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EFFECTIVENESS AND SAFETY OF INTRA-ARTICULAR HYALURONIC ACID IN ATHLETES WITH ARTICULAR LESIONS: A MULTICENTER, PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: To evaluate the effectiveness and safety of a novel intra-articular formulation of hyaluronic acid (HA) to treat athletes with articular lesions. Methods: Multicenter, prospective, interventional, observational study analyzing the clinical evolution of athletes who received 2 or 3 intra-articular injections of HA. The study was scheduled in Visit 1 (week 0), Visit 2 (week 1), Visit 3 (week 2), Visit 4 (week 3), and Visit 5 (end of follow-up, week 24). The change in Visual Analog Scale (VAS) of pain and in Knee Injury and Osteoarthritis Outcome Score (KOOS) and the rate of return to physical activity were evaluated upon treatment initiation for up to 24 weeks. The incidence of adverse events was recorded throughout the study. Results: Sixty patients were recruited: 28 (46.7%) in the 2-injection group and 32 (53.3%) in the 3-injection group. Mean VAS gradually decreased across the visits, with statistically significant reductions in both groups from Visit 2 to Visit 3 and to Visit 5 ($P < 0.0001$). Inter-group differences in the change in VAS from Visit 2 to Visit 5 were statistically comparable ($P = 0.8271$). At Visit 5, the KOOS of all subscales statistically improved in both treatment groups. At the end of follow-up (Visit 5), 75.9% of patients returned to sport in the overall population. Only one patient reported an adverse event. Conclusion: This novel formulation of HA is effective and safe for at least 24 weeks, resulting in a promising treatment option for athletes with articular lesions.

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Introduction. Articular lesions are a major source of pain and disability and represent a serious burden for patients and healthcare systems [1]. Given its multifactorial nature, different factors contribute to their development, being age the main underlying risk factor. In addition, repetitive mechanical and energetic demands exceeding articular cartilage tolerance can also result in joint degeneration [2], and explain the higher susceptibility of athletes to develop articular lesions [3]. Such articular lesions can be localized in specific joints that in the long-term tend to progress to degenerative conditions such as osteoarthritis (OA) [4]. Certainly, previous studies showed that

athletes are 12 times more likely to develop chondral defects and OA [2, 5] and that the prevalence of knee OA in former elite soccer players ranges from 60 to 80% [6].

OA is an inflammatory and chronic musculoskeletal disease and the most common form of arthritis in adults worldwide [7, 8]. The development of OA is the result of a progressive process mainly triggered by the degeneration of cartilage leading to hostile changes in joint environment [8]. This initial phase is followed by the abnormal regulation of inflammatory mediators resulting in further cartilage degeneration, apoptosis of chondrocytes, and imbalance of extracellular matrix components [9]. All this process shifts the cartilage extracellular matrix turnover towards matrix breakdown [10], and determines the main clinical manifestations of the disease: pain, stiffness, limited functionality and deformity [11].

Current guidelines to manage OA recommend lifestyle modifications, pharmacological interventions and surgery in late stages [10]. The goals of pharmacological are to manage symptoms, slow the progression into OA and delay or avoid surgical interventions. Pharmacological options include analgesics; non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase type 2 (COX-2) inhibitors, and intra-articular injections [12, 13]. However, the efficacy of these agents is limited to the management of symptoms, and is characterized by the lack-sustained effects and by the presence of adverse events [14]. Therefore, current research is focused on developing treatments with enduring effects, promoting structural changes and with a better safety profile [15].

Hyaluronic acid (HA) is a natural component of the synovial liquid produced by chondrocytes and synovial cells that promotes the maintenance of articular integrity owing to its lubricant properties [16]. The decreased HA levels found in articular lesions and OA explains the loss of lubrication and chondroprotection that accompanies these conditions [9, 17].

