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Long-term efficacy of intra-articular viscosupplementation in delaying hip osteoarthritis radiographic progression: a retrospective, non-controlled study from the ANTIAGE registry

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Abstract

Objective. Viscosupplementation is a recognized treatment for improving pain and joint function in the long term. The study aimed to analyze the radiological changes after 2 years of treatment with HyalOne® (Hyalubrix® 60 Italian brand name) in patients with symptomatic hip osteoarthritis (OA). The primary objective was to evaluate the ability of delaying hip OA progression, measured by the percentage of patients showing no radiological Kellgren-Lawrence (K-L) grade change ≥1 at 2 years. Secondary objectives included variations in pain at rest, Lequesne index, and non-steroidal anti-inflammatory drug (NSAID) intake after 2 years of treatment.

Methods. Data of patients suffering from symptomatic hip OA treated with HyalOne®/Hyalubrix® 60 were selected from the ANTIAGE national registry. The analysis included 78 patients aged 50 to 80 years with radiological and clinical OA (K-L grade 1-3), body mass index ≤35, and at least 2 years of radiological follow-up. Patients with significant comorbidities or who received previous treatment within two years after HyalOne®/Hyalubrix® 60 were excluded.

Results. This retrospective observational non-controlled study showed that intra-articular injections with HyalOne®/Hyalubrix® 60 were well tolerated and may help maintain clinical and radiographic stability in patients with hip OA. At 2-year follow-up, the K-L grade remained stable in 72 hips (92.31%). Symptom reduction was also observed, supporting lower NSAID consumption and the avoidance of the related adverse events.

Conclusions. These results are clinically meaningful and support the treatment with HyalOne® as a valuable background therapy for maintaining clinical and radiographic stability in patients with hip OA.

Key words: hip osteoarthritis, viscosupplementation, high molecular weight hyaluronic acid, HyalOne®, Hyalubrix® 60.

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Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by the progressive breakdown of cartilage (1, 2). Radiological hallmarks of OA include cartilage erosion - particularly its outermost portion - leading to subchondral sclerosis and cyst formation, joint space narrowing, synovial inflammation, and marginal osteophyte development. In advanced stages, subchondral cyst formation and remodeling or deformity of the articular surfaces become evident (3, 4).

OA is more common in adults and the elderly, as it typically develops slowly over time (5). After the knee, the hip is the second most frequently affected joint (5). Recent literature review shows that hip OA is more common in females than males when defined clinically or symptomatically, irrespective of country or ethnicity (6). Data from the Research on Osteoarthritis/Osteoporosis against Disability cohort showed that the incidence rate of radiographic hip OA in adults aged ≥23 years was 5.6 per 1000 person years for men and 8.4 per 1000 person years for women (7).

OA-related symptoms, such as pain, stiffness, and functional limitation, significantly impact patients' quality of life (QoL) (8-10). Since there is currently no cure for OA, management focuses on delaying the need for surgery while alleviating pain and preserving – or restoring – mobility to ensure an acceptable QoL (11-14). Although total hip arthroplasty achieves high success rates, it is associated with postoperative morbidity, including infection, thromboembolic events, prosthesis loosening or dislocation, and injury to surrounding nerves or blood vessels (15). Therefore, strategies that can slow disease progression and postpone surgical intervention are of considerable clinical relevance. To achieve this, available therapies combine conservative, non-pharmacological, and pharmacological approaches (16).

Pharmacological options include oral or topical non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections (16-18). However, these treatments are associated with potential side-effects, even at standard doses, and their efficacy may be short-lasting (12, 19-22). According to the Osteoarthritis Research Society International expert consensus recommendations (14), viscosupplementation is a recognized non-pharmacological strategy that provides long-term pain relief and improves joint function (13, 14, 16, 21-24). This treatment involves intra-articular injections of high-molecular-weight hyaluronic acid (HA), which enhances joint function by improving lubrication, absorbing shocks, and maintaining the structural integrity of the extracellular matrix (16, 25-27).

