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Efficacy and Safety of One Shot of Hyaluronic Acid in Hip Osteoarthritis: Postmarketing Clinical Follow-Up for Real-World Evidence

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Purpose: This study aims to evaluate the real-world efficacy and safety of intra-articular (IA) hyaluronic acid (HA) injections in patients with hip osteoarthritis (OA). Given the increasing burden of hip osteoarthritis and limited evidence supporting viscosupplementation in this context, this research aims to provide valuable insights under real clinical practice conditions.

Patients and Methods: An observational, cross-sectional and retrospective study was conducted in a cohort of patients with hip OA treated with a single injection of HA (Adant One, Meiji Pharma Spain, Spain) from January 2021 to December 2022. Data on patient demographics, clinical characteristics, and treatment outcomes were collected. Efficacy regarding pain relief and/or function improvement was assessed at 6 months using the Visual Analogue Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Data were pseudonymized. The study was approved by the Research Ethics Committee of the Autonomous Community of Aragon (CEICA).

Results: The study included 40 patients with a mean age of 62.8 years, with 72.5% being female. Significant improvement was observed six-months post-treatment: 25% and 18.5% reduction in pain (VAS and WOMAC, respectively), 11.6% improvement in function (WOMAC), 7.4% improvement in stiffness (WOMAC), and 13.6% improvement in total WOMAC. No adverse events were reported.

Conclusion: A single injection of IA HA significantly improved pain and function in patients with hip OA. These findings support the use of viscosupplementation for hip OA management and underscore the need for further studies to confirm these results and assess the long-term benefits of IA HA in hip OA.

Keywords: rehabilitation, real clinical practice, rheumatology, traumatology

Introduction

Osteoarthritis (OA) is a chronic disease in which progressive disruption of joint homeostasis occurs leading to cartilage degradation, synovial inflammation, osteophyte formation and subchondral bone remodeling.[1,2] Clinical features of the disease include pain, stiffness and decreased joint function, involving considerable morbidity and reduced quality of life.[2] OA is a major public health problem worldwide, frequently affecting the hip joint, and its incidence has increased considerably in recent decades.[3,4] In the case of osteoarthritis of the hip, the incidence has increased by 115.4% between 1990 and 2019, and this trend is expected to continue increasing in the coming years.[5] This rise not only underscores the clinical burden of hip osteoarthritis, but also its socioeconomic impact, which imposes a significant burden on healthcare systems worldwide.[6,7]

Therapeutic modalities for OA, ranging from lifestyle modifications to pharmacological interventions, aim primarily at symptom management and disease modification.[2,8] Among the non-pharmacological treatments, the main recommendations are health education and therapeutic exercise.[9] Regarding pharmacological approaches, viscosupplementation

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with hyaluronic acid (HA) has demonstrated to be a valuable therapy in the management of OA by replenishing the viscoelastic properties of synovial fluid and restoring joint lubrication.[10,11] Despite its widespread use and efficacy in knee OA,[12,13] including its proven usefulness in delaying replacement surgery,[14] evidence supporting the efficacy and safety of viscosupplementation in hip OA is limited, necessitating further investigation. Here the importance of conducting studies under real clinical practice conditions becomes crucial, in line with the new EU Medical Devices Regulation 2017/745 (MDR),[15] which focuses on the importance of assessing the efficacy and safety of medical devices throughout their entire life cycle, advocating for rigorous post-market surveillance and real-world evidence collection.

In light of the growing burden of hip OA and the limitations of current evidence, and in accordance with the MDR, this observational study aims to evaluate the real-world efficacy and safety of Adant One (Meiji Pharma Spain, Alcalá de Henares, Spain), a non-cross-linked, medium molecular weight (1000 kDa)[16] hyaluronic acid (HA) obtained by biofermentation, in patients with hip OA. This study seeks to generate valuable insights into the therapeutic potential of HA in patients with hip OA, thereby contributing to the body of evidence required to support its clinical use and inform future treatment guidelines.

Material and Methods

Ethics

The Research Ethics Committee of the Autonomous Community of Aragon (CEICA) gave approval for the realization of the study and the waiver of informed consent (approval code PI23/217). The study complies with the Declaration of Helsinki. Data were pseudonymized and identified by a code to ensure that patients cannot be identified.

Study Design

This is an observational, longitudinal and retrospective study in a single cohort of 40 patients with hip OA treated with a single injection of Adant One (HA 1%, 4.9 mL). Participants included adult patients with hip osteoarthritis seen at the Rehabilitation Department of the Hospital Provincial Nuestra Señora de Gracia (Zaragoza, Spain) and treated during the period from January 1st 2021 to December 31st 2022 with Adant One following standard clinical practice. In the routine clinical practice at the hospital, the administration of the product is performed under ultrasound guidance.