Therefore, the aim of intra-articular Hyaluronic Acid injections is to restore viscoelastic properties of the normal synovial fluid [18]. Based on this rationale, DIART® is a novel formulation of HA buffered in a sodium succinate solution for intra-articular administration. DIART® received the CE certification as a Class III Medical Device, showing beneficial and prolonged effects in preclinical and clinical data [19]. The aim of this observational study was to assess the effectiveness and safety of this novel formulation of HA in the treatment of articular lesions in athletic patients.

Materials and methods.

Study population.

This multinational, multicenter, open-label, prospective observational study was conducted in 4 centers in Spain and Chile. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and ethical approval was granted by the Independent Ethics Committee of Fundació Unió Catalana d'Hospitals (Barcelona, 24 Spain). Each participant provided written informed consent prior to inclusion.

Eligible patients were athletes aged 18 years or older, with a participation in sport activities of at least 5 hours/week, and with a recent (< 1 month) articular lesion detectable via ultrasounds or Magnetic Resonance (MR). Patients were excluded according to the following criteria: any surgery within the previous 3 months to study initiation, articular infection or pain unrelated to the lesion of study and previous intra-articular infiltration of corticoids, HA, platelet-rich plasma or mesenchymal cells within the last six months.

Study design.

The study lasted 24 weeks and was scheduled in 5 visits: Visit 1 (screening, week 0), Visit 2 (baseline and first injection, week 1), Visit 3 (second injection, week 2), Visit 4 (third injection, week 3), Visit 5 (end of follow-up, week 24). Clinical information was collected at baseline and longitudinally over the visits to assess the change in pain and function, the rate and time to return to physical activity, and the incidence of adverse events upon HA treatment.

At baseline (Visit 1), we exposed the nature, aims and main procedures of the study and eligible patients willing to participate provided written informed consent. At Visit 2, demographic and clinical data were collected, participants completed the Visual Analog Scale (VAS) of pain and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scale and the first injection was administered in both groups. At Visit 3, participants completed the VAS-pain, safety, concomitant treatment data were collected, and individuals of both groups received the second injection of HA. At Visit 4, participants completed the VAS-pain scale, safety data and concomitant medications were recorded and patients in the 3-injection

group received the third administration of HA. At Visit 5, participants completed the VAS-pain and KOOS scales, and safety data and concomitant medications were recorded.

Study intervention.

The study intervention is DIART®, a formulation of HA buffered in sodium succinate for intra-articular administration. Each pre-filled syringe contains 1.8% (18 mg) of HA for intra-articular injection. Patients in the 2-injection group received a total of 2 weekly infiltrations (Visit 2, Visit 3, and Visit 4) of HA; in both groups the same treatment schedule and dosage was followed. The treatment lasted 2 weeks for the 2-injection group and 3 weeks for the 3-injection group. Follow-up period was 24 weeks after treatment initiation.

DIART is a CE certified Class III Medical Device and was administered according to the EU regulation. The injections were performed by experienced medical personnel following the standard techniques for intra-articular administration.

Study outcomes.

The effectiveness of DIART was evaluated by assessing the evolution of patient-reported outcomes related to pain and function. The primary objective was to evaluate the effectiveness of DIART at reducing pain by monitoring the change in VAS from baseline (Visit 2) to the end of follow-up (Visit 5).

Secondary endpoints included: the change in VAS from baseline (Visit 2) to Visit 3, the change in KOOS from baseline (Visit 2) to the end of follow-up (Visit 5), the time and rate of return to physical activity at Visit 5, and the incidence of adverse events throughout the study.

The intensity of pain perceived by the patient was measured using the VAS, consisting of a line ranging from 0 cm (absence of pain) to 10 cm (unbearable pain). Pain is graded by the distance from the left end of the scale to the point marked by the patient according to the intensity of pain.

Symptomatology and knee function were evaluated through the KOOS scale. The KOOS evaluates both short- and long-term consequences of knee injury. The questionnaire is divided in 5 subscales: pain (9 items), symptoms (7 items), function in daily living (17 items), function in sport and recreation (5 items), and knee-related quality of life (4 items). The five subscales are scored separately in a 0-100 scale where 0 represents extreme knee problems and 100 corresponds to no knee problems [20].

