JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 35, no. 3, 1189-1194 (2021)

LETTER TO THE EDITOR

Three-year management of hip osteoarthritis with intra-articular polynucleotides: a real-life cohort retrospective study

A. Migliore[1], E. Graziano[2], L.S.M. Martín[3], A. Sorbino[1], M. Raichi[4] and G. Boni[5]

[1]Rheumatology Unit, S. Pietro Fatebenefratelli Hospital, Rome, Italy; [2]Department of Orthopaedics and Traumatology, Cardinal Massaia Hospital, Asti, Italy; [3]Department of Internal Medicine, Sant'Eugenio Hospital, Rome, Italy; [4]Clinical Pharmacology consultant; [5]Italian Sports Medicine Federation, Umbria Region chapter, Perugia, Italy

Received April 15, 2021 – Accepted June 16, 2021

To the Editor,

The Global Burden of Disease 2010 study certified hip and knee osteoarthritis (OA) as the 38th most potent influence on Disability-Adjusted Life Years (DALYs) among 291 disorders investigated (1). The overall prevalence of radiographic hip OA is about 27.0% after 45 years, with a lifetime risk for symptomatic hip OA of 18.5% for men and 28.6% for women (2).

Intra-articular hyaluronic acid (HA) has been the cornerstone of non-surgical OA management since the 1990s. However, as recently as 2019, evidence-based guidelines and consensus reports have long debated its actual value (3). In addition, the strong viscosupplementation efficacy of HA might not be enough, as it is not complemented by similarly strong inflammation-modulating, anti-fibrotic, and pro-trophic properties (4). Natural-origin polynucleotides are fragments of hydrophilic linear DNA chains, highly purified from trout gonads with technologically advanced procedures to minimize contaminants and known with the acronym PN-HPT™ (HPT™, Highly Purified Technology). Both PN-HPT™ and high-molecular-weight HA have persistent viscosupplementation properties (5); PN-HPT™ also have trophic and bio-restructuring properties on chondrocytes, which might conceivably help slow the joint damage progression, while pain control after PN-HPT™ intra-articular injections is also more vigorous and rapid compared with HA (5). PN-HPT™ is thus a candidate as an alternative, or at least a complementary option, to intra-articular HA in addition to the usual OA core treatments such as structured exercise programs, weight management and non-steroidal anti-inflammatory drugs (NSAIDs).

This paper illustrates the real-life clinical evolution over three years of a retrospective cohort of hip OA patients treated with an intra-articular PN-HPT™ formulation as the cornerstone of their non-surgical OA disease management.

MATERIALS AND METHODS

Study design and retrospective cohort population

This is a retrospective cohort post-marketing study on hip OA patients formerly treated with intra-articular single injections (indefinitely about every six months) with a PN-HPT™ Class-III CE-marked (0373) medical device (Condrotide®, Mastelli Srl, Sanremo, Italy), available as pre-filled, single-use, neutral glass 2-mL vial-syringes with a PN-HPT™ concentration of 40 mg in 2 mL. The

Key words: hip osteoarthritis; intra-articular injection; Lequesne index; polynucleotides; PN-HPT™

Corresponding Author:
Prof. Alberto Migliore,
Department of Internal Medicine,
Ospedale S. Pietro Fatebenefratelli,
Via Cassia 600, 00189 Rome, Italy
Tel.: +39 (0)6 33581
e-mail: migliore.alberto60@gmail.com

0393-974X (2021)

retrospective review of individual baseline and sequential outcome data archived in the ANTIAGE osteoarthritis management register was the study core (6), with a random selection of hip OA patients who satisfied the predefined inclusion criteria as the retrospective cohort. The selected patients began their treatment with intra-articular PN-HPT™ between January and November 2017 with a three-year follow-up.

The retrospective study design did not consider the stratification of enrolled patients to minimize unknown confounding factors. According to cohort size estimates, the rationale for this design choice was the relatively small number of patients who would be required, even in a real-life setting, to arrive at some preliminary outcomes.

All patients signed an informed consent form and consented to eventual anonymous publication of the study outcomes. A preemptive general ethics approval by the ANTIAGE Institutional Review Board (Ethics Committee of Azienda Ospedaliera San Camillo Forlanini, Rome, Italy) covered all retrospective research activities related to the ANTIAGE register and is available on request.

