

Registry of intra-articular hyaluronic acid for the treatment of knee osteoarthritis in Argentina

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ABSTRACT

Background: Treatment of knee osteoarthritis with intra-articular hyaluronic acid (IA-HA) is frequently used in Argentina, with different dosing forms and injection regimens. Our main objective was to provide real world data on the use and efficacy of IA-HA. **Materials and Methods:** In this observational retrospective cohort study, we studied 1227 patients with knee osteoarthritis treated with IA-HA 20 mg/2 mL weekly (76%, 20 mg group) and 40 mg/2 mL (24%, 40 mg group) according to standard practice. Follow-up was 6 months and efficacy was assessed by the 5-point Likert scale and a response of 50% or more. **Results:** Median number of injections was 5 (20 mg) and 3 (40 mg). Both groups had a significant improvement in the Likert scale from baseline to 6 months. Median score improved from 4 (mean 3.77 ± 0.69) at baseline to a median of 2 (mean 1.99 ± 0.76) at 6 months (20 mg group, $p < 0.001$) and from a median of 4 (mean 3.65 ± 0.65) to a median of 2 (mean 1.86 ± 0.72) in the 40 mg group, $p < 0.001$. The percentage of patients with a response of 50% or more at 6 months was 61% and 66% respectively. In the multivariate analysis, the 50% response rate was associated with a higher baseline score, younger age and shorter duration of disease. Only one patient in the 20 mg group (0.1%) experienced a serious treatment-related adverse event (septic arthritis) following injection. **Conclusions:** Our study carried out during routine clinical practice supports the efficacy of IA-HA for the management of knee osteoarthritis, with a clinical advantage observed at a 6-month follow-up.

Key words: Intra-articular; hyaluronic acid; knee; arthrosis; osteoarthritis.

Level of evidence: IV

Registro de ácido hialurónico intrarticular en el tratamiento de la artrosis de rodilla, en la Argentina

RESUMEN

Introducción: El ácido hialurónico intrarticular se suele utilizar con diferentes esquemas para tratar la artrosis de rodilla. Nuestro objetivo fue analizar la eficacia y el uso del ácido hialurónico intrarticular en la práctica habitual. **Materiales y Métodos:** Cohorte retrospectiva observacional. Se evaluó a 1227 pacientes con artrosis de rodilla tratados con ácido hialurónico intrarticular 20 mg/2 ml/semana (76%, 20 mg) y 40 mg/2 ml (24%, 40 mg) según la práctica habitual. Seguimiento de 6 meses. Se evaluó la eficacia con la escala de Likert de 5 puntos y la proporción de respuesta $\geq 50\%$. **Resultados:** La mediana de aplicaciones fue de 5 (20 mg) y 3 (40 mg). El puntaje de Likert mejoró significativamente en ambos grupos a los 6 meses. La mediana del puntaje mejoró de 4 (media $3,77 \pm 0,69$) al inicio a 2 (media $1,99 \pm 0,76$) a los 6 meses con 20 mg ($p < 0,001$) y de 4 (media $3,65 \pm 0,65$) a 2 (media $1,86 \pm 0,72$) con 40 mg ($p < 0,001$). La proporción de respuesta $\geq 50\%$ a los 6 meses fue del 61% y 66%, respectivamente. En el análisis multivariado, la tasa de respuesta $\geq 50\%$ se asoció con un mayor puntaje inicial, edad más joven y menor duración de la enfermedad. Solo un paciente con 20 mg (0,1%) tuvo un episodio adverso serio (artritis séptica). **Conclusión:** Nuestro estudio en la práctica clínica común respalda la efectividad del ácido hialurónico intrarticular para tratar la artrosis de rodilla, con un beneficio clínico a los 6 meses de seguimiento.

Palabras clave: Intrarticular; ácido hialurónico; rodilla; artrosis; osteoartritis.