Statistical Analyses.

Continuous variables were described by mean, standard deviation (SD), median, and extremes (Min, Max) for numerical variables; and categorical variables were described by number and percentage. Comparisons between two independent groups for continuous variables were performed using the Student's t-test for unpaired data or the Chi-square test for categorical variables. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SAS software for Windows, version 9.2 (SAS Institute, Cary, SC, USA).

Results.

Study population.

Sixty patients were included in the study: 28 (46.7%) in the 2-injection group and 32 (53.3%) in the 3-injection group. Among them, seven finished the study prematurely (4 in the 2-injection group and 3 in the 3-injection group) (Fig. 1).

Demographic and clinic characteristics were balanced between groups at baseline. Mean age ±SD was 42.9 ±18.0 years in the 2-injection group and 42.7 ±13.8 years in the 3-injection group ($P = 0.9681$). The proportion of males was higher in the 3-injection group (78.1%) than in the 2-injection group (57.1%), but differences were not statistically significant ($P = 0.0813$) (Table 1).

Sport professionality was homogeneous between groups, and most of the participants were classified as amateurs (89.3% in the 2-injection group and 90.6% in the 3-injection group). The time (hours) devoted to sport practice per day was 2.8 hours in both groups. Neither differences in the duration of symptoms nor in mean time from the last pain episode were statistically significant between groups ($P > 0.05$). Baseline demographic and clinical characteristics are presented in Table 1.

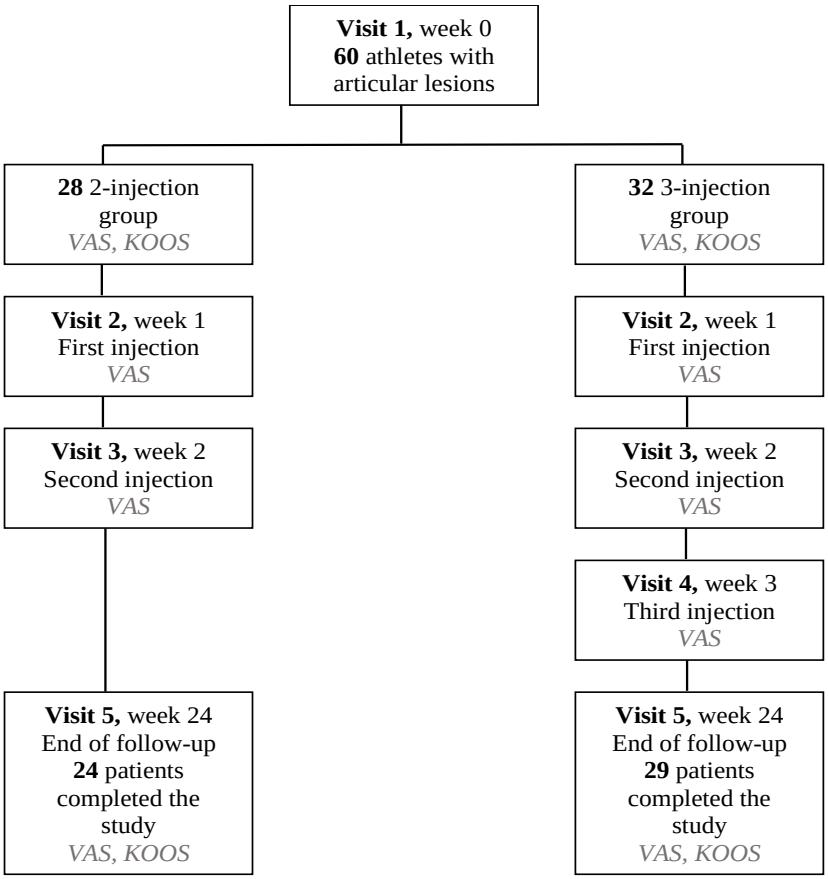

Fig. 1. Flowchart showing study design.
Abbreviations: KOOS = Knee injury and Osteoarthritis Outcome Score; VAS = Visual Analog Scale.

