ONE-YEAR FOLLOW-UP SHOWING EFFECTS OF SINGLE INTRA-ARTICULAR INJECTION OF HYALURONIC ACID (1,500-2,000 kDa) IN SYMPTOMATIC KNEE OSTEOARTHRITIS

A. MIGLIORE[1], B. FREDIANI[2], G. GIGLIUCCI[1], S.E. ANICHINI[1], M. CASSOL[3], S. CRIMALDI[4], O. DE LUCIA[5], G. IOLASCON[6] and C. FOTI[7]

[1]Rheumatology Unit, S. Pietro FBF Hospital, Rome, Italy; [2]Department of Medicine, Surgery and Neurosciences, Rheumatology Section, University of Siena; Osteo-Articular Diagnostic Procedures Hospital, Siena, Italy; [3]Internal Medicine Department, S. Pietro FBF Hospital, Rome, Italy; [4]Orthopaedics 2, Orthopaedic Mininvasive Surgery and New Technologies, Humanitas Hospital, Castellanza, Italy; [5]Rheumatology Department, ASST Gaetano Pini-CTO Orthopedic and Traumatology Specialist Center, Milan, Italy: [6]Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Naples, Italy; [7]Department of Physical and Rehabilitation Medicine, Clinical Sciences and Translational Medicine Department, Tor Vergata University, Rome, Italy

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Clinical evidence on knee osteoarthritis suggests that intra-articular administration of hyaluronic acid may be useful in the management of patients with persistent pain. This study assesses the duration of effectiveness of a single intra-articular hyaluronic acid injection in a large population of patients with knee osteoarthritis. This retrospective post-marketing cohort study collected data from the ANTIAGE Registry (http://www.antiagefbf.it/registro), selecting patients of age ≥ 40 years, with symptomatic knee osteoarthritis (Kellgren-Lawrence grade I-III) of ≥ 12 months duration, and ≥ 12 months of follow-up. Patients had received a single intra-articular injection of high molecular weight hyaluronic acid (1,500-2,000 kDa) at baseline. WOMAC Osteoarthritis Index total scores measured using the LK 3.1 scale and 10 cm VAS pain scores were evaluated before IA Injection and at 6, 9, 10, 11 and 12 months. Blood cell counts, uricemia, erythrocyte sedimentation rates and levels of C-reactive protein were measured at baseline and 12 months. Time from initial treatment to second injection up to 12 months was recorded to assess event-free survival. Included patients (n = 187) were 53.5% female and had a mean (±SD) age at baseline of 62 (±16.6) years and mean (±SD) body mass index of 26.2 (±2.5) kg/m². Mean (±SD) WOMAC index total score and VAS pain scores were 60.9 (±7.1) and 5.9 cm (±1.8), respectively. There were statistically significant reductions compared to baseline in mean WOMAC index total score and VAS pain score at all time points ($p < 0.01$ at 6 and 9 months; $p < 0.05$ at 10, 11 and 12 months for both parameters). These results support the clinical effectiveness and safety of hyaluronic acid for up to 12 months for pain relief and function improvement in patients with knee osteoarthritis, confirming previous data on intra-articular administration of hyaluronic acid as chronic therapy in the management of knee osteoarthritis.

Key words: knee osteoarthritis, viscosupplementation, intra-articular injection, hyaluronic acid

Mailing address:
Prof. Alberto Migliore,
Rheumatology Unit,
San Pietro, Fatebenefratelli Hospital,
Via Cassia 600, 00189, Rome, Italy
Tel.: +06 3358 5802
e-mail: migliore.alberto60@gmail.com

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Osteoarthritis (OA) is a common cause of joint pain in adults, and its incidence is expected to increase with increases in lifespan and obesity (1). OA often causes physical impairment and social isolation, especially when the hip or knee is involved. Synovial fluid from patients with knee OA contains reduced concentration and molecular weight of the glycosaminoglycan hyaluronic acid (HA) (2, 3). Several studies suggest that intra-articular (IA) administration of HA may be useful in the management of patients with persistent knee pain associated with OA (4).