Patient information regarding age, gender, employment status, Kellgren-Lawrence grade,[17] chronic medical conditions, previous HA treatment, osteoarthritis laterality (left / right), date of treatment initiation, pain, stiffness, function, and use of concomitant medication for OA and for other pathologies was pseudonymized and collected in a database. Other observations that may be of interest according to the researcher's criteria (pathologies detected after injection, adverse events etc) were also recorded.

Outcome Measures

The primary objective of this study was to evaluate the efficacy of viscosupplementation in hip OA in reducing pain and stiffness and improving function 6 months after treatment. This was measured using a visual analogue scale (VAS) for pain, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire for pain, stiffness and function. For the VAS scale, a discrete measure from 0 (no pain) to 10 (maximum pain) was used. The WOMAC questionnaire consisted of 5 questions on pain, 2 questions on stiffness, and 17 questions on function, which were scored on a Likert-type scale from 1 (best) to 5 (worst), with a minimum total score of 24 and a maximum of 120. Safety, understood as adverse events occurrence, was established as a secondary objective.

Statistics

Qualitative variables have been described as percentages. Quantitative variables that fit a normal distribution were described by mean, standard deviation (SD), minimum (Min) and maximum (Max); while those that do not meet a normal distribution were described by median, interquartile range (P25 - P75), Min and Max. To demonstrate normality, the Shapiro test was used.

Univariate comparisons between categorical variables were performed using the chi-square test and/or Fisher's exact test. For the comparison of continuous variables, the shape of the distributions was analyzed using the Kolmogorov Smirnoff and Shapiro Wilk tests. Comparisons between two non-dependent variants were made using Student's *t*-tests (in case of normality) or Mann–Whitney *U*-tests (for non-normal distributions). Results with a p-value < 0.05 were considered statistically significant.

Results

Most patients were female (72.5%), with a mean age of 62.8 years (± 11.3 years), and 82.5% were not working. Kellgren-Lawrence grades II and III were most prevalent (42.5% and 45.0%, respectively) while there were a small number of patients with grade IV (12.5%) and no patients with grade I. Among the patients, 30 (75%) had one or more chronic medical conditions, while 10 (25%) had none. Sociodemographic and clinical characteristics are detailed in Table 1. Regarding the use of medication, paracetamol (67.5%) and opioids (35.0%) predominated for the treatment of osteoarthritis, while for the treatment of chronic medical conditions, antihypertensives (57.5%) were the most common (Table 2). All patients have previously received intra-articular (IA) HA injections.

Patients were assessed for baseline pain, stiffness and function (Table 3) and a single IA HA injection was administered. At 6 months, all efficacy variables showed significant improvements from baseline ($p < 0.05$). As shown in Table 3, there was a reduction in pain of 25% in VAS and 18.5% in WOMAC, an improvement of 11.6% in function WOMAC, and 13.6% in total WOMAC (median values). Stiffness decreased by 7.4% on average, but with a median of 0. No treatment-related adverse events were reported.

Discussion

This study evaluated the efficacy of intra-articular hyaluronic acid injections in patients with hip OA over a six-month period, addressing a gap in the literature regarding the efficacy of viscosupplementation in managing hip OA. Nowadays, there is broad evidence that the main effect of hyaluronic acid lies in its shock-absorbing and lubricating

Table 1 Sociodemographic and Clinical Characteristics

Gender[b]	Woman	29 (72.5%)
Age[a]	Mean (SD)	62.8 (11.3)
Employment status	Active Sick leave (due to hip osteoarthritis) Retired	7 (17.5%) 14 (35.0%) 19 (47.5%)
Kellgren-Lawrence grade[b]	I II III IV	0 (0.0%) 17 (42.5%) 18 (45.0%) 5 (12.5%)
Chronic medical condition[b]*	Hypertension Type 2 diabetes Obesity Cancer Depression Other	23 (57.5%) 11 (27.5%) 2 (5.0%) 2 (5.0%) 5 (12.5%) 11 (27.5%)
Previous HA treatment[b]	Yes	40 (100%)
Affected joint[b]	Right	24 (60.0%)

Notes: [a]Mean (SD); [b]n (%). *Multiple options possible per patient.

