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Efficacy and Safety Of Intraarticular Therapy with Cross-Linked Hyaluronic Acid in Patients with Knee Osteoarthritis

Vincenzo Rania [1], Gianmarco Marcianò [1], Cristina Vocca [1], Caterina Palleria [1], Luigi Bianco [1], Antonio Leo [1,2], Rita Citraro [1,2], Giovambattista De Sarro [1,2] and Luca Gallelli [1,2]

[1] Operative Unit of Pharmacology and Pharmacovigilance, "Renato Dulbecco" University Hospital, 88100 Catanzaro, Italy

[2] Research Center FAS@UMG, Department of Health Science, University Magna Graecia, 88100 Catanzaro, Italy

* Correspondence: Luca Gallelli MD, PhD Department of Health Sciences, University "Magna Græcia" of Catanzaro, Clinical Pharmacology and Pharmacovigilance Unit, "Renato Dulbecco" University Hospital Viale Europa 88100 Catanzaro, Italy; gallelli@unicz.it; Tel +390961712322

Abstract: Introduction: Knee osteoarthritis (OA) is degenerative chronic disease, characterized by the reduction of articular cartilage with the insurgence of pain and functional limitations. Clinical management includes lifestyle change, analgesic use, intraarticular injections, and, as a last option, surgery. In this setting, intra-articular injections of hyaluronic acid (HA) are a relevant and diffused therapeutic option. Materials and Methods: In this prospective observational study a cross-linked high molecular weight hyaluronic acid (DIART ONE 90 mg in 3 mL) was administered in single injections to 50 patients aged 18-65 years, with a follow-up at 3, 6, and 12 months. Several scores were evaluated, including the Knee Injury and Osteoarthritis Outcome Score as the primary outcome measure and the Visual Analogue Scale, Time Up and Go Test, Six-Minute Walking Test, General Health Assessment with 36-Item Short Form Health Survey, Zung's Self-Rating Anxiety Scale, and Zung's Self-Rating Depression Scale as secondary outcome measures. Results: We observed a statistically significant improvement in clinical scores at 3 and 6 months, with a reduction of clinical benefit at 12 months. Functional and psychological benefits were significant at 3, 6, and 12 months. No side effects were described except pain associated in the site of injection. Conclusion: we documented that cross-linked high molecular weight hyaluronic acid (DIART ONE 90 mg in 3 mL) represents an effective option in the management of mild-moderate osteoarthritis.

Keywords: hyaluronic acid; single injection; cross-linked; knee osteoarthritis**.**

1. Introduction

According to the Global burden of Disease study, the age-standardized point prevalence and annual incidence rate of osteoarthritis in 2017 were 3754.2 (95% UI 3389.4 to 4187.6) and 181.2 (95% UI 162.6 to 202.4) per 100 000, an increase of 9.3% (95% UI 8% to 10.7%) and 8.2% (95% UI 7.1% to 9.4%) from 1990. The global prevalence estimate was higher in women and increased with age, peaking at the >95 age group for both women and men in 2017 [1].

The number of people affected with symptomatic knee OA is likely to increase because of the aging of the population and the obesity epidemic [2]. Although the disease pathophysiology is not completely understood and under investigation, it is accepted that knee OA has a multifactorial origin inducing articular cartilage damage, bone osteophyte formation, and sclerosis of the subchondral bone, and in advanced cases, subchondral cyst formation [3].

The most common symptom of knee OA is continuous or intermittent pain usually related to the severity of articular damage, with swelling, locking, and giving as common related symptoms [4,5].

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Diagnosis is based on clinical examination, and imaging studies e.g. ultrasonography, radiography, computed tomography and magnetic resonance imaging [6].

According to the international recommendations, the management of knee OA is chosen considering the patient's characteristics, degree of severity of the OA itself, and the pain related to it and requires a combination of non-pharmacological and pharmacological treatments [7–11]. Even if systemic drugs can be used to reduce pain, they could be associated to relevant side effects, especially when used in a chronic setting [12].