Table 1. Demographic and clinic characteristics at baseline. Demographic and clinic characteristics at baseline.

Variable	2 injections	3 injections	Total	P-value
1	*2*	*3*	*4*	*5*
Sex				
Male	16 (57.1%)	25 (78.1%)	41 (68.3%)	0.081
Female	12 (42.9%)	7 (21.9%)	19 (31.7%)	
Age (years)	26	31	57	
Mean (SD)	42.9 (18.0)	42.72 (13.8)	42.80 (15.7)	0.968
Median	42.3	44.7	42.9	
Q1; Q3	29.8; 56.2	35.2; 51.7	34.3; 53.2	
Sport practice level				
Amateurs	25 (89.3%)	29 (90.6%)	54 (90.0%)	
Days per week				
Mean (SD)	4.3 (1.3)	4.5 (1.4)	4.4 (1.3)	0.610
Median	4.0	4.0	4.0	
Hours per day				0.954
Mean (SD)	2.8 (2.3)	2.8 (2.7)	2.8 (2.5)	
Median	2.0	2.0	2.0	
Injured knee				
Left	13 (46.4%)	12 (37.5%)	25 (41.7%)	0.535
Right	15 (53.6%)	19 (59.4%)	34 (56.7%)	

Continuation of table 1.

Both	0	1 (3.1%)	1 (1.7%)	
Time from symptom onset (months)				
Mean (SD)	9.5 (9.7)	7.7 (6.5)	8.5 (8.1)	0.415
Median	07.Tpa	7.0	07.Tpa	
Time from last pain episode (months)				
Mean (SD)	2.8 (2.6)	3.1 (3.2)	3.0 (2.9)	0.685
Median	2.0	2.0	2.0	
VAS				
Mean (SD)	6.36 (1.6)	6.42 (1.4)	6.39 (1.5)	0.871
Median	7.0	7.0	7.0	
KOOS				
Symptoms	66. 5 (17.3)	62.8 (14.9)	64.5 (16.0)	0.387
Pain	67.7 (20.2)	67.1 (15.4)	67.3 (17.6)	0.889
Function, daily living	75.7 (21.3)	73.5 (17.5)	74.5 (19.2)	0.678
Function, sports and recreational activities	39.6 (26.9)	43.3 (23.6)	41.6 (25.0)	0.581
Quality of life	40.3 (19.6)	40.4 (15.9)	40.4 (17.5)	0.974
Total score	58.6 (18.0)	57.4 (14.9)	57.97 (16.3)	0.785

Data are expressed as N (%) or mean (SD), median, Q1, Q3 as indicated. Statistical significance between groups was determined using either the Student's t-test or the Chi-square test for continuous or categorical variables, Abbreviations: SD = standard deviation; KOOS = Knee injury and Osteoarthritis Outcome Score; VAS = Visual Analog Scale.

Effectiveness assessment. Results of the VAS-pain indicate that intra-articular injections of HA were effective at 16 reducing pain throughout the study.

At baseline, mean VAS was similar in the 2- and 3-injection groups (6.36 and 6.42) (Table 1) and gradually decreased across the visits. Differences in VAS score from Visit 2 to Visit 3 were statistically significant in the 2- and 3-injection groups ($P < 0.0001$). Likewise, the reduction in VAS score from Visit 2 to Visit 5 was statistically significant in both groups ($P < 0.0001$). Inter-group differences at Visit 5 relative Visit 2 (after receiving 2 and 3 injections of HA) were not statistically significant ($P = 0.8271$), although slightly higher in patients that received 2 injections (change of 4.3 and 4.2 in the 2- and 3-injection groups, respectively) (Table 2).

Table 2. Change in VAS upon HA treatment.