Nivel de Evidencia: IV

Received on April 20, 2018. Accepted after evaluation on December 17, 2018 • MARIO BERENSTEIN, MD • marioberenstein@gmail.com 

How to cite this paper: Berenstein M, Tacus L, Kobrinsky P, Vaineras D. Registry of intra-articular hyaluronic acid for the treatment of knee osteoarthritis in Argentina. *Rev Asoc Argent Ortop Traumatol* 2019;84(2):122-128. <http://dx.doi.org/10.15417/issn.1852-7434.2019.84.2.846>

INTRODUCTION

Osteoarthritis is the most common condition of the synovial joints, with a growing prevalence parallel to the aging of the population, which produces significant morbidity rates.¹⁻³ The condition is characterized by focal degenerative lesions, cartilage destruction, subchondral sclerosis, formation of large cysts and osteophytes.¹⁻³ Ten percent of men and 13% of women aged 60 or more suffer from symptomatic knee osteoarthritis that produces pain, deformity, joint enlargement, loss of stability and limited mobility.¹⁻³ Conservative management strategies are symptom-based and include nonsteroidal anti-inflammatory drugs (NSAIDs), symptomatic slow-acting drugs for osteoarthritis (SYSADOA), physical therapy, and intra-articular injections of corticosteroids or hyaluronic acid (HA).¹⁻³ HA is a natural component of synovial fluid that acts as a lubricant during shear stress and as a buffer during compression.^{4,5} At the molecular level, HA decreases the expression of various cytokines, including interleukin 1 β , and lower the release of matrix metalloproteinases (MMP-1 and MMP-9), with the consequent anti-nociceptive and anti-inflammatory effects and a potential disease-modifying activity through preservation and restoration of the extracellular matrix.^{5,6}

After intra-articular (IA) administration, HA is rapidly distributed through the synovial membrane. The highest levels are found in the synovial fluid and the joint capsule, followed, in decreasing order, by the synovial membrane, the ligaments and the adjacent muscle, where it remains for days and weeks, contributing to a longer effect after administration.⁷

Intra-articular HA (IA-HA) is approved and frequently used in Argentina, the United States, Europe and many other countries to treat knee osteoarthritis. In Argentina, HA is prescribed in different dosing and injection regimens, ranging from lower doses (20 mg/2 mL) to higher ones (40 mg/2 mL) on each administration. The frequency of administration of these doses varies and can range from weekly injections of lower doses (20 mg) for five weeks to higher doses (40 mg) at more spaced intervals, according to each physician's standard practice. Pharmacological therapy in routine clinical practice settings often differs from the ideal conditions of controlled clinical trials. There is a growing interest in carrying out observational studies that reflect the standard clinical practice and allow to understand how drugs are being used and what their efficacy is, which has led us to carry out the present study.

MATERIALS AND METHODS

Study design and population

This is a substudy of the observational registry (non-interventional cohort study) MAX-ARG-13-01 with patients treated with IA-HA (MaxiOstenil®/Ostenil®, TRB Pharma, Argentina), performed in Argentina in a real and regular practice setting in the field of Orthopedics and Rheumatology and funded by TRB Pharma. This registry included 1402 patients diagnosed with osteoarthritis (of any location) who received IA-HA between January 2012 and December 2015, with a follow-up visit at six months documented in the medical record. Patients who were participating in any experimental study were excluded from the registry. This substudy includes the subgroup of 1227 patients with knee osteoarthritis who had a baseline complete evaluation and a documented follow-up six months after starting the treatment. Of the 1227 patients with knee osteoarthritis included in the study, 953 (76%) were treated with IA-HA at a dose of 20 mg/week, and 274 (24%) of them at a dose of 40 mg at different frequency intervals, according to each physician's standard practice. This registry was based on the collection of secondary data obtained by a retrospective analysis of the medical records of approximately 400 Orthopedics and Rheumatology specialists from the main cities of Argentina.