Therefore, topical intra-articular injections represent an important option depending on both joint characteristics and practitioner skills. Among the injective therapeutic options, corticosteroids, hyaluronic acid (HA), and platelet-rich plasma are the most common [7,13].

Hyaluronic acid is a polysaccharide exerting important actions in synovial fluid and cartilage, including lubrication, protection of cartilage, and shock absorption of the joint [14]. Formulations of HA may vary for their weight (low or high), presence of cross-linking, number of injections and production source [15]. Its action is not limited to mechanical properties, but it can provide a great variety of anti-inflammatory effects through its binding to CD44 type I transmembrane glycoprotein [15–17].

Hyaluronic acid intraarticular injection is a cornerstone of knee OA management since it provides symptom relief and delays time to prosthesis implant with low adverse drug reactions [18] that are commonly represented by local pain or infections increasing with repetitive administrations [14,19].

Therefore, the administration of a single injection of a cross-linked high molecular weight (HMW) HA could be useful to improve the clinical symptoms in patients with OA, reducing the ADRs. Cross-linking is a chemical process that modifies the natural straight-chain structure of the molecule, producing an entangled HA molecule. This structural change may substantially increase the effectiveness of HA formulations [15].

In this study we evaluated the efficacy and the safety of the intraarticular injection of a cross-linked high molecular weight hyaluronic acid in improving symptoms and function of patients with OA.

2. Materials and Methods

2.1. Study Design

This is a prospective observational longitudinal single-center clinical study on knee OA patients treated with cross-linked HA at the Pain Medicine Room of the Clinical Pharmacology and Pharmacovigilance Operational Unit of the “Renato Dulbecco” University Hospital of Catanzaro from January 2023 to June 2024. Patients were enrolled at baseline (T0) and then were monitored at 90 days (T1; 3 months), 180 days (T2; 6 months), and 360 days (T3; 12 months). At the beginning of the study, all enrolled patients signed the informed consent before admission to the study.

The study was conducted in accordance with guidelines of the 1964 Declaration of Helsinki and its later amendments, and with full respect for privacy as per Italian law (Ethic Committee authorization: 120/2018).

2.2. Patients

In this study, patients were enrolled, according to the following eligibility criteria:

1) Patients of both sexes between 18 and 65 years old, with a Body Mass Index lower than 29 kg/m2.
2) Patients with second- or third-degree of OA, according to the Kellgren-Lawrence classification on a weight-bearing radiograph of the knee no older than one year.
3) Patients with VAS (Visual Analogue Scale) intensities higher than 5/10 who did not respond to systemic medication therapy.
4) Patients who can comprehend the study's objectives and (adhere to the orthopedist's instructions, return for follow-up, and complete the evaluation questionnaires).

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5) Patients able to provide their written informed consent to participate to the study and to use their data anonymously for scientific purposes

Patients under 18 years of age were excluded. Othe exclusion criteria were:

1) presence of active malignancy of any type or history of malignancy
2) Grade I, mild or advanced IV arthritis according to the Kellgren-Lawrence criteria.
3) Local or systemic infection.
4) Uncooperative patient or suffering from neurological disorders, therefore unable to follow the orthopedist's instructions or unable to provide informed consent for participation in the study or who have not provided written consent.
5) Any case not described in the inclusion criteria.

2.3. Experimental Protocol

After the enrollment (T0) and during the follow ups (T1-T3), clinical and laboratory data were collected directly by the medical staff involved in the study and Zung SAS, Zung SDS and SF-36 questionnaires were administered. The dedicated database evaluated and recorded any systemic or local side effects, in agreement with our previous studies [20–22].