Change	2 injection H	3 injection	Total	P-value
VAS (V2 - V3)				
Mean (SD)	2.83 (2.12)	1.97 (1.82)	2.35 (1.99) 0.1096	0.1096
Median	2.0	1.0	2.0	
Q1; Q3	(1.0; 5.0)	(1.0; 3.0)	(1.0; 3.0)	
Min; max	0.0; 7.0	-1.0; 8.0	-1.0; 8.0	
P-value	<0.0001	<0.0001		
VAS (V2 - V5)				
Mean (SD)	4.30 (1.98)	4.18 (1.99)	4.24 (1.97) 0.8271	0.8271
Median	4.0	4.0	4.0	
Q1; Q3	3.0; 6.0	3.0; 6.0	3.0; 6.0	
Min; max	1.0; 8.0	0.0; 8.0	0.0; 8.0	
P-value	<0.0001	<0.0001		

Data are expressed as mean (SD), median and Q1, Q3. Statistical significance between groups was determined using the Student's t-test. Abbreviations: SD = Standard Deviation; VAS = Visual Analogue Scale.

Regarding the KOOS scale, the subscale with the lowest punctuation at baseline in both subgroups was 'Function in Sports and Recreational Activities' (Table 1). Upon treatment with HA (Visit 5), the scores of all KOOS subscales statistically improved in both treatment groups. In patients receiving 2 injections, differences from Visit 2 to Visit 5 were statistically significant for each subscale (P = 0.0002 for function in daily living and P < 0.0001 for the other comparisons). In patients receiving 3 injections of HA, the increase in KOOS scores at Visit 5 relative to Visit 2 was statistically significant (P <0.0001 for each comparison). The subscale with the greatest improvement at Visit 5 in the 2-injection group was 'Function in sports and recreational activities' (change of 31.3) and in the 3-injection groups was 'Quality of life' (change of 29.4), whereas in the overall population, the subscale 'Function in sports and recreational activities' achieved the highest improvement upon HA treatment (change of 29.5). Between-group differences were not statistically significant for any of the subscales (P > 0.05) (Table 3).

Table 3. Change in KOOS upon HA treatment.

Change	2 injection H	3 injection	Total	P-value
Symptoms				
Mean (SD)	15.22	18.21	16.91	0.4225
Median	17.9	19.6	17.9	
P-value	<0.0001	<0.0001		
Pain				
Mean (SD)	17.39 (12.26)	18.95 (17.08)	18.27	0.7132
Median	13,9	19,4	16,7	
P-value	<0.0001	<0.0001		
Function, daily living				
Mean (SD)	13.04 (13.90)	16.11 (14.74)	14.78	0.4454
Median	7,4	12,2	11,8	
P-value	<0.0002	<0.0001		
Function, sports and recreational activities				
Mean (SD)	27.17 (19.18)	31.33 (22.74)	29.53	0.4838
Median	30.0	25.0	30.0	
P-value	<0.0001	<0.0001		
Quality of life				
Mean (SD)	29.35 (19.07)	27.92 (18.48)	28.54	0.7840
Median	31,3	25.0	25.0	
P-value	<0.0001	<0.0001		
Total score				
Mean (SD)	20.43 (12.29)	22.50 (14.88)	21.61 0.5913	
Median	19,8	22,8	20,8	
P-value	<0.0001	<0.0001		

Data are expressed as Mean (SD) and median. Statistical significance between groups was determined using the Student's t-test. Abbreviations: SD = standard deviation; KOOS = Knee injury and Osteoarthritis Outcome Score.

After 2 and 3 injections of HA, a high proportion of patients (75.9%) returned to sport activity in both treatment groups: 18 (75.0%) in the 2-injection group and 23 (76.7%) in the 3-injection group (P = 0.8868). The time to return to the pre-injury sport level was shorter in the 2-injection group (47.8 days) compared to the 3-injection group (71.1 days), with no significant differences between groups (= 0.2367) (Table 4).

Table 4. Return to physical activity upon HA treatment.