Study objectives, definitions and treatment

The main objective was to study the differences in the usage pattern (population details, frequency and number of injections) of the dose of 20 mg/2 mL (MaxiOstenil®/Ostenil®) compared to the dose of 40 mg/2 mL (MaxiOstenil Plus®/OstenilPlus®) of IA-HA in a standard clinical practice setting. The secondary objective was to analyze the efficacy and the safety of the 20 mg and 40 mg doses of IA-HA after six months of treatment. Efficacy was evaluated by the investigators before starting the treatment (baseline) and at six months by means of a 5-point Likert scale, with which pain and functional limitation were assessed (scores ranged from 1 = asymptomatic to 5 = very serious), and also by the proportion of patients with a response of 50% or more on the Likert scale. Patients received IA-HA 20 mg/week (20 mg group) or 40 mg administered at intervals that depended on each physician's standard practice (40 mg group). Safety was assessed through the review of treatment-related adverse events recorded in the patients' medical records.

Ethical considerations

The study (MAX-ARG-13-01) was approved by a central Independent Ethics Committee and was carried out according to the Guidelines for Good Pharmacoepidemiology Practice and the local regulations of our country for observational clinical research (Resolution 1480/10 of the Argentine Ministry of Health) and in accordance with the Declaration of Helsinki.

Statistical analysis

All continuous variables were summarized by mean and standard deviation, or by median and quartile (Q1-Q3), according to distribution. Categorical variables were summarized by number of patients, percentages and 95% confidence intervals (95% CI), where applicable. For the comparison of the groups that received 20 mg and 40 mg of IA-HA, the appropriate parametric or non-parametric test was used, according to the distribution of the quantitative variables and chi-square or Fisher's exact test (as appropriate) for categorical variables. Predictive factors of a response of 50% or more were studied by a logistic regression analysis (generalized linear model, binomial family), calculating the odds ratio (OR) if applicable. Statistical significance was considered at $p < 0.05$.

RESULTS

Baseline characteristics and intra-articular administration patterns

Patients of both groups had similar baseline characteristics: older age (69 ± 9 years and 66 ± 11 years, $p < 0.001$) and a shorter duration of the disease (6.4 ± 4.7 and 7.13 ± 4.9 years, $p = 0.036$) in the 20 mg group compared to the 40 mg group. No differences were observed in sex, oral concomitant treatment or previous treatment with IA medications (Table 1).

Table 1. Baseline patient details

	Hyaluronic acid 20 mg (N = 953)	Hyaluronic acid 40 mg (N = 274)	p-value
Age (years \pm SD)	69 ± 9	66 ± 11	<0.001
Women (N, %)	617 (65%)	162 (59%)	NS
Duration of the disease (years \pm SD)	6.4 ± 4.7	7.1 ± 4.9	0.036
Concomitant oral medications			
NSAIDs (N, %)	636 (67%)	180 (66%)	NS
Glucosamine (N, %)	434 (46%)	119 (43%)	NS
Diacerein (N, %)	299 (31%)	86 (31%)	NS
Chondroitin (N, %)	182 (19%)	45 (16%)	NS
Avocado/soybean unsaponifiables (N, %)	63 (7%)	20 (7%)	NS
Previous IA medications			
Corticosteroids	143 (15%)	39 (14%)	NS
Hyaluronic acid	65 (7%)	30 (11%)	NS

SD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs; NS: non-significant.

As stated in the Registry protocol, all patients treated with 20 mg received weekly injections. Those in the 40 mg group received injections at different intervals according to each physician's standard practice: weekly (23%), every two weeks (23%), monthly (36%) and other frequency (18%). The total number of injections also differed in both groups. Patients treated with 20 mg/week received more injections (5.7 ± 3.1 injections, median: 5, Q1-Q3: 5-5) than those in the 40 mg group (3.7 ± 2.1 injections; median: 3; Q1-Q3: 3-4) ($p < 0.01$).

Efficacy and safety evaluation after six months

The investigator evaluated efficacy through changes on the 5-point Likert scale for pain and functional deterioration before starting treatment (baseline) and six months later. The median Likert scale improved significantly from the beginning to six months in both treatment groups: 20 mg (median: 4, mean: 3.77 ± 0.69 and median: 2, mean: 1.99 ± 0.76 , respectively, $p < 0.001$); 40 mg (median: 4, mean: 3.65 ± 0.65 and median: 2, mean: 1.86 ± 0.72 , respectively, $p < 0.001$) (**Table 2**). There was no difference between the two groups in the proportion of patients who had an improvement of 50% or more at six months on the symptoms scale. In the 20 mg group, 61% (95% CI 58-64) of patients had an improvement of 50% or more on the symptoms scale at six months compared to 66% (95% CI 60-71) of patients of the 40 mg group ($p = 0.159$).