This treatment has generally been accepted in OA management guidelines; however, there are discrepancies between guidelines and clinical practice (5). It was not recommended in the 2014 NCC-CC guidelines (6), nor in the 2013 AAOS guidelines (7), and received a rating of 'uncertain' in the 2014 OARSI statement (8). It has been suggested that the conflicting results of some of the meta-analyses that informed these decisions may have resulted from methodological differences or flaws (9, 10). In particular, some guidelines do not differentiate among HA-based products, but considered them as a single class of compounds. However, HA-based preparations for intra-articular administration vary in concentration, molecular weight and injection protocol. Their molecular structure can also vary, including native HA, and HA derivatives engineered to increase viscoelasticity and IA residence time.

Clinical experience with a high molecular weight HA (1,500–2,000 kDa) fraction is summarised in a meta-analysis by Guidolin et al. (11). The authors review treatment of a variety of different joints, with a focus on knee and hip, and conclude that the IA injection of HA (1,500–2,000 kDa) reduces symptoms, and improves both function and quality of life. Priano et al. (12). conducted a multicentre, randomised, open label, controlled study on 100 patients undergoing arthroscopic meniscectomy, showing that post-operative administration of high molecular weight (1,500-2,000 kDa) HA was associated with significantly better clinical outcomes, both in terms of function and pain symptoms, compared with the surgical procedure alone. Recently, a prospective study of 168 patients treated with a single IA injection of the same high molecular weight (1500-2000 kDa) linear HA fraction showed significant improvement in symptom outcome measures and knee function for up to 6 months (13).

In the present study, we evaluated the long-term effectiveness and safety of IA injections of this high molecular weight HA (1,500-2,000 kDa) fraction in patients with symptomatic knee OA using improvement in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index total scores and VAS pain scores as clinical outcomes. Our hypothesis was that the effectiveness of a single IA injection of high molecular weight (1500-2000 kDa) may extend beyond 6 months.

MATERIALS AND METHODS

Study design

This is a retrospective analysis of data from the multicentre ANTIAGE osteoarthritis registry (http://www.antiagefbf.it/registro). We identified patients with mild to moderate knee OA who had received IA injections of a highly purified solution of sodium hyaluronate with a molecular weight (MW) of 1,500–2,000 kDa in the affected knee, with the first injection between January 2015 and November 2016.

Study population

Included patients were ≥ 40 years of age with an X-ray-confirmed diagnosis of mild to moderate knee OA of Kellgren-Lawrence (KL) grade 1-3 in the treated knee and moderate to severe walking pain with 10 cm visual analogue scale (VAS) pain scores between 4 and 8 cm in the treated knee, who had received IA injections of high molecular weight HA (1,500-2,000 kDa) and had complete follow-up data in the ANTIAGE osteoarthritis registry. All data were obtained with prior ethics committee approval and presented following the STROBE checklist for cohort studies. Patients gave written informed consent to participate in the study.

Exclusion criteria were: severe OA (KL grade 4); concomitant use of oral anticoagulant therapy, severe comorbidities (e.g., rheumatologic disease, low back pain, femoral head osteonecrosis), significant varus or valgus deformity requiring surgical correction, inflammatory diseases that might affect joints, positive history of sepsis or subacute infection in any joint, relevant lymphatic stasis in the treated knee, hypersensitivity to any component of the HA-based preparation, treatment with HA or HA derivatives in the previous 6 months or with IA steroids in the previous 3 months.

We enrolled 187 patients meeting all criteria. Mean age was 62 (±16.6) years and there was a tendency toward

overweight. Most patients had moderate knee OA (93.6% KL grade 2 or 3) affecting only one knee (unilateral 89.6%). Characteristics of the study cohort at baseline are presented in Table I.