Patient selection, study procedures and data management

Patients from the ANTIAGE register had to satisfy the following conditions for inclusion in the retrospective cohort: age ≥40 years, monolateral or bilateral symptomatic hip OA according to the ACR criteria (7) of at least 1-year duration or mild to moderate hip OA Kellgren-Lawrence grade 2 or 3 (confirmed on a non-weight bearing X-ray taken no more than six months before the first PN-HPT™ intra-articular injection); baseline score pain at the affected hip more severe than 4.0 (10-cm VAS); up to 36 months of follow-up. Criteria leading to exclusion from the retrospective cohort were concomitant intake of oral anticoagulants, lack of visible articular space at radiological or ultrasound assessment, clinically significant comorbidities (e.g., rheumatologic disease, inflammatory or auto-immune diseases), hypersensitivity to PN-HPT™, chronic systemic steroid treatment, local skin infection or disease at target hip.

Finally, all ANTIAGE patients included in the retrospective cohort should have received ultrasound (US)-guided intra-articular treatment, the entire content of two 2-mL vials of CONDROTIDE® for a total of 4 mL and 80 mg PN-HPT™ every six months (also patients showing improvements in clinical parameters). The protocol allowed up to two additional injections per year if clinically required, with no more than one additional injection in any three months. The US-guided technique avoided all risk of lesions and extra-articular content dispersal (6, 8).

The baseline and follow-up assessments were based on a standard 10-cm Visual Analogue Scale (VAS) for pain, the 11-item Lequesne Index score (9), NSAID intake (days per month), and on the Global Medical Assessment (GMA) and Global Patient Assessment (GPA) scores. Control standard X-rays were taken every 24 months. According to the described inclusion and exclusion criteria, the data extraction from the digital ANTIAGE register occurred in February 2020.

The frequency of pain and functional assessments was every three months for the whole 36-month follow-up period following the standard real-life clinical routine in each author's institution. The paper reports the 6-month pain and functional outcomes. Dropouts were patients lost to control or to the injection sessions; patients referred to other clinical institutions; deceased patients; patients undergoing a total hip replacement.

Previous double-blind studies with intra-articular polynucleotide injections in OA management, with the most careful attention to pain, were the basis for estimating the retrospective cohort size (5). The expected attrition of enrolled cohort patients was also considered, based on available medium-term, real-life-like studies (5). The OA nature and discomfort and the study's exploratory nature tentatively made spontaneous losses to follow-up projected to less than 20% after one year and less than 40% after 24 months acceptable. That assumption led to an estimated 40 hip OA patients at least being retrospectively enrolled to get a reasonable estimate of long-term efficacy over a follow-up period of at least 36 months.

All the authors directly involved carried out all activities with standardized procedures, including baseline and follow-up Lequesne and VAS scoring interviews and registration of outcomes in the ANTIAGE register. The principles of the Declaration of Helsinki were always respected.

Statistical analysis

Estimated descriptive statistics included sample means ± standard error of the means, ranges and numerosity for continuous variables, and count and proportions for discrete variables.

The general linear model for repeated non-parametric

measures (Kruskal–Wallis one-way analysis of variance on ranks) after correction of means for age, body mass index and Kellen-Lawrence grade was the basis of inferential statistics. Pairwise post-hoc Mann-Whitney multiple comparisons identified the study parameters' divergence points during the follow-up (stochastic domination *vs* baseline) without Bonferroni correction. Inferential statistics were applied only to data gathered every six months.

RESULTS

Table I details the demographics of the retrospective cohort of 43 hip OA patients; The number of dropout patients every 12 months and the leading dropout reasons at the end of the 36-month follow-up period are detailed in Table II.

Visual Analogue Scale (VAS, 0-10 cm)

Hip pain (mean VAS scores) almost halved after six months compared with baseline (from a mean of 4.94 to 2.64 or –46.6%, <0.05), and more than halved after 12 months down to a mean of 2.38 or –51.8% (Fig. 1). The pain remained steady on average over the second year of follow-up (mean VAS scores, 2.41 and 2.40 after 18 and 24 months, respectively), then fell steadily again up to the end of the 36-month follow-up (sequential mean VAS scores: 2.19 after 30 months and 2.10 after 36 months or –57.5% ($p < 0.01$ *vs* baseline after 24 and 36 months).