Table 2 Use of Concomitant Medication

Medication for osteoarthritis [n (%)]	
Paracetamol	27 (67,5%)
SYSADOAs	1 (2,5%)
NSAIDs	6 (15,0%)
Metamizole	6 (15,0%)
Corticosteroids	2 (5,0%)
Opioids*	14 (35,0%)
Medication for other pathologies [n (%)]	
Antihypertensives	23 (57,5%)
Oral antidiabetics	7 (17,5%)
Antidepressants	9 (22,5%)
Oral anticoagulants	1 (2,5%)
Other	8 (20,0%)

Notes: Multiple options possible per patient. *Short-acting opioids were prescribed for patients with mild pain, while long-acting opioids were prescribed for moderate to severe cases.

properties. Nevertheless, it also exerts anti-inflammatory and chondroprotective effects.[18–20] These properties contribute to its clinical efficacy, which has been extensively proven in other joints such as knee,[14,21–23] either alone or in combination with other therapies.[24] However, the information regarding its efficacy in hip OA is scarce and more studies are needed to provide further evidence. This area is of particular interest given the increasing global burden of this disease[5] and the limited available evidence, due to results variability among studies.[25,26] Although clinical practice guidelines often do not recommend the use of IA HA in the treatment of hip OA,[27] mainly due to lack of evidence, our findings demonstrated significant improvements in pain and function 6 months post-treatment with a single IA AH injection. Furthermore, no treatment-related adverse events were reported, reinforcing the safety profile of IA HA injections.

Notably, 75% of the patients had one or more chronic medical conditions, highlighting the complexity and multimorbidity often associated with OA, underlining the need for a holistic approach.[28] The prevalent use of paracetamol and opioids for OA pain management underscores the chronic pain burden faced by these patients.

Limitations of our study include the small sample size and the lack of a control group, which may limit the generalizability of our findings. However, these circumstances reflect the routine clinical practice and allow to obtain real-world evidence. Future research with larger sample size and control group is warranted to validate our results and to provide further insights into the long-term efficacy and safety off IA HA injections for hip OA.

Furthermore, our study aligns with the objectives outlined in the new MDR,[12] emphasizing the importance of evaluating the efficacy and safety of medical devices through their entire lifecycle. By conducting real-world observational studies, we provide valuable information on the actual use of viscosupplementation in routine clinical practice. By addressing gaps in current knowledge and highlighting the need for further research, there is a potential to advance understanding and improve treatment strategies for hip OA.

Table 3 Efficacy Assessment

INITIAL ASSESSMENT			
	Median (P25-P75)	**Range**	
VAS	8.0 (8–9)	7–9	
WOMAC Pain	20.0 (20–22)	14–23	
WOMAC Stiffness	3.0 (2–3)	1–8	
WOMAC Function	59.0 (56–60)	50–65	
WOMAC Total	82.00 (80.8–85.3)	66–92	
6 MONTHS ASSESSMENT			
VAS	6.0 (6–7)	4–9	
WOMAC Pain	16.0 (14.8–16.0)	5–22	
WOMAC Stiffness	2.0 (2–3)	1–4	
WOMAC Function	51.0 (48.0–55.3)	27–62	
WOMAC Total	69.5 (66.3 −74.5)	33–85	
DIFFERENCES BETWEEN INITIAL AND 6 MONTHS ASSESSMENTS			**p (*T* test)**
VAS % difference	−25 (−28.6 / – 12.5)	−42.9 / 0	< 0.001
VAS difference	−2 (−2 / −1)	−3 / 0	< 0.001
WOMAC Pain % difference	−18.5 (−25.6 / −13.0)	−72.2 / 7.14	< 0.001
WOMAC Pain difference	−4 (−5 / −3)	−14 / 1	< 0.001
WOMAC Stiffness % difference	0 (−33 / 0)	−87.5 / 100	0.013
WOMAC Stiffness difference	0 (−1 / 0)	−7 / 1	0.013
WOMAC Function % difference	−11.6 (−14.9 / −7.88)	−54.2 / 12.0	< 0.001
WOMAC Function difference	−6.0 (−9.25/ −5.00)	−32 / 6	< 0.001
WOMAC Total % difference	−13.6 (−18 / −9.2)	−61.2 / 10.6	< 0.001
WOMAC Total difference	−10.5 (−15.0 / −8.0)	−61.2 / 10.6	< 0.001

Notes: All distributions were non-normal according to Shapiro's test ($p < 0.05$).

Conclusion

In conclusion, IA HA single injection have demonstrated to offer significant pain relief and functional improvement for patients with hip OA, with a favorable safety profile. These findings contribute valuable evidence supporting the use of viscosupplementation as treatment for hip OA. Further studies are warranted to confirm these results and to explore the long-term benefits of HA injections in hip OA management, including their potential impact in the delay of hip arthroplasty.

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Disclosure

P. Coronel and E. Gómez-Rubio are employees of Meiji Pharma Spain. The other authors declare no conflicts of interest.

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