2.3.1. Questionnaires

The 36-Item Short Form Health Survey (SF-36), consisting of 36 questions and used to assess quality of life in relation to pathology and the effectiveness of treatment. Quality of life is defined as the subjective perception of one's own well-being within socio-cultural context or as the satisfaction of desires and pleasures. Questions are summarized in two component summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores representing eight concepts of health: physical functioning (PF), bodily pain (BP), role limitations due to physical health problems (RP), role limitations due to personal or emotional problems (RE), general mental health (MH), social functioning (SF), energy/fatigue or vitality (VIT), and general health perceptions (GH). A higher score represents better health while a low score corresponds to a lower quality of life [23,24].

Zung's Self-Rating Anxiety Scale (Zung SAS), consisting of 20-items question scale that rates the four common characteristics of anxiety both psychological and somatic. Responses are given on a 4-point scale which range from 1 (*none, or a little of the time*) to 4 (*most, or all of the time*). Items include both negative and positive experiences. The final score ranges from 20 to 80 points. Anxiety is classified as normal (score 0 to 44), moderate (score 45 to 59) and severe (score 60 to 80)[25].

Zung's Self-Rating Depression Scale (Zung SDS), consisting of 20-items question scale that rates the four common characteristics of depression. Items tap psychological and physiological symptoms: 10 express negative experience and 10 express positive experience. Responses are given on a 4-point scale ranging from 1 (*none, or a little of the time*) to 4 (*most, or all the time*). Total raw scores range from 20 to 80. Depression is classified as normal (score 20 to 49), mild (score 50 to 59), moderate (score 60 to 69) and severe (score 70 to 80)[25].

2.3.2. Efficacy end points

The first efficacy end-point of this study was the statistically significant difference ($P<0.05$) in the Knee Injury and Osteoarthritis Outcome Score (KOOS) measured at follow-ups (T1-T3) respect to T0.

Secondary end points were:

- the statistically significant difference ($P<0.05$) in VAS scale between T2 and T0 and between T3 and T2
- the statistically significant difference ($P<0.05$) in functional mobility and walking ability (six minutes walking test**)** between T2 and T0 and between T3 and T2
- the statistically significant difference ($P<0.05$) in general health assessment (SF-36) between T2 and T0 and between T3 and T2

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- the statistically significant difference (P<0.05) in mood disorders (Zung SAS and Zung SDS) between T2 and T0 and between T3 and T2

2.3.3. Safety end points

During the study we recorded the development of adverse drug reactions related to the intraarticular injection of HA. We recorded the frequency, predictability, duration, severity, seriousness, course, and consequences of the adverse drug reactions, and the ADRs leading to the withdrawal of the subject from the study.

2.4. Statistical Analysis

Gaussian continuous variables were described by mean and standard deviation. Median and interquartile range were used in cases of skewness. Counts and percentages were used for categorical variables. The normal distribution of continuous variables was verified by the Shapiro-Wilk test. A T-test was used to compare normally distributed continuous variables between males and females. Non-parametric Friedman test followed by post hoc analysis using Wilcoxon signed-rank test was also applied. Data are expressed as mean ± standard deviation. For all comparisons, differences were considered significant for $p < 0.05$. Statistical analysis was performed using SPSS 22.0 (International Business Machines Corporation, Armonk, NY, USA) and JASP accessed on 10 June 2024 and 20 October 2024.

3. Results

3.1. Patients

Seventy-four patients with knee OA were enrolled between the 1 March 2023 and 31 May 2023. Twenty-four patients (32.4%) were excluded because they did not meet the study inclusion criteria. Fifty patients, 14 females (28%) and 36 males (72%), underwent the treatment and signed the informed consent (Table 1).

Table 1. Demographic characteristic of the enrolled patients. Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.

