Hymovis MO.RE. in the treatment of knee and ankle chondropathy in elite athletes: preliminary results of the CHAMPS (Cohort study about HYADD4-G Administration for Pain relief on Soccer players) prospective clinical study


1Fondazione Poliambulanza, Brescia; F.C. Brescia Calcio, Brescia, Italy
2U.C. Sampdoria Calcio, Genoa, Italy
3Atalanta Bergamasca Calcio, Bergamo, Italy
4U.S. Sassuolo Calcio, Sassuolo, Italy
5Orthopaedic Surgery and Trauma Medicine at Quirónsalud Barcelona Hospital, Barcelona, Spain
6Hellas Verona Football Club, Verona, Italy
7A.C. Milan, Milan, Italy
8S.P.A.L. Calcio, Ferrara, Italy
9Bilbao Athletic Club, Barcelona, Spain
10F.C. Bari, Bari, Italy
11Udinese Calcio, Udine, Italy
12Cagliari Calcio, Cagliari, Italy
13Atlético de Madrid, Madrid, Spain

Abstract. – OBJECTIVE: This study evaluated single intra-articular injections of Hymovis MO.RE., a hyaluronic acid hexadecyl derivative (HYADD4-G), to manage post-traumatic or degenerative knee or ankle chondropathy in professional soccer players.

PATIENTS AND METHODS: Twenty-five patients affected by knee (n = 12) or ankle (n = 13) chondropathy were prospectively enrolled and treated by two single Hymovis MO.RE. (32 mg/4 ml) injections at the beginning of the football season (V0, baseline) and at mid-season (V1, 19-20 weeks thereafter), and were followed-up until the end of the season (V2, after further 19-20 weeks). Knee cases were evaluated using the 2000 IKDC knee subjective examination form and the modified Lysholm scoring system. Ankle cases were evaluated using the American Orthopaedic Foot Ankle Society (AOFAS) ankle-hindfoot score. Patients were also evaluated using a VAS Likert scale and a four-category scale recording both the patient’s and the doctor’s assessment on joint mobility in degrees and overall treatment efficacy. Adverse events, patient withdrawals and local reaction to injections were also assessed.

RESULTS: In knee patients, the 2000 IKDC subjective score improved from 46.8 ± 11.4 at V0 to 83.1 ± 12.5 at V2. Their modified Lysholm score improved from 58.8 ± 8.9 at V0 to 90.6 ± 8.3 at V2. In the ankle patients, the AOFAS score improved from 52.2 ± 5.6 at V0 to 96.4 ± 4.5 at V2. VAS Likert values and subjective evaluations improved at V1 and were maintained at V2. No side effects were recorded.

CONCLUSIONS: A single Hymovis MO.RE. (32 mg/4 ml) intra-articular injection, repeated after 19-20 weeks, may be a viable option to improve symptoms and function in professional soccer players suffering from knee and ankle chondropathy.

Key Words: Osteoarthritis, Hyaluronic acid, Viscosupplementation, Knee, Ankle, Chondropathy, Sport.

Introduction

The influence of sport activities on early osteoarthritis (OA) development is a cause of concern,
especially considering the widespread diffusion of sport practice\textsuperscript{1-4}. The occurrence of early OA following an intense period of physical activity has been frequently described\textsuperscript{5}. Frequent or intense mechanical stress can contribute to cartilage wear and inflammation, resulting in overuse injuries and OA onset at different joints\textsuperscript{6}. Joint tears represent a major risk factor for developing OA in the years following injury\textsuperscript{7-10}. Single acute ligamentous injuries producing joint instability, as it often happens at the ankle, are associated to chondral lesions in $>80\%$ of cases\textsuperscript{11}. Traumatic sports injuries also commonly lead to subchondral bone lesions\textsuperscript{12}.