HA intra-articular injections have been widely studied for knee OA, demonstrating reduced NSAID dependence and, consequently, a lower risk of adverse effects associated with long-term NSAID use (16, 28-31). Conversely, the use of viscosupplementation for hip OA is less extensively documented. However, it has gained traction as a viable treatment, particularly following the development of ultrasound (US)-guided injection techniques, which enhance the accuracy of intra-articular administration (32, 33). In this context, previous reports demonstrated a high efficacy, safety, and tolerability of the HA-based device HyalOne® (Hyalubrix® 60, Fidia Farmaceutici S.p.A., Abano Terme, Italy) when administered *via* US-guided intra-articular injections for hip OA (34-36). HyalOne® has also shown effectiveness in the treatment of glenohumeral OA, leading to significant pain reduction and improvements in QoL (37). This sterile, non-pyrogenic, viscoelastic solution contains high-molecular-weight HA sodium salt (1.500-2.000 kDa) with a prolonged residence time (37, 38). Clinical evidence has shown significant improvements in pain and disability, as indicated by reductions in the Lequesne functional index and Visual Analog Scale (VAS) scores, with benefits lasting up to 7 years (35, 38). Notably, repeated injections at least twice a year have been reported to sustain these improvements (38), suggesting a potential role in delaying OA progression. However, no definitive evidence currently links these benefits to a slower progression of OA-related radiological changes. To address this knowledge gap, the primary objective of the present study was to assess radiological changes in hip OA patients following 2 years of treatment with HyalOne®/Hyalubrix® 60.

Materials and Methods

Study design

This study is a retrospective, observational, non-pharmacological clinical investigation conducted at San Pietro Fatebenefratelli Hospital, Rome, Italy. The study received approval from the Ethical Committee (protocol number 1697/CE Lazio), and it was performed from December 2021 to April 2023 in accordance with the Declaration of Helsinki, the ISO (EN) 14155, the ICH-Good Clinical Practice, and the Regulation (EU) 2017/745.

The clinical records of outpatients suffering from symptomatic hip OA and treated with HyalOne®/Hyalubrix® 60 between 2008 and 2022 were selected from the ANTIAGE national registry (35). This registry stores baseline patients' characteristics, including sex, age, body mass index (BMI), weight, height, smoking habit, presence of concomitant knee OA, presence of diabetes mellitus, and indication of the hip affected (monolateral or bilateral). The registry also includes radiological data collected from a non-weight-bearing X-ray image of the affected hip, Lequesne questionnaire scores, VAS scores for pain at rest, and data on NSAIDs consumption (days/month).

Patients

Patients included in this study were all treated at the involved center. All participants received intra-articular injections of HyalOne®/Hyalubrix® 60 administered as a single 4 mL (60 mg) dose into the affected hip(s) every 6 months. To maintain clinical benefit and to prevent the flare of disease, injections were performed even in patients reporting clinical improvements. Following a standardized technique, US guidance was used to ensure accurate injection placement (32, 33).

Inclusion criteria were: i) age between 50 and 80 years old at baseline; ii) diagnosis of hip OA radiologically and clinically confirmed according to the American College of Rheumatology criteria (39); iii) radiological Kellgren-Lawrence (K-L) grade 1, 2, or 3 confirmed by an X-ray performed within 6 months before treatment; iv) at least 2-years of radiological follow-up from the first injection; v) BMI≤35 at baseline. Exclusion criteria were: i) patients not fulfilling the above-mentioned inclusion criteria; ii) patients with significant comorbidities, *e.g.*, rheumatologic disease, low back pain, and femoral head osteonecrosis; iii) patients treated by intra-articular injection of other HA-based products, or intra-articular steroids within 2 years following the treatment with HyalOne®/Hyalubrix® 60; iv) patients treated using any other investigational drug or device.

Objectives and outcome measures

The primary objective of the study was to evaluate the treatment's capability of delaying hip OA radiographic progression from baseline. This objective was evaluated by measuring the percentage of patients not showing a radiological K-L grade change ≥1 at 2-year follow-up. Assessment of radiological OA changes after 6 and 10 years of treatment compared to baseline was considered as a secondary objective. X-ray images available at baseline and follow-up visits were evaluated by a radiologist blinded to treatment and study design. The radiologist was unaware of the chronological order of the radiographs for each patient, thereby preventing any potential bias in assessing the progression of OA. Specifically, OA was graded according to the K-L scale, with grade 0 signifying no presence of OA and grade 4 indicating severe OA (40).