	Male	Female
Number, (%)	36 (72.0)	14 (28.0)
Age	49.44 ± 11.01	49.46 ± 12.63
BMI	25.60 ± 2.02	24.55 ± 2.91
Osteoarthritis; Kellgren-Lawrence classification	n (%)	n (%)
Stage I	5 (13.9)	2 (14.3)
Stage II	26 (72.2)	10 (71.4)
Stage II/III	2 (5.6)	0
Stage III	3 (8.3)	2 (14.3)

3.2. Effects on Pain

At T0 the mean VAS value was 7.0, the mean KOOS value was 40, Walking test was positive after 3 minutes. Time up and Go test at this time was 5 seconds. At T1 we documented a significant improvement in VAS, KOOS, and in time up and go test (Table 2).

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Table 2. Clinical and functional scales changes at T1 vs T0. Data are expressed as median (interquartile range). **P<0.01.

Score	T0	T1	P
KOOS	44.90 ± 14.10	78.71 ± 12.68**	0.000
VAS	6.90 ± 1.23	1.70 ± 1.37**	0.000
Walking test min	3.43 ± 1.60	3.71 ± 2.61	0.553
Walking test VAS	7.16 ± 1.12	1.51 ± 1.40**	0.000
Time Up and Go test	5.0 ± 2.1	3.4 ± 2.3	0.644

A further improvement in clinical symptoms was recorded at T2, that was maintained up to the next months when we recorded a significant worsening in walking ability and in the Time up and go test. At T3 we also observed a worsening in KOOS and VAS in comparison to T2 (Table 3).

Table 3. Clinical and functional data recorded at T2 (6 months) and T3 (12 months) after the admission (T0). Data are expressed as mean ± standard deviation. In bold significant values.

Score	T0	T2	P T2vsT0	T3	P T3vsT2	P T3vsT0
KOOS	40.15 ± 15.22	78.37 ± 20.54	**0.000**	48.31 ± 15.42	**0.000**	0.823
VAS	7.49 ± 2.04	1.85 ± 1.28	**0.000**	6.58 ± 2.15	**0.000**	0.796
Walking test min	3.21 ± 2.43	2.78 ± 3.52	0.732	3.01 ± 2.18	0.868	0.939
Walking test VAS	7.32 ± 1.83	1.38 ± 1.18	**0.000**	1.07 ± (3.26)	0.787	**0.032**
Time Up and Go test	5.08 ± 2.15	4.16 ± 2.34	0.856	5.23 ± 1.46	0.812	0.978

3.3. Effects on Quality of Life

SF-36 questionnaire score revealed a time-related significant improvement in the quality of life (P < 0.01) (Table 4). Compared to T0, we recorded a statistically significant (P < 0.01) improvement in the SF-36 score during the follow-ups (T1-T2) (Tables 4 and 5), with a worsening at 1 year (Table 6).

Table 4. Short Form Health Survey 36 recorded in enrolled patients 3 months (T1) after the admission (T0). Data are expressed as mean ± standard deviation. **P<0.01.

SF-36			
	T0	T1	P
Physical functioning	49.95 ± 9.35	62.28 ± 8.42**	< 0.01
Role limitations due to physical health	59.40 ± 13.21	68.60 ± 10.96**	< 0.01
Role limitations due to emotional problems	48.20 ± 5.84	61.56 ± 5.85**	< 0.01
Energy/fatigue	56.00 ± 6.55	66.90 ± 7.68**	0.001
Emotional well-being	59.50 ± 7.29	66.24 ± 13.75)	0.082
Social functioning	57.70 ± 6.73	69.30 ± 6.73**	< 0.01
Pain	47.70 ± 9.17	61.80 ± 9.80**	< 0.01

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General health	50.90 ± 11.57	54.00 ± 10.68	0.095
Health change	51.90 ± 8.02	63.20 ± 8.07**	< 0.01

Table 5. Short Form Health Survey 36 recorded in enrolled patients 6 months (T2) after the admission (T0). Data are expressed as mean ± standard deviation. *P<0.05; **P<0.01.