According to several studies\textsuperscript{13-15}, knee and ankle OA are more frequent in former professional soccer players, volleyball and basketball players than in the normal population. Common injuries include muscle strains (37\%), ligament sprains (19\%), and contusions (13\%). These usually involve the thigh (23\%), ankle (17\%), and knee (17\%) among professional soccer players, most of which are subject to knee or ankle joints and chondral injuries\textsuperscript{16}. Treating high-demand patients, like professional athletes, may be challenging because of their willingness to early return to competition, which may result in reduced compliance to long-term therapies.

The main symptoms of knee OA are joint pain and loss of function\textsuperscript{17}, which negatively impact on daily living, economic and social costs\textsuperscript{18,19}, as well as performance or premature retirement from sport\textsuperscript{15,20}.

Conservative OA management aims to alleviate symptoms, allow function recover, slow down and possibly stop the progression of cartilage degeneration\textsuperscript{21-26}. Recent guidelines\textsuperscript{22,26-31} and systematic reviews indicate hyaluronic acid (HA) viscosupplementation as a viable solution for treating patients not responding to pharmacological therapies. HA is, in fact, widely used in the treatment of degenerative joint diseases as a synovial fluid supplement based on its effectiveness in cartilage lubrication and protection\textsuperscript{32-34}. Products based on high molecular weight HA, cross-linked HA, and mobile reticulum HA are regarded as especially useful to manage mild to moderate OA symptoms and may have a chondroprotective effect if administered at early stages of the disease\textsuperscript{34,35}.

Hymovis [(HYADD-4G), Fidia Farmaceutici, Abano Terme, Italy] is a novel HA amide derivative that has been recently placed on the market as a viscosupplementing agent. It features some aliphatic amines (hexadecylamine) bound to HA at some carboxylic groups. This results in hydrophobic and hydrophilic interactions that stabilize the linear polymers and form a mobile reticulum (MO.RE Technology) that recovers its original structure even after repeated mechanical stresses\textsuperscript{36,37}. Recent trials demonstrated that the administration of 8 to 24 mg Hymovis, delivered by two injections one week apart, is effective and well-tolerated in patients with knee or shoulder OA, improving pain, WOMAC indexes, and quality of life\textsuperscript{16,38-42}. A pilot study\textsuperscript{46} involving 30 professional soccer players affected by traumatic or degenerative knee OA showed that two HYADD4-G (24 mg/3 ml) intra-articular (i.a.) injections at one-week interval improved knee resting, walking pain and the joint range of motion for at least 6 months after injections.

A new Hymovis formulation, (HYADD-4G, 32 mg/4 ml), known as Hymovis MO.RE., has been recently placed on the market. The increased HA-derivative dosage that can be delivered through each Hymovis MO.RE. injection might provide more relevant and/or more long-lasting benefits than the variants at a smaller dosage. This opens the possibility of envisaging different administration protocols, that is increasing the time interval between repeated injections or even reducing their number. Pavelka et al\textsuperscript{44} compared the safety and the performance of two different doses of a single Hymovis injection to those of Synvisc-One, a well-known single-injection formulation. The results confirmed that one injection of Hymovis 32 mg/4 ml was as safe and effective as one injection of Synvisc-One 48 mg/6 ml in the treatment of symptomatic knee OA. Moreover, Migliore et al\textsuperscript{44} observed that a single Hymovis One (also called Hymovis MO.RE.) i.a. injection allowed to achieve a significant 6-month reduction of the mean Lequesne index and VAS pain scores of patients aged $>40$ and suffering from symptomatic Kellgren-Lawrence grade I-III hip OA, with the benefit lasting up to 12 months. Single injection protocols might be more viable for high-demanding patients, such as professional sport players, as they might enhance compliance and provide benefits relevant and durable enough to guarantee the expected performance throughout the competing season. To preliminarily explore this hypothesis, this study aimed to prospectively investigate how a protocol involving two single i.a. Hymovis MO.RE. injections, administered at the beginning and
halfway (18-20 weeks after the first injection) of the competing season, modulate knee pain and function in professional soccer players affected by traumatic or degenerative knee or ankle OA.