Secondary objectives included the evaluation of safety, assessing the occurrence, and reporting the nature of adverse events (AEs). Additional secondary objectives were variations in pain level at rest, Lequesne index (41), and NSAID intake after 2, 6, and 10 years from baseline. Outcome measures were accordingly the patient's subjective evaluation of pain at rest measured on a 100 mm VAS (points 1-10), the NSAID intake (days/month), and the change in the Lequesne index.

Statistical analyses

The study consisted of a per-joint analysis. Demographic and clinical characteristics at baseline and at each follow-up visit were analyzed through descriptive statistics. Categorical variables were described as frequencies and percentages, while continuous variables were reported as means and standard deviations.

K-L grade frequencies after 2, 6, and 10 years of treatment were compared to baseline by means of McNemar tests (42). Post-hoc analyses were performed after stratification according to K-L grading and age classes (50-59 years, 60-69 years, 70-79 years),

where appropriate. Changes in VAS pain scores at rest, Lequesne indexes, and NSAID consumption at each follow-up visit were compared to baseline using paired *t*-tests. Data normality was assessed through the Shapiro-Wilk test and visual representation. When the normality assumption was violated, the non-parametric equivalent (Wilcoxon test for paired data) was applied. Additional analyses were performed to account for potential within-patient correlation in bilateral cases. For the primary objective, a cluster-bootstrapped McNemar test (5,000 patient-level iterations) and a one-hip-per-patient analysis (selecting the hip with the highest baseline K-L grade, or the right hip in case of ties) were conducted, while secondary outcomes were analyzed through generalized linear mixed models with patient-level random intercepts and a variance component for hip nested within patient. Statistical analysis was carried out using R software (version 4.1.3).

Results

A total of 125 patients treated between 2008 and 2022 were preliminarily selected. After applying the inclusion/exclusion criteria, 74 patients were chosen for analysis (32 males and 42 females; mean age 63.35±7.11 years). Six of them (8.11%) were affected by bilateral hip OA, and of these, 2 hips were excluded as presenting K-L grade 4. Overall, the final dataset included 78 hip observations at 2 years follow-up (Figure 1). At 6 years follow-up, 16 hip observations were evaluated, while only 3 cases were available at 10 years follow-up. Baseline characteristics of patients are summarized in Table 1. Mean BMI was 24.37±3.23 kg/m^2, mean weight was 68.88±13.42 kg, and mean height was 1.68±0.11 m. A total of 17 patients (24.10%) were smokers, 14 (19.28%) were ex-smokers, and 43 (56.63%) did not smoke at all. Concomitant pathologies and knee OA were observed in 40.96% and 27.71% of cases, respectively. There were 18 diabetic subjects (22.89%) and 26 patients (37.35%) assumed concomitant medications.

Table 1. Patients' characteristics at baseline. Categorical variables are reported as frequency (n) and percentage (%); continuous variables are reported as mean ± standard deviation.

Patients – n	74
Sex - n (%)	
F	42 (53.01)
M	32 (46.99)
Hips - n	78
Treatment site – n (%)	
Bilateral	6 (8.11)
Right	40 (54.05)
Left	28 (37.84)
Age (years) – mean±SD	63.35±7.11
Body mass index (kg/m^2) – mean±SD	24.37±3.23
Weight (kg) – mean±SD	68.88±13.42
Height (m) – mean±SD	1.68±0.11
Smoke – n (%)	
Ex-smoker	14 (19.28)
Yes	17 (24.1)
No	43 (56.63)
Other pathologies – n (%)	
Yes	29 (40.96)
No	45 (59.04)
OA knee – n (%)	
Yes	19 (27.71)
No	55 (72.29)
Diabetes – n (%)	
Yes	18 (22.89)
No	56 (77.11)
Other drugs – n (%)	
Yes	26 (37.35)
No	48 (62.65)

F, female; M, male; SD, standard deviation; OA, osteoarthritis.