Variable	2 injections	3 injections	Total	P-value
Return to physical activity level				
Yes	18 (75.0%)	23 (76.7%)	(75.9%)	0.8868
N missing	6	4	10	
Time to return to the previous level (days)				
Mean (SD)	47.83 (73.60)	71.14 (48.43)	60.65 (61.34)	
Median	47.5	81.5	73.0	
N missing	0	1	1	

Data are expressed as N (%), Mean (SD), and median. Statistical significance between groups was determined using the Student's t-test or the Chi-square test, as appropriate Abbreviations: SD = Standard deviation

Safety assessment. Only one patient in the 3-injection group reported an adverse event at Visit 2. At Visit 3, Visit 4, and Visit 5, no patient registered an adverse event in the overall population (Table 5).

Table 5. Summary of adverse events at each visit.

Variable	2 injections	3 injections	Total	P-value
Visit 2	0	1 (3.4%)	1 (2.0%)	0.3790
N missing	6	3	9	
Visit 3	0	0	0	
N missing	3	3	6	
Visit 4	0	0	0	
N missing	24	4	28	
Visit 5	0	0	0	
N missing	5	2	7	

Data are expressed as N (%). Statistical significance between groups was determined using the Chi-square test.

Discussion. This prospective observational study demonstrated the sustained effectiveness and safety of DIART treatment in athletes with articular lesions, as evidenced by the improvement of patient-reported outcomes related to pain and functioning. These beneficial effects agree with the high rates of return to physical activity and with the low incidence of adverse events.

OA is a degenerative inflammatory condition whose treatment is mainly based on palliative interventions. Likewise, it is clinical course deeply affects functioning and quality of life, and is associated with a higher risk of mortality [21] and other comorbidities such as depression [22]. These drawbacks are particularly evident in the athletic population, in which articular lesions can also lead to sport withdrawal. Indeed, a literature review identified that 37% of former players with OA suffer from moderate or severe problems related to anxiety/depression [23].

This study was carried out in athletes of different sport disciplines, likely conditioning that, on average, our patient population was younger (40 years) than that in most of the randomized clinical trials performed in the elderly. This fact further reinforces how high-demand sports are precipitant factors of articular lesions [3]. Notably, we observed a differential male/female ratio between groups at baseline, which could have conditioned outcome evolution. Despite this, mean baseline VAS score was similar between groups (6.36 and 6.42) and corresponded to a moderate-severe classification of pain.

After treatment initiation, VAS score of pain gradually and significantly decreased across visits in both treatment groups. Importantly, a 37% reduction in pain was observed shortly after treatment initiation (one week after first injection) in both groups, showing the rapid action of this new formulation. This early effect contrasts with the delayed onset of action previously described for viscosupplementation, with a reported peak of effectiveness 5 weeks after injection [24].

Moreover, at the end of follow-up (24 weeks), VAS-pain was reduced by 66.4% in the overall population, showing the enduring effect of DIART. This encouraging result highlights the need to perform further studies assessing the evolution of pain upon this treatment over longer periods of follow-up.

Notably, differences in pain improvement at Visit 5 relative to baseline were slightly higher in patients receiving 2 injections than in those receiving 3 injections. However, this trend was also observed for the change in pain from Visit 2 to Visit 3, when both groups had taken the same number of injections, which could indicate that differences are dependent on the population analyzed and not on the number of injections. In this regard, as previously mentioned, these subtle differences could have arisen from the different gender distribution between groups. In addition, they could be also attributed to the different distribution of sport disciplines at baseline, as the specific requirements of each type of sport likely contribute to the different progression of lesions [25]. Therefore, confirming whether 2 injections of this HA formulation would suffice to achieve the observed long-lasting effects warrants further confirmation.