**Patients and Methods**

The present study, named CHAMPS (Cohort study about HYADD4-G Administration for Pain relief on Soccer players), was a multicentre, prospective, investigator-initiated investigation. Patients were first enrolled, and then, evaluated over the following 40 weeks. All procedures performed in this study involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Investigational Device**

Hymovis MO.RE. (Fidia Farmaceutici, Abano Terme, Italy) is made of HYADD4-G, a HA-derivative achieved by bonding a hexadecylamine as a side chain to 2-3% of the disaccharide repeating units after activating the carboxyl group of the glucuronic unit by using carbonyldiimidazole (CDI)37. HA used as starting material for the synthesis of HYADD4-G is produced through fermentation by non-pathogenic strains of *Streptococcus* bacteria such as *Streptococcus equi* and possesses a molecular weight of 500 to 730 kDa. When HYADD4-G is in an aqueous solution, the added aliphatic side chains create hydrophobic interactions allowing the polymer to form physical hydrogels that are stable at very low polymer concentrations, where the polymer to form physical hydrogels that are hydrophobic interactions allowing chains create hydrophobic interactions allowing.

**Inclusion and Exclusion Criteria**

Patients were eligible for the study if meeting all the following criteria: (1) age ≥18 years; (2) a professional sport player; (3) evidence of knee or ankle chondropathy; (4) provision of written informed consent for the participation in the study.

Exclusion criteria were the presence of marked inflammatory signs of the joint, outcomes of joint fracture or infection, ligament or meniscal pathology, cartilage lesions requiring surgical treatment and a known history allergy/hypersensitivity to HA.

**Objectives and Endpoints**

The study aimed to evaluate the efficacy of two single Hymovis MO.RE. (32 mg/4 ml) i.a. injections, administered at the beginning and halfway (18-20 weeks after the first injection) of the competing season. The primary study objective was to assess pain relief by collecting subjective measurements of pain on movement, at rest, at night and under load from all patients through 0-4 Likert VAS scales and assessing the improvement in joint mobility and the effectiveness of treatment by recording the patient’s and the doctor’s evaluations again through a 0-4 categorical scale. Secondary objectives involved measuring improvement by recording the International Knee Documentation Committee 2000 subjective knee (IKDC 2000) score and the modified Lysholm knee questionnaire as far as the knee was concerned, and the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score concerning the ankle.

The Likert VAS scales used in the present study allowed the patient to provide a subjective assessment of pain on movement, at rest, at night or under load on a 0-4 basis, with 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = extreme pain. The four-category scale used by either the patient or the doctor to assess the joint mobility and the effectiveness of treatment involved 4 grades, namely 0 = unchanged; 1 = slightly improved; 2 = moderately improved; 3 = much improved; 4 = very good condition.

The evaluation of the IKDC 2000 score45 involves recording the patient subjective assessment concerning symptoms (7 items); sports activities (2 items); function (2 items). The overall IKDC 2000 score is calculated by first summing the scores for each item, to achieve an overall Raw Score, and then transforming this into the IKDC 2000 score measuring improvement by recording the International Knee Documentation Committee 2000 sub-score concerning symptoms (7 items); sports activities (2 items); function (2 items). Secondary objectives involved assessing eight items (limp, support, locking, instability, pain, joint effusion/swelling, stair climbing, squatting). Each item is given a score, the higher the better, and the overall modified Lysholm score is calculated by summing each item’s score. The max-
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The minimum modified Lysholm score is 100, in which: 91 to 100 is considered excellent; 84 to 90, good; 65 to 83, fair; and 64 or less, unsatisfactory. The AOFAS ankle-hindfoot score, developed by Kitaoka et al, combines subjective and objective pain and function scores. The scale includes nine items that can be divided into three subscales (pain, function, and alignment). Pain is measured by one item, whose maximum score, equal to 40, indicates no pain. Function is assessed by seven items, whose overall maximum score, 50 points, indicates full function. Alignment is represented by one item, with good alignment scoring maximum 10 points. An AOFAS score equal to 100, therefore, corresponds to the patient showing no symptoms and impairment. The present study used the Italian validated version of the AOFAS score.