Kellgren-Lawrence grade

Average K-L grade showed slight variations from baseline to follow-up visits (Table 2). The mean value was 2.33±0.78 at baseline, and varied to 2.38±0.83 at 2 years, 2.5±0.52 at 6 years, and 2.33±0.58 at 10 years. At baseline, K-L grade 1 was assigned to 15 hips (19.23%), K-L grade 2 to 22 hips (28.21%), and K-L grade 3 to 41 hips (52.56%) (Table 2). As per the inclusion criteria, no K-L grade 4 was observed at baseline (Figure 2). At the 2-year follow-up, the K-L grade remained stable in 72 hips (92.31%), while it improved in 1 case (1.28%) and worsened in 5 cases (6.41%) (Figure 3). This resulted in 14 hips (17.95%) with K-L grade 1, 23 hips (29.49%) with K-L grade 2, 38 hips (48.72%) with K-L grade 3, and 3 hips (3.85%) with K-L grade 4. No significant worsening after 2 years of treatment occurred compared to baseline (χ^2=3.2, d.f.=1, p=0.074), as also confirmed by sensitivity analysis. This result was independent of the K-L grade and the patients' age at baseline (p>0.05). Of the 16 hips analyzed at the 6-year follow-up, 11 cases (68.75%) showed no variation in the K-L grade, and 5 hips (31.25%) worsened (Figure 3), resulting in 8 hips (50%) with K-L grade 2 and 8 hips (50%) with K-L grade 3 (Figure 2). No significant variations from baseline were detected (χ^2=2.25, d.f.=1, p=0.13), even after stratifying data by K-L grade and by age classes (p>0.05). At 10 years follow-up, 2 cases reported K-L grade 2 (66.7%) and 1 case K-L grade 3 (33.3%) (Figure 3), corresponding to one case of worsening (33.3%) and the remainder showing

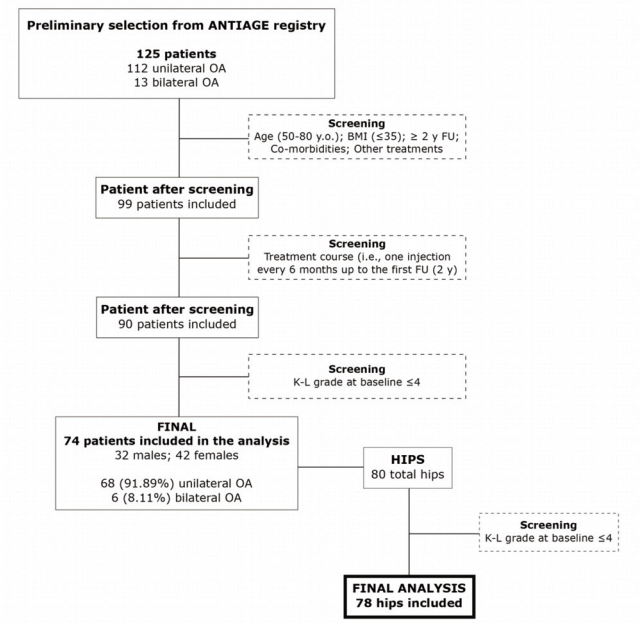

Figure 1. Flow chart showing the screening process of the records retrieved from the ANTIAGE registry. OA, osteoarthritis; BMI, body mass index; K-L, Kellgren-Lawrence; FU, follow-up.

maintenance (Figure 3). Also in this case, no significant variation from baseline was observed (χ^2=0, d.f.=1, p=1).

Safety

No major or minor systemic AEs were reported throughout the study period, including at 2-, 6-, and 10-year follow-up assessments.

Visual Analog Scale – pain at rest

Pain levels recorded after 2 years (mean VAS score=3.4±1.84) and 6 years (mean VAS score=3.88±1.09) follow-up were significantly lower (p<0.001 and p=0.008, respectively) with respect to baseline observations (mean VAS score=5.33±1.69). At 10 years follow-up, the mean VAS score (4.33±0.58) remained lower than the baseline value, with no significant differences (p=0.59) (Figure 4a).

Lequesne Index

At baseline, the average Lequesne Index value was 5.84±3.56. At 2 years, 6 years, and 10 years of follow-up, the average value decreased to 5.05±3.39, 4.78±3.21, and 1.0±1.0, respectively. When compared to baseline, Lequesne Index variations at follow-up visits were not significantly different (p=0.06, p=0.21, and p=0.17, respectively) (Figure 4b).