SF-36			
	T0	T2	P
Physical functioning	49.95 ± 9.35	60.03 ± 11.24**	< 0.01
Role limitations due to physical health	59.40 ± 13.21	65.40 ± 7.51*	0.04
Role limitations due to emotional problems	48.20 ± 5.84	61.15 ± 10.37**	< 0.01
Energy/fatigue	56.00 ± 6.55	69.82 ± 15.44**	< 0.01
Emotional well-being	59.50 ± 7.29	64.10 ± 12.56	0.091
Social functioning	57.70 ± 6.73	70.34 ± 13.45**	< 0.01
Pain	47.70 ± 9.17	65.34 ± 10.28**	< 0.01
General health	50.90 ± 11.57	55.32 ± 11.46	0.093
Health change	51.90 ± 8.02	62.38 ± 13.47**	< 0.01

Table 6. Short Form Health Survey 36 recorded in enrolled patients 12 months (T3) after the admission (T0). Data are expressed as mean ± standard deviation. *P<0.05; **P<0.01.

SF-36			
	T0	T3	P
Physical functioning	49.95 ± 9.35	55.34 ± 9.53	0.065
Role limitations due to physical health	59.40 ± 13.21	62.18 ± 12.36	0.072
Role limitations due to emotional problems	48.20 ± 5.84	62.34 ± 11.47**	< 0.01
Energy/fatigue	56.00 ± 6.55	62.67 ± 14.52	0.059
Emotional well-being	59.50 ± 7.29	65.73 ± 9.24	0.088
Social functioning	57.70 ± 6.73	67.33 ± 12.85**	< 0.01
Pain	47.70 ± 9.17	56.44 ± 10.37*	0.042
General health	50.90 ± 11.57	57.34 ± 12.48	0.075
Health change	51.90 ± 8.02	60.56 ± 15.47*	0.038

3.4. Effect on Mood Symptoms

Evaluating the effects on mood using both Zung SDS (depression) and Zung SAS (anxiety) scales, we observed a statistically significant improvement of mood disorders ($P < 0.01$) (Table 7).

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Table 7. Zung depression and anxiety scales recorded in enrolled patients 3 months (T1), 6 months (T2), and 12 months (T3) after the admission (T0). Data are expressed as mean ± standard deviation. **P<0.01.

	T0	T1	P
Depression	61.30 ± 9.85	74.30 ± 8.31**	< 0.01
Anxiety	56.60 ± 8.53	35.90 ± 9.51**	< 0.01
	T0	T2	P
Depression	61.30 ± 9.85	76.50 ± 13.82**	< 0.01
Anxiety	56.60 ± 8.53	32.35 ± 12.72**	< 0.01
	T0	T3	P
Depression	61.30 ± 9.85	71.42 ± 11.28**	< 0.01
Anxiety	56.60 ± 8.53	37.44 ± 9.51**	< 0.01

Moreover, statistical evaluation of the data recorded in T3 vs T2 revealed a statistically significant worsening of symptoms (P<0.01) since the patients reported an improvement of the symptoms respect to the admission.

3.5. Safety

We did not document any adverse drug reaction during the study, except for 3 patients experiencing injection site pain, which did not impair study adherence.

4. Discussion

In the present study, we documented that in knee OA patients, the injection of DIART ONE (90 mg in 3mL) induced an improvement of clinical symptoms without the development of adverse drug reactions.

Several years ago, Chevalier et al. [26] compared the effect of a high molecular weight (average 6000 kDa) cross-linked HA to placebo (the two treatments administered after arthrocentesis) documenting a nearly statistically significant difference in primary outcome (p=0.047), and in WOMAC A1, PGA, and COGA. Safety was comparable (slightly superior in the HA group) between the two groups, with joint effusion, joint stiffness, joint swelling, and arthralgia as the most common adverse events. It is noteworthy to observe that no significant improvement in WOMAC C (function) was observed in the study, but only in the post-hoc analysis.