For all these variables, the null hypothesis revealed that their values at halfway and at the end of the soccer season were not significantly different from those before the first injection (baseline). As a further secondary objective, the study aimed to assess the safety of the Hymovis MO.RE. i.a. injections, delivered as described, by evaluating the frequency and nature of any adverse events as well as local tolerability assessing the presence of swelling, tenderness, crepitus, redness/inflammation or effusion. Rescue medication consumption was monitored during the study; the team doctor reported drug intake (date and dosage) all over the study period.

**Patient Enrollment, Treatment, and Assessment**

Patients were enrolled during a screening visit involving also examining the MRI scans of the affected joint to assess the lesions depth and morphology as well as the extent of perilesional bone bruise. Scanning was performed at 1.5-3T, and sequences weighed at both T1 and T2. Assessment was performed on scans from T2 sequences weighted through the fast Spin-Echo technique, allowing faster image capturing and an increase of the signal-to-noise ratio, using fat suppression to enhance minimal signal changes that occur in the early stages of chondropathy. Perilesional bone bruise was assessed according to the Brittberg technique and Winalski grading (Table I and II; Figure 1) and the lesion depth was assessed according to the Yulish adapted classification (Table III).

Enrolled patients underwent a single Hymo-

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**Table I. Brittberg and Winalski’s Classification of Bone Bruise Depth on Fat-Suppressed MRIs.**

<table>
<thead>
<tr>
<th>Brittberg and Winalski’s Classification of Bone Bruise Depth on Fat-Suppressed MRIs</th>
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<tbody>
<tr>
<td>Superficial</td>
</tr>
<tr>
<td>Just beneath the subchondral bone</td>
</tr>
<tr>
<td>Shallow</td>
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<tr>
<td>Extends up to one third of the distance from the articular surface to physeal scar</td>
</tr>
<tr>
<td>Deep</td>
</tr>
<tr>
<td>Extends from one third to two thirds of the distance to the physeal scar</td>
</tr>
<tr>
<td>Extensive</td>
</tr>
<tr>
<td>Extends from two thirds of the distance to the physeal scar, but not beyond the scar</td>
</tr>
<tr>
<td>Generalized</td>
</tr>
<tr>
<td>Extends beyond the physeal scar</td>
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</tbody>
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**Table II. Brittberg and Winalski’s Classification of Bone Bruise Intensity on Fat-Suppressed MRIs.**

<table>
<thead>
<tr>
<th>Brittberg and Winalski’s Classification of Bone Bruise Intensity on Fat-Suppressed MRIs</th>
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<tbody>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Signal intensity less than that of muscle</td>
</tr>
<tr>
<td>Moderate</td>
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<tr>
<td>Signal intensity equal to that of muscle</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Signal intensity brighter than that of muscle</td>
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**Figure 1. Brittberg and Winalski’s Classification of Bone Bruise Depth on Fat-Suppressed MRIs.**
vis MO.RE. (32 mg/4 ml) i.a. injection at the beginning of the soccer season (this visit being regarded as the study baseline, V0). They were subjected to a second single injection halfway through the season (approximately 19-20 weeks later, this visit being regarded as V1), and underwent a follow-up visit at the season end (V2, after further 20 weeks).

The injections were performed using either a 18G- or a 20G-long needle, after disinfection with povidone-iodine or alcohols. Knee injections were performed through a superolateral or anterolateral approach, ankle injections were carried out anteromedially.

Patients were clinically evaluated at baseline (V0), before the first i.a. Hymovis MO.RE. injection; at V1, before the second i.a. injection and finally at the V2 follow-up, collecting at each visit the VAS scores and the doctor and patient evaluation as previously described, as well as the IKDC 2000, modified Lysholm, and AOFAS scores. Local reactions to injections as well as adverse events were monitored at each visit and throughout the study period.