Table 2. Likert score of pain and functional limitation after six months of treatment with intra-articular hyaluronic acid at a dose of 20 mg and 40 mg

	Hyaluronic acid 20 mg (N = 953)	Hyaluronic acid 40 mg (N = 274)
Baseline (mean \pm SD)	3.77 ± 0.69	3.65 ± 0.65
6 months (mean \pm SD)	1.99 ± 0.76	1.86 ± 0.72
p-value	<0.001	<0.001

SD: standard deviation.

Patients who achieved an improvement of 50% or more were younger (68 ± 10 years vs. 70 ± 9 years, $p < 0.001$), had a shorter duration of the disease (6 ± 5 years vs. 7 ± 5 years, $p < 0.001$) and a higher baseline score on the Likert scale (median: 4 and 3, $p < 0.001$) than non-responders. Patients who experienced an improvement of 50% or more did not show differences in the frequency of indication of the highest dose (24% and 20%, $p = 0.18$) and in the number of injections of IA-HA (5.2 ± 2.6 and 5.2 ± 3.2 administrations, $p = 0.53$) in relation to the non-responder group.

Using logistic regression, we studied the potential association of a response of 50% or more with older age, duration of the disease, baseline score on the Likert scale, HA dose received (20 mg or 40 mg) and number of injections. The analysis showed that the baseline Likert score (OR: 2.41, 95% CI: 1.98-2.95, $p < 0.001$) was an independent response predictor. We also found weak negative associations, although significant, of a response of 50% or more and age (OR: 0.96, 95% CI: 0.95-0.98, $p < 0.001$) and duration of the disease (OR: 0.95; 95% CI: 0.92-0.97, $p < 0.001$), with a non-significant trend towards a better response in the group treated with 40 mg (OR: 1.31, 95% CI: 0.97-1.77, $p = 0.07$). In the logistic regression, no independent association was found with the number of IA-HA applications.

The assessment of the general improvement of patients after six months of treatment was also carried out using a 5-point Likert scale (ranging from 1 = no improvement to 5 = very good improvement). Overall good or very good improvement (4/5 or 5/5 on the Likert scale) was 75% (95% CI: 72-77%) in the 20 mg group and 81% (95% CI: 77-86) in 40 mg group.

The most common treatment-related adverse event reported was mild or moderate reactions at the injection site (11/953 [1.2%] in the 20 mg group and 1/274 [0.36%] in the other group). The only serious treatment-related adverse event was a case of septic arthritis (1/953 [0.1%]) in the 20 mg group.

DISCUSSION

Knee osteoarthritis is an increasingly common condition in our field of work that increases parallel with the aging of the population.¹⁻³ The characteristics of our study population were: older age, predominance of women and high proportion of concomitant treatment with NSAIDs and SYSADOAs (in both groups, 20 mg and 40 mg), which represented the expected population in standard clinical practice. IA-HA is often administered to symptomatic patients with moderate disease who do not respond to initial oral treatment.¹⁻³

The weekly administration of lower doses (20 mg) was the most common (76%) dosing schedule of IA-HA in this study, reflecting the standard practice in our country. Efficacy evaluated six months after treatment showed a significant improvement in the Likert scale for both groups (20 mg and 40 mg): 61% and 66% of patients, respectively, had an improvement of 50% or more with respect to the beginning of the treatment. Results show a clinically relevant effect consistent with the results obtained from randomized controlled trials and several meta-analyses.⁸⁻¹⁴ The studies included in the meta-analyses have different follow-up periods (from one day to one year after the last injection) and several control arm designs (placebo, IA steroids and nonsteroidal anti-inflammatory drugs). Combined analyses of the effects of HA compared to placebo support the efficacy of HA for treating knee osteoarthritis, improving patient's pain, functional status and overall condition. The benefit was observed in different timepoints, but especially at 5-13 weeks of the injection and, to a lesser extent, at 14-26 weeks.⁸⁻¹⁴