Non-steroidal anti-inflammatory drug consumption

Mean NSAID consumption at baseline was 2.90±5.76 days/month. The NSAID intake decreased at all evaluated time-points, reporting values of 1.37±2.23 days/month at 2 years, 0.88±1.15 days/month at 6 years, and 0.67±1.15 days/month at 10 years. Differences from baseline were significant at 2 years (p=0.016) and 6 years (p=0.014) follow-up, while no significant difference was observed at 10 years follow-up (p=0.35) (Figure 4c).

Discussion

Managing OA is complex and requires a multidisciplinary approach focused on symptom relief and lifestyle modifications (16, 17). While previous observational and prospective studies have demonstrated the safety and efficacy of HA-based devices administered *via* US-guided intra-articular injections for hip OA (32-34), to the best of the authors' knowledge, this is the first study to evaluate mid- and long-term radiological changes associated with the use of HyalOne®/Hyalubrix® 60 in patients with symptomatic hip OA. The findings indicate a potential slowing of OA progression associated with this treatment. At 2-year follow-up, 93.59% of cases showed no radiological worsening, regardless of initial K-L grade and patients' age. Similarly, retrospective data collected at the 6-year follow-up may further support the role of

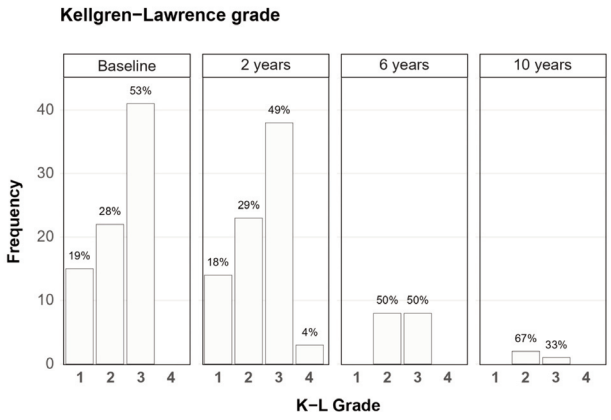

Figure 2. Frequency of hips presenting a Kellgren-Lawrence (K-L) grade 1, 2, 3 or 4 at baseline and follow-up visits. Numbers reported in abscissa are the K-L grades. Numbers reported above the bars indicate percentages.

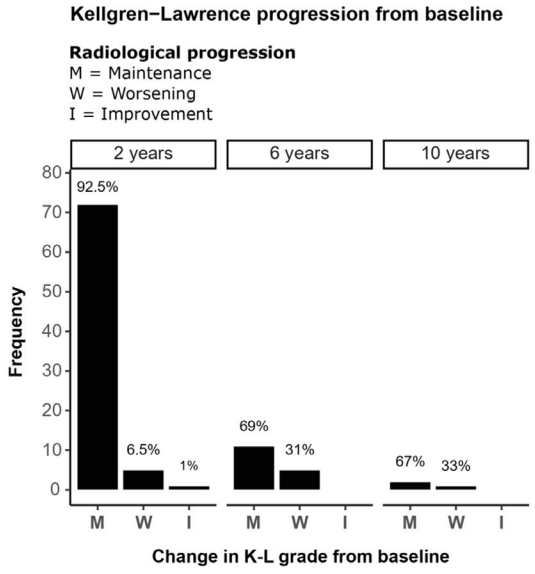

Figure 3. Changes in Kellgren-Lawrence (K-L) grade from baseline to follow-up visits at 2 years, 6 years, and 10 years. The histogram shows the frequency of hips showing maintenance of K-L grade from baseline (M), worsening of K-L grade from baseline (W) and improvement of K-L grade from baseline (I). Percentages are shown above the respective bar in the histogram.

Table 2. Kellgren-Lawrence (K-L) grade scores observed after radiological assessment at baseline, 2 years follow-up, 6 years follow-up and 10 years follow-up. Mean ± standard deviation is reported along with median values. The number of hips reporting the different K-L grade scores (1, 2, 3, 4) at baseline and follow-up visits is reported.