### Statistical Analysis

The study was designed as a descriptive study, series of cases. The patient characteristics at baseline as well as the values of the endpoints of interest at the different study time points were described by descriptive statistics. To evaluate the statistical significance of VAS scores, IKDC 2000, modified Lysholm, and AOFAS scores, t-tests for paired data were used to compare the values obtained at the follow-up visits with those at baseline. Score changes were regarded as statistically significant if $p<0.05$.

### Results

Twenty-five elite soccer players (11 athletes of the Spanish Liga, 14 of the Italian Serie A) affected by knee ($n=12$) or ankle ($n=13$) chondropathy were enrolled during a screening visit. All 25 patients completed the study. Considering the Likert VAS scales, pain on movement improved from 2.6 (1-3) at V0, to 0.8 (0-1) at V1 and was 0.5 at the final follow-up (Figure 2). VAS pain at rest measured at V1 (0.6, range 0-2) was decreased compared to baseline (2.0, range 1-3; $p<0.05$) and was 0.2 (range 0-1; $p<0.05$) at V2. At V1, pain at night decreased from 2.5 (range 1-3) at baseline to 1 (range 0-2; $p<0.05$) at V1 and 0.5 (range 0-1; $p<0.05$) at V2. Pain under load decreased from 2.5 (range 2-4) at baseline to 1 (range 0-2; $p<0.05$) at V1 and 0.6 (range 0-1; $p<0.05$) at V2.

Both the doctor and patient’s scored joint mobility and treatment effectiveness as “3” at mid-season and gave the same score at the end of the season. No athletes missed any training session or competition throughout the season.

In the knee patients, the IKDC 2000 score showed an improvement from $46.8 \pm 11.4$ at V0 to $83.2 \pm 12.5$ at V2 ($p<0.05$), as reported in Figure 3. The modified Lysholm score of knee patients improved from $58.8 \pm 8.9$ at baseline to $90.7 \pm 8.3$ ($p<0.05$) at the final follow-up, as shown in Figure 3. The AOFAS score of the ankle patients improved from $52.2 \pm 5.6$ at V0 to $96.4 \pm 4.5$ ($p<0.05$) at the final follow-up, as shown in Figure 4.

Two players affected by ankle chondropathy with a severe and deep bone bruise at V0 according to MRI evaluation needed to intake painkillers.
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(NSAIDs) twice before the first two matches of the soccer season. No systemic or local side effects were recorded throughout the study duration.

Discussion

The results of the present study suggest that treatment of active elite soccer players suffering from knee or ankle traumatic or degenerative OA by Hymovis MO.RE. – delivered through a protocol involving two single i.a. injections administered about 20 weeks apart – may reduce pain and improve function, with no side effects to such an extent that the athlete may continue training and competing effectively. The demand for symptomatic relief and function recovery of elite, competing athletes, may be regarded as one of the highest requests among all patients suffering from joint OA, as it is reasonably expected that few other patient groups experience a similar necessity to continuously subject their joints to high-energy, repeated mechanical stress. Thus, results of the present study might imply that similar single-injection Hymovis MO.RE. delivery protocols might be as or better effective, in patients with a less active lifestyle. Indeed, Migliore et al\textsuperscript{44} supports the clinical efficacy and safety of a single Hymovis One (also called Hymovis MO.RE.) injection for managing symptoms in patients with hip OA (Kellgren-Lawrence grade I-III of $\geq 1$-year duration), allowing significant improvement of mean Lequesne index and VAS pain scores for up to 12 months.

