

Intra-articular therapy in athletes: recommendations from the International Consensus promoted by the FMSI (Federazione Medico Sportiva Italiana)

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Summary. Intra-articular therapy is commonly used in athletes. The Italian Sports Medicine Federation (FMSI) called a Consensus to shed light on the indications and procedures of intra-articular therapy in athletes and subjects engaging in professional or sport at non-agonistic level. Eighteen IA therapy experts from the FMSI representing multiple disciplines made up the Consensus Board. Through two meetings and two Delphi rounds, and after a systematic literature search, the consensus pinpointed open questions and respective recommendations. Only those recommendations that achieved an agreement of more than 66% were accepted. The systematic literature search produced 12 articles. The consensus processed 31 questions and their answers. Only the 29 recommendations that reached agreement of more than 66% were included in the recommendations; the remaining four were not accepted. The intensity of the recommendation was broad (range between 7.93-9.93). A research agenda of outstanding questions was also drawn up.

Terapia intra-articolare negli atleti: raccomandazioni dall'International Consensus promosso dalla FMSI (Federazione Medico Sportiva Italiana)

Riassunto. La terapia intra-articolare è comunemente utilizzata negli atleti. La Federazione Medica Sportiva Italiana (FMSI) ha convocato un Consensus per fare luce sulle indicazioni e le procedure della terapia intra-articolare negli atleti e nei soggetti che praticano sport a livello professionistico o non agonistico. Diciotto esperti di terapia IA della FMSI in rappresentanza di più discipline hanno costituito il Consensus Board. Attraverso due riunioni e due round Delphi, e dopo una ricerca sistematica della letteratura, il Consensus ha individuato le domande aperte e le rispettive raccomandazioni. Sono state accettate solo le raccomandazioni che hanno raggiunto un accordo superiore al 66%. La ricerca sistematica della letteratura ha prodotto 12 articoli. Il Consensus ha elaborato 31 domande e le relative risposte. Sono state incluse nelle raccomandazioni solo le 29 raccomandazioni che hanno raggiunto un accordo superiore al 66%; le restanti quattro non sono state accettate. L'intensità della raccomandazione era ampia (intervallo tra 7,93-9,93). È stato inoltre redatto un programma di ricerca delle domande in sospeso.

Key words. Intra-articular therapy, consensus statement, Sports medicine, Delphi method, professional athletes.

Parole chiave. Terapia intra-articolare, documento di consensus, medicina sportiva, metodo Delphi, atleti professionisti.

Introduction

Local administration of therapeutic agents by both intra-articular (IA) or peri-articular injections are widely used in the treatment of osteoarticular and muscle-tendon pathologies in athletes. There are studies and recommendations produced by scientific societies for IA therapy of patients suffering from degenerative and inflammatory osteo-articular pathologies, while there is a lack of international guidelines for the indications and procedures about IA and muscle-tendon therapy in athletes.

The main objective of IA injections in the athlete must aim at the prompt regression of painful symptoms and the rapid return to sporting activity, as well as the secondary prevention of post-traumatic osteoarthritis (OA) and permanent muscle-tendon degeneration. The first two aspects are crucial for the athlete of high competitive level from both a personal and financial point of view: a prolonged separation from the sports activity could have significant economic repercussions for the athlete and for the team he or she belongs to. Returning to activity in full shape and in a short time must be a fundamental prerogative of IA treatment. Clinical experience suggests that the resumption of normal athletic training and competitive competition is subject to complete recovery of joint function and resolution of pain.

The Italian Sports Medicine Federation (FMSI) promoted an International Consensus Conference to clarify the indications and procedures for the use of IA and muscle-tendon local therapy in athletes and individuals who carry out competitive sports activities, both at at agonistic and non-agonistic level.

Methodology of the Consensus

The FMSI has called an International Consensus Conference on the use of IA therapy in sports medicine. To form the Board of the Consensus Conference, the FMSI has therefore designated among its members doctors (18 members) who are experts in IA therapy from various sports disciplines.