	Baseline	2 years	6 years	10 years
Mean±SD	2.33±0.78	2.38±0.83	2.50±0.52	2.33±0.58
Median	3.00	3.00	2.50	2.00
Grade 1 (n)	15	14	0	0
Grade 2 (n)	22	23	8	2
Grade 3 (n)	41	38	8	1
Grade 4 (n)	0	3	0	0

SD, standard deviation.

HyalOne®/Hyalubrix® 60 in preventing hip OA progression across different baseline OA severities and age groups (38). Although the 10-year follow-up results hint at the persistence of treatment efficacy over time, they remain indicative due to the limited number of available observations. Overall, findings support a treatment regimen of 60 mg/4 mL administered every 6 months as a valid long-term approach for managing hip OA.

The observed delay in OA radiographic progression may be attributed to both the product's formulation and the injection technique. On one hand, the high molecular weight HA in HyalOne®/Hyalubrix® 60 ensures long term effects, enhancing shock absorption and lubrication. In this regard, the effect of high molecular weight HA is also confirmed by a recent systematic review and meta-analysis that reported superior symptom relief in hip OA with this therapy compared to low- or moderate-molecular weight formulations (31). On the other hand, the US-guided injection technique ensures precise intra-articular delivery, minimizing the risk of extra-articular placement and associated local side-effects. Confirming this, no AEs were reported throughout the extended follow-up period, underscoring the excellent safety profile of both the product and the injection technique.

Additionally, the present study provides evidence supporting the effectiveness of HyalOne®/Hyalubrix® 60 in reducing pain and NSAID consumption, with no safety concerns. Patients receiving US-guided viscosupplementation every 6 months reported mild symptoms, with long-lasting effects. Consequently, NSAID use significantly decreased, reducing the risk of associated AEs. Alongside confirming previous retrospective studies and randomized controlled trials supporting the effectiveness of viscosupplementation in managing hip OA symptoms for up to 12 months (32-35, 38, 43-45), the present study adds to the existing literature by providing long-term observations, extending follow-up to 6 years. In 2024, Ghanta *et al.* conducted a retrospective study in 357 patients with primary hip OA. They reported that intra-articular corticosteroid injections were associated with a mean of pain relief duration of approximately 6.7 weeks, and that nearly 75% of patients underwent total hip arthroplasty within 1 year (46). These findings suggest a limited persistence of symptomatic benefit in that context. In contrast, our results showed a significant reduction in pain at rest maintained at both 2- and 6-year follow-up, supporting the potential for a longer-lasting effect of US-guided HA injections within a conservative treatment strategy. Given the chronic nature of OA and the need for continuous management over a decade, long-term evaluations are crucial for determining whether initial benefits persist and whether any adverse effects emerge over time. Overall, US-guided intra-articular viscosupplementation with HyalOne®/Hyalubrix® 60 emerges as a safe and effective background therapy for hip OA management, demonstrating both efficacy in delaying disease progression and alleviating symptoms. However, these results should be interpreted in light of the study's limitations, including its retrospective nature, the limited number of cases available for long-term follow-up, and the absence of a control group, which potentially affected internal validity. Although the standardized treatment protocol and consistent follow-up strengthen the descriptive value of the results, the potential influence of natural disease progression, placebo effects, or unmeasured confounding factors cannot be excluded. The single-center retrospective design may also limit the generalizability of the findings to broader clinical settings. These limitations are consistent with those observed in other recent investigations (47).

Counterbalancing these limitations, the study's main strength lies in providing valuable real-world evidence, capturing not only subjective but also objective aspects of OA pathology and symptomatology. The integration of radiological assessments offered objective insights into disease progression and treatment response by documenting structural joint changes, while US-guided intra-articular injections ensured precise treatment delivery. The consistent semi-annual treatment schedule and adequately sized study population reinforce the reliability and robustness of our results. As such, the findings presented here may serve as a foundation for future randomized controlled trials, offering additional evidence on the role of intra-articular viscosupplementation in slowing radiographic OA progression and potentially revealing further functional insights.