NSAID consumption

The NSAID intake significantly fell from 4.42 days per month at baseline down to 2.74 days per

Table I. *Description of the retrospective cohort at baseline (VAS, visual analogue scale; GMA, Global Medical Assessment; GPA, Global Patient Assessment).*

Retrospective cohort demographics	
Enrolled patients (baseline, n)	43
Males	20 (46.5%)
Females	23 (53.5%)
Cohort mean age (years)	60 ± 18.5
Males (years, mean)	61 ± 18.9
Females (years, mean)	59 ± 17.8
Cohort mean weight (kg)	71 ± 10.1
Males (kg, mean)	72 ± 10.9
Females (kg, mean)	68 ± 9.9
Cohort mean height (cm)	162 ± 7.1
Males (cm, mean)	166 ± 8.4
Females (cm, mean)	157 ± 6.7
Kellgren–Lawrence grades	162 ± 7.1
Second grade	47%
Third grade	53%
Smokers	13 (30.2%)
Lequesne Index (mean)	7.51 ± 2.6
Pain VAS (mean)	4.94 ± 1.3
NSAID intake (days/months, mean)	4.42 ± 4.3
GMA (mean)	4.68 ± 1.34
GPA (mean)	5.23 ± 1.84

Table II. *Reasons leading to drop out over the 36-month retrospective follow-up.*

Dropout history	
Retrospective cohort (baseline, n)	43
Dropped-out patients after:	
12 months	7
24 months	15
36 months	22
THR and surgery	11
Lost to follow-up	9
Deaths	2

month after six months (–38.0% *vs* baseline; p <0.05), 2.41 days per month after 18 months (–45.8% *vs* baseline: p <0.01), 2.17 days per month (–50.9% *vs* baseline; p <0.001) at the end of the 36-month study (Fig. 1). Regarding the NSAIDs administered, diclofenac sodium (50-mg or 100-mg tablets or 75-mg vials) was the agent of choice to control pain; ibuprofen (400-mg or 600-mg tablets or 400-mg vials) or etoricoxib (60-mg or 90-mg tablets or 120-mg vials) were the leading alternatives.

Lequesne Index

The mean Liquesced algofunctional Index score significantly improved over the first six months of follow-up (from 7.51 at baseline down to 4.61 or –38.6% *vs* baseline; p <0.05) (Fig. 1). Differently from the mean VAS scores, the hip function appeared to improve over the second year of follow-up as reflected by the steadily falling mean Lequesne scores (4.43 after 12 months or –41.0% *vs* baseline; p <0.01, 3.98 after 18 months, and finally 3.76 or –49.9% *vs* baseline after 24 months). The hip algofunctional performance slowly kept improving up to the end of the 36-month follow-up period (means of 3.33 after 30 months and 3.29 at the end of the 36-month study (respectively, –55.7% and –56.2% *vs* baseline; p <0.001).

Global medical assessment

The overall structured medical assessment of hip pain and function showed a steady improvement over 36 months (Fig. 2): from a mean GMA score of 4.68 at baseline to 2,67 after six months (–42.9% *vs* baseline; p <0.05), 2.18 after 24 months (–53.4% *vs*