The board members (18 members) were asked to respond to two rounds of consultations organized by email by the steering committee (SC) according to a modified two-stage Delphi process. The first consultation (June 2024), concerned the formulation of questions on the issues inherent to IA therapy in sports medicine, divided into 31 questions. These requests were developed by the SC, based on scientific literature, the experience of professionals and the ethical guidelines established by the FMSI. The first round of the modified Delphi process consisted of reviewing, commenting and improving the first draft of the general framework designed by the SC. The board

members were asked to add topics deemed necessary to include in the general structure or to eliminate others because they were redundant or superfluous. This first round took place in December 2023. A summary of all comments received has been made and the original draft has been adapted based on contributions from all board members. The SC identified the final questions and established, in agreement with the librarian expert in this field, the key words for the systematic literature search (SLR) and approved the report form for data extraction from the selected articles. The librarian conducted an extensive literature review, from the analysis of different databases (Medline, Cochrane Database of Systematic Reviews, Google Scholar) and selected all the publications related to IA therapy in sports medicine. The SC, after analyzing the SLR data and based on clinical experience, drafted the proposal for the wording of the answers to the selected questions. The second consultation was then launched and took place in July 2024 for the global discussion of the wording of the questions and answers. After extensive discussion, the final draft of 3 overarching principles and 28 questions and answers (divided in two sections: IA Injection and Peritendinous Injection) was submitted to an anonymous vote via email to all members of the Consensus. Board members had to vote on their level of agreement with the questions and answers presented, using a 9-point Likert scale (1-9), scores from 1 to 3 meaning "I disagree", scores 4 to 6 "I agree with reservations", and from 7 to 9 meaning "I agree". The answers were aggregated into tertiles (1-3 = disagree; 4-6 = neutral agreement; 7-9 = agreement) and the consensus is defined as "good" when 66% of the answers fall within one of the tertiles considered. The "good consensus" expresses a consensus opinion of the experts in "agreement" or "disagreement" with the proposition presented (and in this case it is possible to draw indications about the behaviors recommended by the panel of experts), or a "neutral" opinion. The strength of the recommendation (SOR) was classified according to the median score value for each issue. It was classified as strong if the median score was >8 and moderate if the median score was between 7 and <8. The SC, having obtained the results of the votes, drafted the final version of the article including the recommendations and the key points of the research agenda, which was submitted for sharing and acceptance by all members of the Consensus.

Results

Of the 3 overarching principles and 28 questions and answers, 29 obtained more than 66% of the agreement and were therefore accepted and defined in the recommendations. Two questions did not obtain the

expected agreement and were not accepted in the recommendations. The approved statements are reported in the table 1 and 2.

Comment on the approved recommendations

OVERARCHING PRINCIPLES

In the overarching principles, the Consensus wants to express the priorities that inspired the collection and formulation of the questions and related proposed answers. First, it was agreed unanimously that the long-term safety and health of athletes considered as patient-subjects should be the main focus of IA therapy above other aspects or goals such as immediate recovery from competition or the interests of the team or federation to which they belong. Indeed, IA therapy should be used exclusively for the treatment of the current pathology and any joint and/or tendinous - muscle damage and even if oriented to return to the agonistic activity as soon as possible, it must always consider long-term safety as the basic objective: a false or weak recovery of an articulation in an organism subjected to repeated stress could over time lead to an early or accelerated OA. Furthermore, the Consensus wants to insist on the need and duty to adhere to all the ethical warnings and universal principles of sport, as well as the limitations or indications that WADA expresses regarding the use of therapeutic substances in athletes.

Questions and statements

1. *What volumes of hyaluronic acid (HA) should be used in an athlete's intra-articular therapy?*

“With regard to the volumes of HA to be injected into an athlete's joint, it is recommended to follow the instructions on the information leaflet of individual products, according to joint's size”.