The observations of the present study, as well as those by Migliore et al\textsuperscript{44}, lead to the hypothesis that a single Hymovis One i.a. injection may be clinically effective in improving symptoms and function in moderate to mild, and possibly severe, OA patients. Further research is required to collect additional evidence on specific patient subgroups, and to assess the persistence of benefits at longer follow-ups to fine tune the administration protocol. Evidence is available on the treatment of knee OA with two lower-dosage (8 to 24 mg) HYADD4-G i.a. injections delivered two weeks apart. While considering differences in study design and patient subgroups involved, results of the present study as well as those by Migliore et al\textsuperscript{44} indicate that a single HYADD4-G injection at higher dosage (32 mg, as in the present study, or more) might be equally effective. Comparative studies are needed to verify this hypothesis. In that case, patient would benefit of an intrinsically safer injection protocol, as a single i.a. injection involves a smaller risk for the patient of developing swelling, arthralgia or other adverse events\textsuperscript{51,52}. Further, single dose administration might increase the patients’ compliance to treatment, reducing their psychologic and economic burden\textsuperscript{53}. Single-injections protocols, moreover, might be preferred by patients leading an active lifestyle, as well as by those regularly practicing sports, by better addressing the need for rapid resolution of symptoms and fast recovery, thus reducing to a minimum the abstinence from sports. This would better address the current scenario, where an increasing fraction of relatively young patients develop post-traumatic osteoarthritis (PTOA) prematurely because of joint injuries sustained in their youth\textsuperscript{54,55} and indeed up to 12\% of arthritis cases are caused by PTOA (roughly 12.7 million people), costing the healthcare system up to 3 billion dollars/year\textsuperscript{56}.

Results of the present study may be at least partially explained by, and are consistent with, the structural and rheological characteristics of the HYADD4-G formulation, whose molecular reticulum can continuously recover its 3-dimen-

Figure 3. 2000 IKDC and Modified Lysholm scores in the patients treated for knee chondropathy.

Figure 4. AOFAS score (minimum, medium and maximum) of patients treated for ankle chondropathy.
sional configuration, even after intense and repetitive mechanical stress, acting as an ideal shock absorber\textsuperscript{27,36,37}. They also confirm that even at the 32 mg/4 ml dosage HYADD4-G is safe, as no adverse reactions were recorded, thus strengthening the current evidence about the safety of this hexadecyl HA derivative. Tolerability and lasting effects of Hymovis One when delivered by single i.a. injections imply it might be viable as a long-term treatment that might effectively delay surgical intervention\textsuperscript{27}, in line with recommendations of international guidelines indicating delaying surgery as one of the main aims of conservative OA management, including viscosupplementation by HA\textsuperscript{26,28-30}. This should be the subject of appropriately designed prospective investigations. Further investigations should also assess how other HA-based formulations having a similar molecular weight, but different rheological properties, compare with Hymovis MO.RE. when administered by a single i.a. injection, in sportsmen, as well as in other patient subgroups.

While robust evidence exists concerning HA viscosupplementation of the knee, investigations concerning HA i.a. injections to manage ankle OA are still few, as it has been recently highlighted by several authors\textsuperscript{31,57,58}. Thus, results of this study provide some additional positive evidence concerning the effectiveness of i.a. HA (or HA derivatives) injections in managing ankle OA.

**Limitations**

Limitations of the present study are the lack of a control group, the absence of a blinded procedure, the limited number of patients, and the short follow-up duration. The team doctors were not allowed by their teams to share with the authors whether or how the players were rehabilitated through any physical or instrumental therapies. Moreover, no MRI evaluation was performed at the final follow-up. The results of this study should, therefore, be regarded as altogether preliminary and indicative until all these limitations are addressed by appropriately designed investigations.

**Conclusions**

Within the limitations of the present study, Hymovis MO.RE. (32 mg/4 ml) single i.a. injections showed to be a safe and effective therapeutic option for managing knee and ankle OA in a high-demanding subgroup of active lifestyle patients. These observations suggest that single Hymovis MO.RE. injections might be a viable option to manage active OA patients, increasing their compliance and allowing them to maintain their usual level of physical activity, including training and competing. Further investigations should be conducted to confirm the efficacy of this treatment option.

**Conflict of Interest**

The Authors declare that they have no conflict of interests.

**Funding Interests**

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**ORCID ID**

Loris Perticarini ORCID ID: 0000-0002-7318-3878.

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