Procedures

Radiological evaluations using the KL OA scale were made on an X-ray taken no more than 6 months prior to treatment. Pain was evaluated on a 10-cm VAS. The WOMAC Osteoarthritis Index (WOMAC) total score was assessed with the WOMAC LK 3.1 scale, which provided a composite measure of pain, function and joint stiffness. Changes from baseline greater than 16 points were considered clinically significant (14). Data from patient records matching the above-mentioned inclusion and exclusion criteria were extracted from the ANTIAGE registry. Clinical history and demographic information had been recorded at baseline, when all patients had received a single 4 ml (60 mg) IA injection in the affected knee of HyalOne® (second brand name Hyalubrix®60), a viscoelastic solution containing HA sodium salt with a molecular weight range of 1,500–2,000 kDa obtained by bacterial fermentation (Hyalubrix®60 package insert: http://www.hyalubrix.it/foglietto_illustrativo_hyalubrix_60.pd). Additional injections were administered if clinically requested during follow-up. Data were collected on follow-up visits at 6, 9, 10, 11 and 12 months after injection, when VAS pain and WOMAC OA index were assessed.

A blood sample routinely collected at baseline and yearly thereafter was used to assess blood cell counts, uricemia, erythrocyte sedimentation rates and levels of C-reactive protein; patients with clinically significant abnormalities are not injected and are examined and/or treated for comorbidities. Time to second injection was recorded to perform an event-free survival analysis, defined as the time from initial treatment to retreatment.

Study endpoints

The primary endpoint was the change from baseline in the WOMAC total score. Secondary endpoints included duration of symptom relief after a single IA injection of

Table I. *Characteristics of the study cohort at baseline.*

Patients (n)	**187**
Men	87 (46.5%)
Women	100 (53.5%)
Age, years, mean (±SD)	62 (±16.6)
BMI, mean (±SD)	26.2 (±2.5)
Weight, kg, mean (±SD)	74.7 (±10.9)
Height, cm, mean (±SD)	168.3 (±7.8)
Smokers, n (%)	48 (26%)
WOMAC index total score, mean (±SD)	60.9 (±7.1)
10 cm VAS Pain, mean (±SD)	5.9 (±1.8)
NSAID intake, mean days/month (±SD)	6.4 (±6.2)
Diabetes mellitus, n (%)	12 (6.4%)
Knee affected, n (%)	
Right	80 (42.7%)
Left	86 (45.9%)
Bilateral	21 (11.4%)
Kellgren-Lawrence radiological index, n (%)	
Grade I	12 (6.4%)
Grade II	79 (42.2%)
Grade III	96 (51.4%)

HyalOne®, measured with VAS pain score, time to second injection, safety of single or repeated IA injections and changes in hematochemical tests.

Statistical analysis

After the first IA HA injection at baseline, data were collected on follow-up visits at 6, 9, 10, 11 and 12 months. All included patients had attended the baseline visit and all 5 follow-up visits. Data for continuous variables are expressed as mean ±standard deviation (SD), whereas those for discrete variables are reported as counts and proportions. WOMAC index total score and VAS pain scores were recorded at each study visit, and changes from baseline were assessed using the Wilcoxon test for paired data. Significance was defined as $p < 0.05$. Statistical analyses were carried out using Stata software version 13 (StataCorp, College Station, TX, USA). Data on blood cell counts and serum values were compared at baseline and study end using Pearson's tests.

RESULTS

Over the 12 months of follow-up, pain scores and WOMAC total scores were lowest at the 6-month time point, before gradually increasing during the subsequent 6 months for patients not yet requiring a second intra-articular injection of HA (Fig. 1).

We assessed the time to treatment failure, when a second IA injection of HyalOne® was administered. The effect duration was approximately 9 or 10 months in 62% of patients, whereas the effect duration in the remaining 38% was between 11-12 months. At 9, 10, 11 and 12 months, the second injection was administered to 60 (32%), 56 (30%), 39 (21%) and 32 (17%) patients. Event-free survival after the first injection was assessed using Kaplan–Meier analysis of the time to second injection up to 12 months (Fig. 2).

The clinical course of patients receiving HA injections was followed by assessing pain, stiffness and physical function at each visit, up to treatment failure. The 10 cm VAS pain and WOMAC total scores at treatment failure, when patients with knee OA required a second IA HA injection, are presented in Table II.