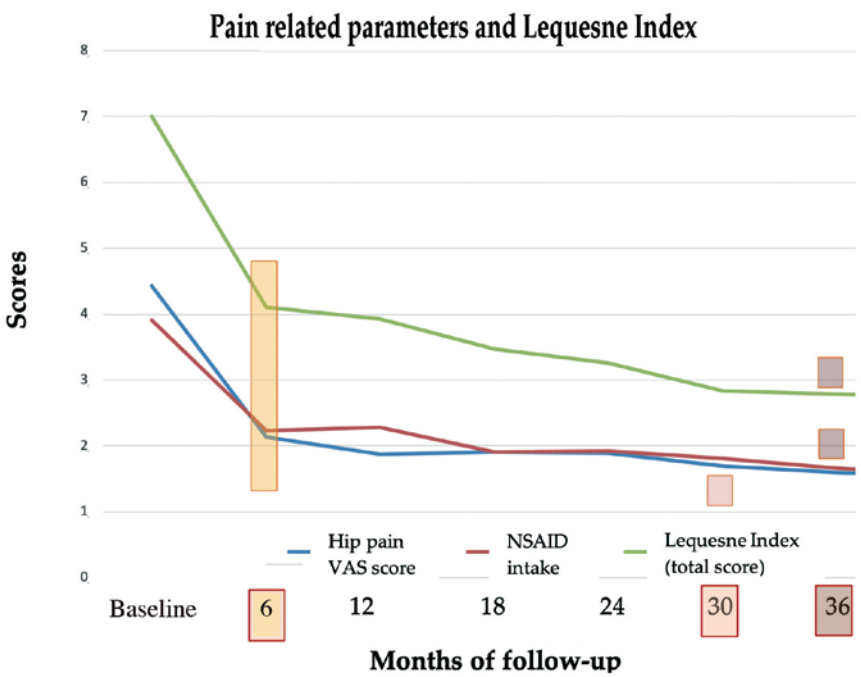

Fig. 1. *Evolution of the mean hip pain VAS scores, mean NSAID consumption (days per month) and mean Lequesne Index scores over the 36 months of the study. Yellow box (month 6, all parameters): p <0.05 vs baseline; light red marker (month 30, VAS score): p <0.01 vs baseline; dark red marker (month 36, Lequesne score): p <0.001 vs baseline.*

baseline; p <0.01), 1.91 after 36 months (–59.2% *vs* baseline; p <0.001).

Global patient assessment

The subjective assessment of their overall condition by the patients of the hip OA cohort also showed a steady improvement over the 36 months of the retrospective study (Fig. 2): from a mean GPA score of 5.23 at baseline to 3.12 after six months (–40.3% *vs* baseline; p <0.05), 2.76 after 24 months (–47.2% *vs* baseline; p <0.01), 2.34 after 36 months (–55.3% *vs* baseline; p <0.001).

Safety

Neither the patients nor the attending physicians reported systemic or severe local side effects. A few minor and transient local pains or burning sensations substantiated all reported side effects. The overall procedure cost, not eligible for reimbursement in Italy, and the concomitant comorbidities were the two main reasons reported in the ANTIAGE register for dropouts.

DISCUSSION

This study is the first to explore the long-term, real-life efficacy and safety data of patients with KL grade 2-3 hip OA treated with intra-articular PN-HPT™. The lack of a retrospective control group is a significant bias, although the extended three-year follow-up might partially compensate. The ANTIAGE-based design might also attenuate the lack-of-control bias; the US-guided technique eliminates a further cause of distortion due to morbidity and extra-articular PN-HPT™ dispersal (6, 8).

The present study confirms the efficacy and safety shown by PN-HPT™ in previous studies, including a recent study on knee and ankle OA (10). These studies were the rationale to recommend PN-HPT™ intra-articular injections in traumatology and sports medicine (11). The dropout rate at the end of the follow-up period (22 over three years out of 43 retrospective patients), although seemingly high, might be compatible with physiological attrition because the cost and