Strand et al., [27] obtained similar results with the single injection of Gel-200 or saline solution in 379 knee OA patients. In fact, they reported that efficacy was higher for hyaluronic acid formulation until week 13 for WOMAC pain subscore (P=0.037) and over weeks 3-13 for WOMAC total score, physical function, and physician global evaluations (P < 0.05).

Petterson et al., [28] in 369 knee OA patients showed the complete effectiveness using a single-injection hyaluronic acid in comparison to saline solution (0.9%). The authors showed an overall statistically significant superiority compared to saline solution (p=0.043). Clinical improvement was observed from week 2. Interestingly, primary outcome clinical benefit was higher in the first weeks, with a progressive loss of statistical significance from week 8 (p=0.090) vs saline. Nevertheless, clinical symptoms improvement in comparison to baseline was observed at week 26. Safety (few adverse events like swelling and pain) was similar between the two groups. Furthermore, the authors compared this formulation to Orthovisc™ a three formulation HA, analysing data from other studies. Monovisc™ was generally non-inferior or superior when compared to Orthovisc™. Authors also observed that Monovisc™ had better clinical results if compared to the previously tested single

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injection HAs. The authors discuss also the role of saline solution (placebo) in improving clinical outcome. In fact, joint lavage, dilution of inflammatory mediators, cleaning of joint debris may account for the minimal statistical significance of the results and for the biological effect of placebo, also in agreement with the results of Concoff and colleagues [29], highlighting the similarity between placebo and single injection effects and the major efficacy of multiple injections.

HA formulations were compared by Bahrami et al., [30] based on their molecular weight as well. Ninety patients were randomized to receive a single injection of high molecular weight (HMW) cross-linked HA (Arthromac) or three weekly injections of low molecular weight (LMW) HA (Hyalgan). Prior to injection, as well as at two and six months, clinical results were assessed using WOMAC, Lequesne, and VAS. Apart from the WOMAC stiffness subscale, which was noticeably improved in the LMW-HA group ($p = 0.021$), the two groups demonstrated similar efficacy.

An interesting study by Perruchet et al., [31] evaluated in 51 patients the factors conditioning patients responses to a single injection of extended release (HA HANOX-M-XL). The primary outcome was duration of effectiveness (DE) self-measurement. They assessed the variables influencing 51 patients' reactions to a single extended-release injection of HA HANOX-M-XL. Duration of effectiveness (DE) self-measurement was the main result. They found that, like gender (longer duration in men, P=0.02) and older age (P=0.04), K-L grade was a significant factor in determining DE (P=0.007). For almost a year, even patients with severe OA demonstrated improvement. Patients with K-L III and IV did not have different outcomes, despite the fact that the latter typically requires surgery. This outcome most likely stems from the inclusion of participants who had previously received cycles of HA injections and those who did not exhibit severe symptoms. Additionally, contrary to previous research, obesity and body mass index were not linked to a worse outcome.

A recent paper by Safali et al., [14] compared two different dosages of HMW HA (SEMICAL®) triple 30 mg injections with one-week interval and 60 mg single injections in 128 patients. Lequesne Score, VAS and WOMAC were evaluated showing more favourable results for the 30 mg formulation (follow up period of a year), despite both formulations being highly effective. Nevertheless, this result may be associated with this specific formulation only and with the different total dosage (90 mg vs. 60 mg). Other reasons indicated by the authors are a sustained release of HA related to multiple doses with repeated anti-inflammatory and chondroprotective effects and the better HA distribution related to low-dose injections. However, the authors themselves acknowledge the study's several shortcomings, such as its retrospective design, lack of a comparison group with a different molecule, and the selection of a population between the ages of 50 and 60. This paper is in disagreement with other previous studies like that of Conrozier et al. [32] that showed a comparable efficacy of single vs triple injection of HMW HA (hylan G-F 20) with the same total dosage. The advantage of a single injection becomes clear in patients managed with anticoagulants, busy subjects or those not tolerating three injections.