Blood values for markers of inflammation were in the normal range at both baseline and after up to 12 months of follow-up, without statistically significant

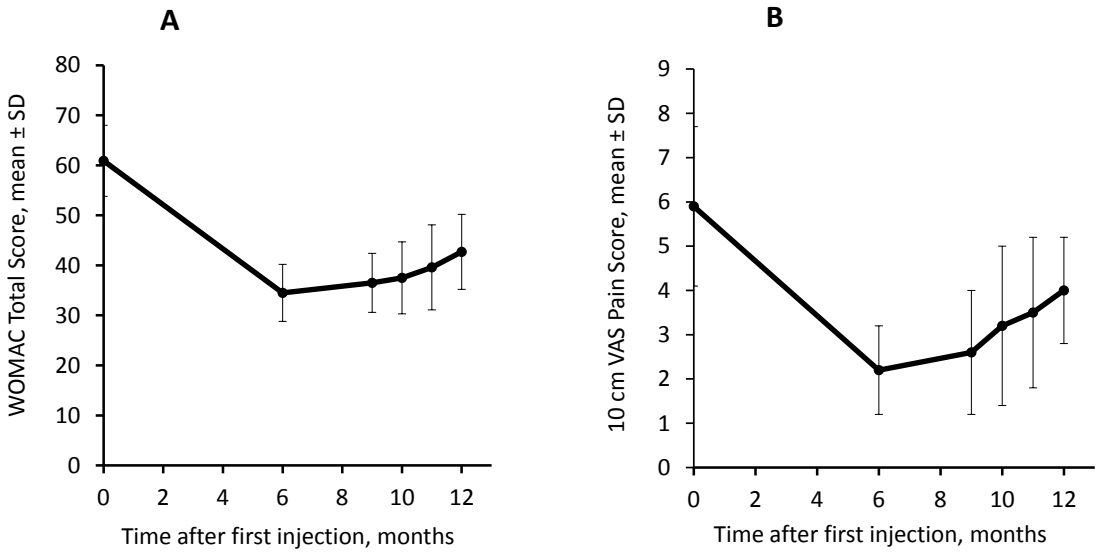

Fig. 1. *Changes in WOMAC total score (**A**) and pain (**B**) over 12 months of follow-up for patients not yet requiring a second intra-articular injection of hyaluronic acid. There were 187 patients at baseline, 6, and 9 months, 127 patients at 10 months, 72 patients at 11 months and 32 patients at 12 months.*

differences (Table III). However, there was a non-significant trend toward reduction in the level of CRP after 12 months.

Safety

No systemic or severe local side effects were reported after the first or the second injection. In 8 cases, there was a sensation of pain lasting from several hours to a few days, regressing spontaneously without requiring medical intervention.

DISCUSSION

IA injection of HA and HA derivatives has gained consensus among practitioners who recognize this approach as a safe and effective treatment of OA (15, 16). Meta-analysis of 54 eligible trials that included 7545 patients demonstrated the effectiveness of this treatment for knee OA, with improvements in pain scores, function and patient global assessment (17).

The molecular weight of HA is an important characteristic that influences its physical and biological properties. HA molecular weight fractions between 500 and 2000 kda are associated with improved lubrication and resistance to surface wear in *in vitro* tests. In addition to improving the rheological properties of synovial fluid, high molecular weight HA has long-term anti-inflammatory effects that are not observed with low molecular weight (< 40 kDa) HA fractions (18,19). Higher molecular weight HA has longer residence time in synovial fluid. HA molecular weight can be increased through cross linking to provide higher viscosity, improve rheological properties and longer joint residency times; however, cross-linked preparations are associated with a higher frequency of adverse events (20).

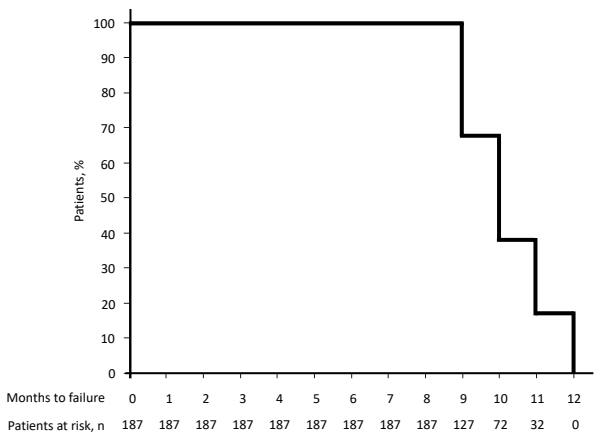

Fig. 2. *Kaplan-Meier survival analysis of time to second IA Injection of high molecular weight hyaluronic acid (HyalOne®), in 187 patients who received more than one injection.*