The decrease in mean VAS lead to a mean score of 2.4 after 24 weeks of treatment initiation, which corresponds to mild-moderate rating of pain and corroborates the change in pain perception upon treatment. Taken together, VAS score results showed both the rapid and long-lasting benefit of this formulation of HA in athletes, with significant reductions observed one week after treatment initiation and lasting for at least 24 weeks. Results on pain management are of outstanding importance given that pain is the hallmark symptom of articular lesions and OA, having major consequences in sport continuity and quality of life [23]. Although further research is needed to shed light into the specific mechanism of action responsible of this enhanced effectiveness, it is likely that the protective effect of HA on viscoelastic properties and joint friction is preserved by the buffering properties of sodium succinate.

The importance of complementing pain evaluations with other patient-reported outcomes such as the KOOS upon response to treatment has been previously acknowledged [26]. After 24 weeks of treatment initiation (Visit 5), the scores of the five subscales of KOOS significantly improved in both treatment groups. The subscales with highest improvement were ‘Function in sports and recreational activities’ and ‘Quality of life’ in the 2- and 3injection groups, respectively. The increase in the score related to sport activity agrees with the substantial improvement in pain and with the high rates of return to physical activity that we observed. In general, the improvement was higher in the group that received 3 injections, but between-group differences were not statistically significant for any subscale. Again, the differential sociodemographic characteristics at baseline between groups difficult the comparison.

Regarding the safety profile of DIART, only one patient reported one adverse event in the 3-injection group throughout the study, suggesting that this formulation of HA is safe. Although a more detailed description of the safety profile of this agent is needed, these preliminary results reinforce the beneficial effects of local treatments for articular lesions as opposed to the toxicity associated to systemic treatments [7]. For example, it has been largely acknowledged that the use of NSAIDs is tightly correlated with the presence of serious gastrointestinal effects [7]. Moreover, previous studies on HA treatment in osteoarthritic patients showed that most common adverse events were pain, swelling [27] and arthralgia [28, 29].

Importantly, treatment with HA resulted in a high proportion of patients returning to physical activity (75.9%) in a mean time of 61 days. This result, apart from corroborating effectiveness and safety data, reflects the actual impact of this treatment on patients’ life. The high rates of sport activity return agree with the improvements in pain and function and with the lack of serious adverse events reported in the study. In addition, the proportion of patients returning to sport practice is substantially higher than the 60% observed in athletes treated with microfracture after 2 years of follow-up [30]. Data on return to physical activity could pave the way for future work studying the proportion of patients resuming sports upon intra-articular injections of DIART according to specific sport disciplines.

Regarding the onset of action and duration of effects, a meta-analysis of 54 randomized clinical trials of OA knee pain demonstrated that HA was efficacious between 4-24 weeks and that corticosteroids provided a shorter pain relief [31]. Furthermore, in 10 trials comparing intra-articular injections of HA and corticosteroids, both treatment showed comparable results 4 weeks after injection, but a greater effectiveness of HA was observed 5-13 weeks post-injection for several variables [29]. Although the different target population in our study complicate the comparisons with other studies, both the early onset of action and long-lasting effects observed with this formulation of HA seem promising and require further comparison with other pharmacological agents.

The main limitations of this study are related to its observational design, which could lead to risk of selection bias and cannot prove direct causality between symptom improvement and treatment administration. In addition, the lack of comparator and open-label design are important limitations that should be addressed in the future, considering the high placebo effect associated with OA treatments [32]. Additional drawbacks of the study are the lack of MR to document cartilage status and the succinct safety evaluation.

In contrast, this is the first study reporting the effectiveness and safety of DIART and providing valuable information from a comprehensive range of variables addressing different aspects of the disease. In addition, this study is one of the few focusing on the athletic population, a particularly vulnerable subset of patients for which disease management remains a challenge.

Long-term studies with a larger sample size are important avenues for future research to validate these results and find potential subgroups of patients with higher response rates and to establish the optimal treatment schedule (2 or 3 injections).

Conclusions. In conclusion, the findings described in this prospective study suggest that intra-articular injections of HA are safe and effective in reducing pain and improving function and are not associated with serious adverse events. All these beneficial effects, altogether, result 13 in the high rates of return to physical activity. The early effect of DIART contrasts with 14 the delayed onset of action reported with other agents.

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