HA treatment has anti-inflammatory properties in addition to mechanical activity in articulations. Although HA interacts with other structures such as lymphatic vessel endothelium receptor 1, Intercellular Adhesion Molecule, Receptor for hyaluronan-mediated motility, and tool like receptors, the primary receptor for HA is CD44. The cascade that results from the binding of HA and CD44 has subchondral, chondroprotective, anti-inflammatory, and proteoglycan production effects. There is a decrease in the breakdown of joint cartilage and a decrease in interleukin-1β and metalloproteinases [33].

The recent analysis of the available papers by Ferkel et al. [15] showed that HMW-HA has a greater probability of modulating this pathway than LMW and greater clinical efficacy, especially after 3 and 6 months. Nevertheless, no comparison between single injections and triple injection HMW-HA has been made. The same authors observed that avian-derived and cross-linked HA were associated with a higher inflammatory reaction if compared to non-avian and non-cross-linked HA. Cross-linking determines a different interaction with CD44 and a gel-like state that is different from human HA. Despite this, cross-linking may confer an advantage due to its rheological properties and increased residence in the joint.

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Rutjes and colleagues [34] observed that cross-linking determines better clinical outcomes. Nevertheless, it has not been proven if this effect is related to cross-linking or simply to HMW, and studies comparing similar-weighted (cross-linked vs. non-cross-linked) HA are lacking.

Few clinical studies were designed to compare the different formulations of IA-HA produced by different companies. It would be very important to understand structural differences and their impact on the differential pharmacodynamic effect. The differential molecular weight, dosage, number of injections, cross-linking, and source used to create the IA-HA are all key points to consider in these studies. This kind of analysis is very expensive and needs a long time to be performed and may not always produce clear results [35].

Ranawat et al. [36] confirm that hyaluronic acid injections have an advantageous economic profile considering their implications: reduced use of opioids, NSAIDs and corticosteroids; delay of total knee arthroplasty; reduced absence from work; lower expense for patients and healthcare. Among all HA formulations the authors suggest Bio-HA as the best considering cost/effectiveness. No specifical comparison of single injection and triple injections has been made in this paper. A single injection is certainly less expensive than three injections and may be an interesting solution for low-income patients, especially considering its superiority to placebo in the forementioned clinical studies.

It is not futile to remember that intraarticular injections are only a part of knee OA management. In fact, their utility may be limited if patients do not follow a healthy lifestyle, including weight loss, exercise, and diet. Conversely, pain may prevent patients from doing physical activity and therefore a combination therapy is generally the best choice. Factors like obesity may also theoretically reduce HA efficacy [37].

Our paper is the first, to our knowledge, to analyze also psychological improvements before and after injection of HA in knee OA. Despite the good basal emotional well-being of our patients, we testify to a substantial improvement of anxiety and depression, typically associated with chronic pain [38]. The improvement at T1 and T2 is comparable to other effective HA formulations. Perhaps an intermediate measure between T2 and T3 would have demonstrated a longer clinical benefit. Our study has several limitations. Firstly, our work was not placebo-controlled to notice a statistically significant difference between DIART ONE (90 mg in 3 mL) and saline solution. Secondly, we did not compare single injection with triple injection formulation of the same molecule. Thirdly, the number of patients is relatively low and needs to be increased in a multicenter context, avoiding the possible bias related to physician ability.

5. Conclusion

According to our research, intra-articular single cross-linked hyaluronic acid therapy is a legitimate, secure, and successful conservative therapeutic choice for OA. The therapy is well-tolerated and helps patients improve their mobility and pain management. Adverse effects associated with repeated injections are less likely when a single injection is used. Patients with symptomatic knee OA between the ages of 18 and 65 who may choose an alternate treatment option and who are not candidates for partial or total knee replacement can benefit from a single injection of hyaluronic acid (DIART ONE), according to the study's findings.

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