In our study, patients treated with the lowest weekly dose (20 mg) received significantly more injections (median: 5) than those treated with the highest dose (40 mg) (median: 3, $p < 0.001$) administered at different intervals according to each physician's standard practice. The baseline Likert score was the most important independent response predictor (OR: 2.14), possibly related to a regression to the mean in patients with moderate knee osteoarthritis. Younger age and shorter duration of the disease were also independently associated with the response. These results correlate with those of other studies that have shown that younger age and moderate disease (Kellgren-Lawrence's grade 2) are good prognostic factors associated with the response to treatment.^{15,16}

The effect of treatment at different doses and types of HA is controversial and a current research topic. In the regression analysis, no significant differences were found in the response rate according to the dose (20 or 40 mg): only one trend towards a greater benefit was observed in the group treated with the highest dose. There were also no differences in the number of IA-HA injections after adjusting for other variables (age, duration of the disease and baseline score). The trend towards a greater response in the higher dose group may have clinical significance and warrants further prospective controlled trials with a follow-up of three to six months.

Evidence from meta-analyses suggests that there is considerable heterogeneity in the clinical response that may be due to the different therapeutic effects of various HA products, dosing schedules, and study designs.¹⁷⁻¹⁹ A recent single-dose controlled study showed a greater reduction in pain score as measured by a visual analogue scale and an improvement in WOMAC stiffness score at six months with high doses of HA compared to lower doses.²⁰ However, another randomized controlled study which compared frequent administration (up to three per week) of high doses of HA found no difference in WOMAC pain score at six months compared to lower doses.²¹

These findings are supported by the meta-analysis of Concoff *et al.*¹⁹, who studied the efficacy of multiple HA injections by comparing single doses and IA saline. This study showed that two to four and ≥ 5 injections of HA relieved the pain compared to IA saline, whereas a single injection did not. The greatest benefit was achieved with the regimen of two to four injections at three months and, to a lesser extent, at six months of follow-up, with no subgroup difference in relation to the total dose administered.¹⁹

Very few treatment-related adverse events and serious adverse events were reported (all reactions at the injection site), most likely due to information bias related to the lack of registration of treatment-related mild adverse events on the case report form during the retrospective review of medical records. However, the analysis of HA controlled studies has consistently shown that the application of IA-HA is safe and has a low incidence of adverse events and serious adverse events (mainly reactions at the injection site), and have concluded that there are no safety concerns arising from the treatment with IA-HA for knee osteoarthritis.^{8-14,19}

One limitation of our study is that it is a non-interventional, retrospective, observational cohort study, which has multiple biases, such as screening and information, due to the collection of secondary data during standard clinical practice and a limited follow-up of six months. There may be a bias in the evaluation of the patients' response and, since it is a retrospective study, the presence of confounding variables that have not been collected in the medical record or in the case registration form cannot be ruled out. We have also not been able to rely on a visual analogue scale and imaging studies using the Kellgren-Lawrence classification system due to the large number of physicians and the lack of systematic documentation of these variables in medical records during standard practice. However, and in line with the objective of being able to provide data from local standard practice, the large number of patients treated by approximately 400 Orthopedics and Rheumatology specialists in the main cities of Argentina is a potential strength that enhances generalization of the results.

CONCLUSIONS

Despite the inherent biases of retrospective studies, we believe that our study adds external evidence from standard clinical practice to the previously published evidence that supports the use of IA-AH in the stepwise approach to managing knee osteoarthritis. IA-HA provides a sustained benefit that lasts six months after a short course of 3-5 weekly injections and correlates with recent clinical practice guidelines.²²

Acknowledgments

We would like to thank the researchers of the MAX-ARG-13-01 study and also Raúl Bozzo, MD, of IC-Projects, who assisted in the writing and the statistical review of this paper.

Conflicts of interests: Authors have received fees as speakers on events, symposia and workshops organized by TRB Pharma SA in Argentina.
Funding: This study was funded by a research grant from TRB Pharma SA in Argentina.

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