Researchers have sought to improve and prolong the effectiveness of IA HA by combining HA with other agents, including polyols, corticosteroids and platelet-rich plasma (PRP). The addition of a polyol such as mannitol or sorbitol is thought to increase viscosity and prolong residency time by reducing the oxidative degradation of HA that occurs after IA injection (21). The efficacy and safety of IA HA combined with mannitol has been tested in a double-blind, controlled clinical trial and found to be similar to IA HA alone (22). Corticosteroids have been combined with HA for OA. High doses of IA corticosteroids are indicated for severe acute inflammatory flares not responding to treatment with NSAIDs (23); however, they are not suitable for long-term therapy. A meta-analysis of 7 trials comparing IA corticosteroids with IA HA revealed that corticosteroids are more effective during the first 4 weeks, after which IA HA provides superior benefits that continue for months (24). A preliminary controlled study comparing IA HA with or without a much lower dose of corticosteroid (10 mg triamcinolone acetonide) revealed earlier onset of pain relief with the combination (25), however these preliminary results require confirmation in a larger study. Platelet-rich plasma (PRP), a source of growth factors that influence chondrocyte proliferation and extracellular matrix production, has also been combined with IA HA for treating knee OA. Clinical studies have had mixed results, with one study showing no additive effect (26), and another study showing a synergistic effect between PRP and HA (27).

It has been suggested that data from controlled trials of IA HA treatment should be integrated with data from the real-world setting and from studies with longer follow-up (5). We report data on the

impact of a single IA injection of a 1.5% formulation of natural HA with MW in the range 1500-2000 kDa in a real-world setting, showing control of symptoms and functional improvement in a large cohort of patients followed retrospectively for one year.

Previously, Vetro et al. (13) conducted a 6-month open study on a prospective cohort of 168 patients treated with a single IA injection of the same high molecular weight (1500-2000 kDa) linear HA fraction, demonstrating a significant improvement from baseline in all symptom outcome measures and an improvement in knee function confirmed by results on both the WOMAC index and Knee injury and Osteoarthritis Outcome Score (KOOS) instruments that was maintained through 6 months. The study population in that cohort was younger than ours (mean age 54 *vs* 62 years), had more severe knee OA (VAS pain scores 77 *vs* 59 mm) and a shorter follow-up (6 months *vs* 12 months). Our results show that the findings of significant continuing response after a single IA injection of high molecular weight (1500-2000 kDa) in the 6-month study conducted by Vetro et al. (13) may be extended for several months beyond the six-month time point. This has important

Table II. *VAS pain and WOMAC total scores from baseline to the time of the second intra-articular injection of high molecular weight hyaluronic acid (HyalOne®) for knee osteoarthritis.*

Time of second injection (pts., n)	Study visit					
	Baseline	6 months	9 months	10 months	11 months	12 months
9 months (60)						
VAS Pain	6.5±2.1	1.8±1.3*	2.4±1.4*			
WOMAC	63.4±6.3	38.2±4.3*	39.1±5.2*			
10 months (56)						
VAS Pain	7.3±1.8	2.6±1.5*	2.8±1.7*	3.2±2.4**		
WOMAC	58.7±7.2	34.3±6.3*	35.3±5.5*	38.1±6.1**		
11 months (39)						
VAS Pain	5.9±1.4	2.1±0.9*	2.8±1.6*	3.1±1.8**	3.3±1.7**	
WOMAC	61.3±8.1	31.1±6.2*	34.2±5.9*	35.3±7.1**	38.1±8.1**	
12 months (32)						
VAS Pain	6.8±1.2	2.4±0.4*	2.7±0.7*	3.4±1.3*	3.8±1.6**	4.0±1.2**
WOMAC	59.5±6.8	33.7±5.9*	36.4±7.2*	39.3±8.4*	41.4±8.8**	42.7±7.5**