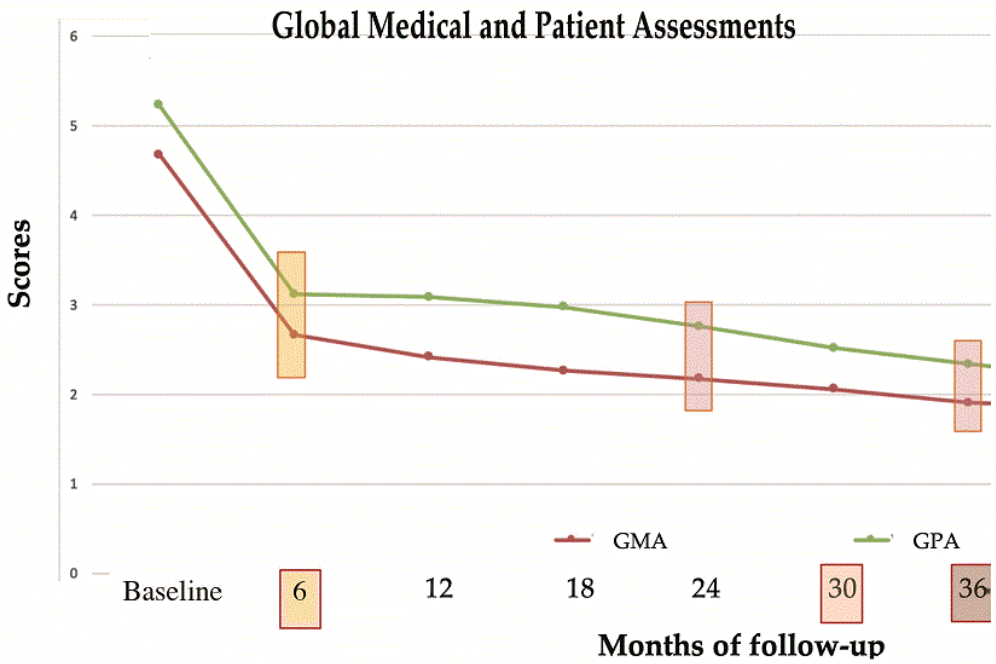

Fig. 2. *Evolution of Global Medical Assessment and Global Patient Assessment (GMA and GPA mean scores, respectively) over the 36 months of the study. Yellow box (month 6, both parameters): p <0.05 vs baseline; light red box (month 30, both parameters): p <0.01 vs baseline; dark red box (month 36, both parameters): p <0.001 vs baseline.*

concomitant comorbidities were the two most common reasons for interrupting treatment.

The study demonstrated that PN-HPT™ does not lose efficacy over time and more than two injection cycles. The steady improvement of all study parameters suggests the adopted injection protocol — 80 mg PN-HPT™ every six months, not excluding patients already showing improvements with up to two additional injections per year if clinically required — allows widely-spaced injections and might be ideal for long hip OA treatments. If needed, the dosage may be increased to 1-2 syringes per month (40-80 mg PN-HPT™ per month).

The rapid and steady improvement of pain and other parameters suggests that PN-HPT™ viscosupplementation and relief of symptoms are likely helpful in all age groups. Pain, NSAID intake, and other parameters rapidly fell over the first six months of follow-up, and all parameters steadily progressed over the residual 30 months of follow-up.

Further studies will be helpful to identify the predictors of response, therapy persistence, and long-term improvements following the short-term progress achieved after six months.

ACKNOWLEDGEMENTS

Mastelli S.r.l., Sanremo, Italy, is the producer of polynucleotides HPT™ (Highly Purified Technology) and Condrotide®, the formulation of polynucleotides for intra-articular injection investigated in this 3-year retrospective study. The authors wish to acknowledge the contribution of Mastelli S.r.l. for financial support of the publication.

Conflict of interest statement

Prof. Alberto Migliore received grants from PFIZER, ABBVIE, MSD, FIDIA, SANOFI, IBSA for national and international studies and courses. All other authors declare they have no conflict of interest. Support with the article processing is the only funding provided by the corporate sponsor, Mastelli S.r.l., Sanremo, Italy.

REFERENCES

1. 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):1323-30.
2. Lespasio MJ, Sultan AA, Piuzzi NS, Khlopas A, Husni ME, Muschler GF, Mont MA. Hip osteoarthritis: a primer. Perm J 2018; 22:17-084.
3. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27(11):1578-89.
4. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab 2015; 12(1):31-3.
5. Giarratana LS, Marelli BM, Crapanzano C, et al. A randomized, double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronan viscosupplementation. Knee 2014; 21(3):661-8.
6. Migliore A, Tormenta S, Laganà B, et al. Safety of intraarticular hip injection of hyaluronic acid products by ultrasound guidance: an open study from ANTIAGE register. Eur Rev Med Pharmacol Sci 2013; 17(13):1752-9.
7. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34(5):505-14.
8. Qvistgaard E, Kristoffersen H, Terslev L, Danneskiold-Samsøe B, Torp-Pedersen S, Bliddal H. Guidance by ultrasound of intra-articular injections in the knee and hip joints. Osteoarthr Cartil 2001; 9(6):512-7.
9. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatology 1997; 24(4):779-81.
10. Guelfi M, Fabbrini R, Guelfi M. Polynucleotide intra-articular treatment of knee and ankle osteoarthritis: prospective case record cohort vs historical controls. J Biol Regul Homeost Agents 2020; 34(5):1949-53.
11. Boni G, Giannini S, Beltrami G, et al. Recommendations by the experts of intra-articular therapy in athletes emerging from the FMSI Consensus Conference. Medicina dello Sport (Official Journal of the European Federation of Sports Medicine Associations) 2020; 73(3):473-502.