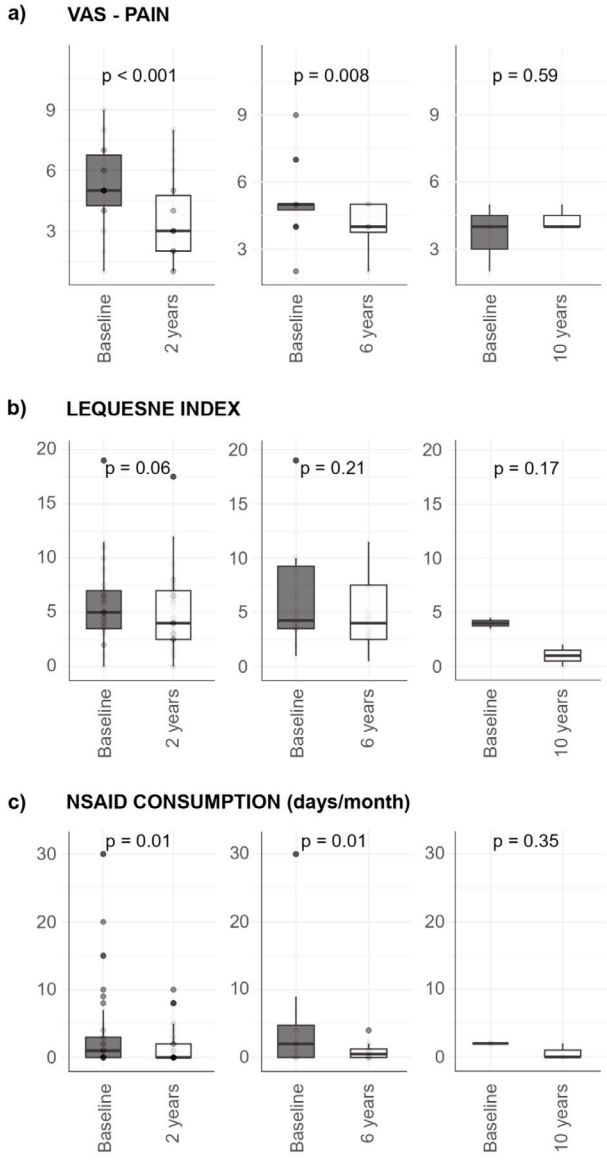

Figure 4. Boxplots for: **a**) pain Visual Analog Scale (VAS); **b**) Lequesne Index; **c**) non-steroidal anti-inflammatory drug (NSAID) consumption (days/month) at baseline and follow-up visits – 2 years, 6 years, 10 years. Differences from baseline were analyzed through a non-parametric Wilcoxon test for paired data; the p-value obtained from each test is reported. Significance was considered with α=5%.

Conclusions

This retrospective observational study showed that intra-articular injections with HyalOne®/Hyalubrix® 60 were well tolerated and may contribute to maintaining clinical and radiographic stability in patients with hip OA, preventing its progression in the medium and long term, regardless of baseline OA grade or patient age.

The treatment was also associated with a reduction in symptoms, supporting lower NSAID consumption and potentially reducing the risk of associated AEs. These findings are clinically relevant, as the proposed approach may represent a valuable long-term strategy to delay the need for more invasive surgical interventions. However, additional clinical investigations are necessary to further substantiate the efficacy and safety of intra-articular viscosupplementation for hip OA management. In this regard, randomized controlled trials incorporating radiological assessments over the medium and long term will be crucial in clarifying the role of high molecular weight HA in slowing OA progression.

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Conflict of interest: IB and MG are employees of Fidia Farmaceutici SpA. The remaining authors declare that they have no competing interests.

Ethics approval and consent to participate: the study received approval on 29 December 2021 from the Ethical Committee "Lazio I" (A.O. San Camillo Forlanini, Roma), protocol number 1697/CE Lazio.

Informed consent: considering the retrospective nature of this study and the fact that the clinical records have already been collected and logged into a national patients' registry (ANTIAGE), the patient Informed Consent Form (ICF) of the study "Attivazione del Registro ANTIAGE sulle terapie intra-articolari" (approved by the Ethical Committee in June 2014) was considered valid and approved also for the present study.

Patient consent for publication: not applicable.

Availability of data and materials: the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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