(19):1967–1975.
34. Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Expert Opin Drug Saf*. 2005;4(2):157–169.
35. Wernecke C, Braun HJ, Dragoo JL. The Effect of Intra-articular Corticosteroids on Articular Cartilage: A Systematic Review. *Orthop J Sports Med*. 2015;3(5):2325967115581163.
36. Welsch P, Petzke F, Klose P, Häuser W. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. *Eur J Pain*. 2020;24(4):685–703.
37. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006;113(12):1578–1587.
38. Dinçer D, Ulukal Karancı E, Akın M, Adanır H. NSAID, antiaggregant, and/or anticoagulant-related upper gastrointestinal bleeding: Is there any change in prophylaxis rate after a 10-year period? *Turk J Gastroenterol*. 2019;30(6):505–510.
39. Olsen AM, Fosbøl EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. *Circulation*. 2012;126(16):1955–1963.
40. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011;342:c7086.
41. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010;105(10):1776–1782.
42. Kane-Gill SL, Rubin EC, Smithburger PL, Buckley MS, Dasta JF. The cost of opioid-related adverse drug events. *J Pain Palliat Care Pharmacother*. 2014;28(3):282–293.
43. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559–574.
44. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. *Am J Sports Med*. 2016;44(8):2158–2165.
45. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180–191.
46. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis*. 2010;69(1):113–119.
47. De Lucia O, Jerosch J, Yoon S, Sayre T, Ngai W, Filippou G. One-year efficacy and safety of single or one to three weekly injections of hylan G-F 20 for knee osteoarthritis: a systematic literature review and meta-analysis. *Clin Rheumatol*. 2021;40(6):2133–2142.
48. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46–54.
49. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage*. 2004;12(5):389–399.
50. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Annals of the Rheumatic Diseases*. 2005;64(1):29–33.
51. Hummer CD, Angst F, Ngai W, et al. High molecular weight Intraarticular hyaluronic acid for the treatment of knee osteoarthritis: a network meta-analysis. *BMC Musculoskeletal Disorders*. 2020;21(1):702.
52. Abate M, Pulcini D, Di Iorio A, Schiavone C. Viscosupplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. *Curr Pharm Des*. 2010;16(6):631–640.
53. Aggarwal A, Sempowski IP. Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature. *Can Fam Physician*. 2004;50:249–256.
54. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006;2006(2):Cd005321.
55. Hermans J, Bierma-Zeinstra SMA, Bos PK, Niesten DD, Verhaar JAN, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial. *BMC Musculoskeletal Disorders*. 2019;20(1):196.
56. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. *Ann Intern Med*. 2015;163(5):365–372.
57. Vannabouathong C, Bhandari M, Bedi A, et al. Nonoperative Treatments for Knee Osteoarthritis: An Evaluation of Treatment Characteristics and the Intra-Articular Placebo Effect: A Systematic Review. *JBJS Rev*. 2018;6(7):e5.
58. Raynauld JP, Goldsmith CH, Bellamy N, et al. Effectiveness and safety of repeat courses of hylan G-F 20 in patients with knee osteoarthritis. *Osteoarthritis Cartilage*. 2005;13(2):111–119.
59. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. *Semin Arthritis Rheum*. 2018;48(2):168–175.

60. Cooper C, Rannou F, Richette P, et al. Use of Intraarticular Hyaluronic Acid in the Management of Knee Osteoarthritis in Clinical Practice. *Arthritis Care Res (Hoboken)*. 2017;69(9):1287–1296.
61. Conrozier T, Raman R, Chevalier X, et al. Viscosupplementation for the treatment of osteoarthritis. The contribution of EUROVISCO group. *Ther Adv Musculoskelet Dis*. 2021;13 1759720x211018605.
62. Raman R, Henrotin Y, Chevalier X, et al. Decision Algorithms for the Retreatment with Viscosupplementation in Patients Suffering from Knee Osteoarthritis: Recommendations from the EUROpean VIScosupplementation COnsensus Group (EUROVISCO). *Cartilage*. 2018;9(3):263–275.
63. Uson J, Rodriguez-García SC, Castellanos-Moreira R, et al. EULAR recommendations for intra-articular therapies. *Ann Rheum Dis*. 2021;80(10):1299–1305.
64. Day SJ, Altman DG. Blinding in clinical trials and other studies. *BMJ*. 2000;321(7259):504.
65. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can J Surg*. 2010;53(5):345–348.
66. Alghadir AH AS, Iqbal A, Iqbal ZA. Test–retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res*. 2018;11:851–856.
67. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med*. 2001;8(12):1153–1157.
68. da Costa BR, Saadat P, Basciani R, Agarwal A, Johnston BC, Jüni P. Visual Analogue Scale has higher assay sensitivity than WOMAC pain in detecting between-group differences in treatment effects: a meta-epidemiological study. *Osteoarthritis Cartilage*. 2021;29(3):304–312.
69. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage*. 1995;3(4):213–225.
70. Scale D, Wobig M, Wolpert W. Viscosupplementation of osteoarthritic knees with hylan: a treatment schedule study. *Current Therapeutic Research*. 1994;55(3):220–232.
71. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan GF 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clinical therapeutics*. 1998;20(3):410–423.
72. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Journal of Pharmacology & Pharmacotherapeutics*. 2010;1(2):100–107.
73. A proposal for structured reporting of randomized controlled trials. The Standards of Reporting Trials Group. *JAMA*. 1994;272(24):1926–1931.
74. Fazeli MS, McIntyre L, Huang Y, Chevalier X. Intra-articular placebo effect in the treatment of knee osteoarthritis: a survey of the current clinical evidence. *Therapeutic Advances in Musculoskeletal Disease*. 2022;14 1759720X211066689.
75. Saltzman BM, Leroux T, Meyer MA, et al. The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1 Studies. *Am J Sports Med*. 2017;45(11):2647–2653.