*Scores are expressed as mean ±SD: before treatment and then after 6, 9, 10, 11 and 12 months. *Significant difference compared to baseline (p <0.01). **Significant difference compared to baseline (p <0.05).*

Table III. *Biochemical values for serum markers of inflammation at baseline and after up to 12 months of follow-up.*

	Baseline	Follow-up	p-value	Reference value
Hematocrit, %	47±6	45±7	0.631	38-54
Red blood cells/µl	5.20±2.1 x 10^6	5.32±2.2 x 10^6	0.761	4.0-5.6 x 10^6/µl
White blood cells/µl	5.600±3.700	6.100±3.900	0.568	4.000-11.000/µl
CRP, mg/dl	1.8 ±1.3	1.1 ±0.7	0.074	< 3 mg/dl
ESR, mm/h	18.4 ±11,8	18.1 ±13,4	0.713	< 25 mm/h
Uric Acid, mg/dl	4.3±1.7	4.1±1.5	0.589	< 6 mg/dl

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

implications for the timing of subsequent injections, and may mean that it is possible delay retreatment, with associated cost savings over the course of long-term treatment.

In our study population, the effect duration, determined by the timing of a request for a second injection, was between 9 and 10 months in 62% of our patients. The remaining 38% of patients required retreatment more than 11 months after the first injection. Putting this in perspective, it means that IA HA treatment in patients with KL radiological grade 1-3 knee OA results in 2 out of 3 patients requiring a second treatment after 9 to 10 months, and 1 out of 3 patients requiring a second treatment after 10 months.

In the future, it would be useful to identify factors that predict the timing of the need for retreatment with HA. There was a rapid effect at 6 months in all patients, corresponding to a clinically significant improvement in the WOMAC total score, followed by a modest progressive worsening of outcome measures that did not return to initial baseline levels during the observation period, and more importantly, the improvement remained clinically significant throughout follow-up. The non-significant trend toward reduction of CRP level after 12 months (Table III) could be compatible with a reduction in the local level of inflammation, which would also be supported by the reduction of NSAID consumption and absence of flares during follow-up. The anti-inflammatory effects of IA injection of HA in knee OA have been attributed to interactions mediated by the cell surface receptors CD-44, toll-like receptors 2 and 4, intercellular adhesion molecule-1, and layilin (19).

Limitations of this study include the retrospective design and absence of a control arm with placebo or active comparator. Moreover, we did not assess the effectiveness of subsequent injections on outcomes. However, long-term follow-up of patients with symptomatic OA of the hip treated with IA injection of HA at least every six months supported the continuing effectiveness after 7 years of follow-up. In that study, patients were evaluated with the Lequesne index, pain VAS, NSAIDs intake, global medical and patient assessments every six months from baseline. Patients were categorized by age class, gender and body mass index (BMI), and all groups had statistically significant reductions ($p < 0.05$) at all time points compared to baseline for the Lequesne index, pain VAS, NSAIDs intake and global medical and patient assessments, confirming the long-term efficacy and safety of HA in the treatment of osteoarthritis (28). This is also reflected in the findings from a retrospective cohort of 182,000 patients with a diagnosis of knee OA identified in an administrative claims database (29). Patients who had received IA HA injections had a significantly longer time to total knee replacement ($p < 0.0001$). Moreover, there was a dose-dependent increase in the mean time to knee replacement: no HA, 0.7 years; one cycle, 1.4 years ($p < 0.0001$); ≥5 cycles 3.6 years ($p < 0.0001$). These results were confirmed in a similar study of 267,345 patients with incident knee OA from a Medicare database. Receiving IA HA was associated with a median 8.7-month delay in total knee replacement compared to patients not receiving HA (95% CI 8.3-9.1 months; $P < 0.001$) (30).

Our results support the clinical effectiveness and safety of IA injections of high molecular weight HA (1,500-2,000 kDa) in patients with symptomatic knee OA. After 9 months of follow-up, a second injection was requested by 60 patients (32%), at 10 months by 56 (30%), at 11 months by 39 (21%) and at 12 months by 32 (17%) patients, demonstrating the long-term effectiveness of intra-articular HyalOne® injection therapy, which was associated with a clinically significant improvement in WOMAC total scores.

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