In literature there are no specific data on athletes, but only on OA patients about knee and hip joints. For other joints, we have limited available literature and clinical experience. In practice, the following dosage can be used, according to the data sheet:

- knee: 2 mL × 3 IA injections at distance of a week, 2 mL × 5 IA injections, 6 mL × 1 single IA injection, or 4 mL for 1 single IA injection

- hip, 2-4 mL up to 6 ml can be injected every six months
- shoulder and ankle, an injection of 2-4 mL volume is considered appropriate
- small joints, injections should always be performed with ultrasound (US) guidance, the recommended volume is 0.3 to 0.7 mL depending on the capacity of the joint.

2. *Which is more advantageous for athletes: single IA or multiple IA injections?*

“The smallest number of injections together with the greatest biomechanical capacity of the product may generally be better indicated for the treatment of the athlete”.

In literature we have no data about this subject. However, one or no more than two injection cycles seem the most appropriate choice, in order to provide a faster mechanical action. Moreover, the lower the number of injections, the lower is the risk of infection, especially in patients with comorbidities. Athletes (particularly soccer player), with degenerative joint pathology (hip, knee, ankle), can require periodic IA injections, to take under control symptoms and progression of the articular damage.

Literature shows, for knee OA, the advantage of administering a single dose of cross-linked HA knee injections, compared to three doses of linear HA, in particular with regard to faster recovery times, lower costs and less discomfort associated with the IA injection¹.

Regarding PRP injections in OA, literature shows that single PRP injections have a lower pain score than multiple PRP injections until three months of follow-up, while at six months, single PRP injections have no better effect than multiple PRP injections. Multiple PRP injections have a higher reduction in the intensity of pain when compared to single PRP injections during the follow-up period².

3. *How to choose the most suitable HA in athlete intra-articular therapy?*

“Several products of HA are available in the market, they differ for origin, concentration, MW (molecular weight), volume, physical and biologic characteristics. There is no sufficient data to express an EBM based indication”.

Table 1. Overarching principles.

1	Fast-medium and long term patients' safety has to be the main objective of every intra-articular treatment, on the 9.80 top of all other purposes.
2	The main objective of intra-articular therapy is to effectively treat injuries/diseases and facilitate an early return 9.53 to pre-injury sporting activities level, while prioritising overall long-term health.
3	The substances utilised for IA therapy must adhere to ethical and sporting principles 9.93

Table 2. Questions and statements

Questions & statements	Agreement	Strength
1) What volumes of HA should be used in an athlete's intra-articular therapy? "With regard to the volumes of HA to be injected into an athlete's joint, it is recommended to follow the instructions on the information leaflet of individual products, according to joint's size"	17/18 (94%)	9.00
2) Which is more advantageous for athletes: single IA or multiple IA injections? "The smallest number of injections together with the greatest biomechanical capacity of the product may generally be better indicated for the treatment of the athlete"	15/18 (83%)	9.33
3) How to choose the most suitable HA in athlete intra-articular therapy? "Several products of HA are available in the market, they differ for origin, concentration, MW, volume physical and biologic characteristics. There is no sufficient data to express an EBM based indication"	14/18 (77%)	9.00
4) What would you choose between achieving a biological or mechanical effect through hyaluronic acid injections? "In athletes, both biological than mechanical effects must be the target in intra-articular therapy, to solve pain, to raise a faster recovery and to permit a complete return to sport activity"	17/18 (94%)	9.60
5) Which type of PRP is optimal for IA therapy in athletes? "At the moment, there are no data in the literature that privilege the use of one PRP over another"	13/18 (75%)	8.60
6) When is ultrasonography guidance necessary and beneficial for IA injection? "It is essential to use ultrasound guidance to inject deep joints such as the hip, as well as imaging guidance in the vertebral area, in all peritendinous IA injections and when using complex and/or costly products. The use of ultrasound guidance in all other joints is recommended to ensure proper IA product placement and distribution"	17/18 (94%)	9.27
7) What precautions must be adopted to ensure an aseptic procedure? "Careful skin disinfection is necessary and the skin region where the injection is given should be free from any type of injury. The operator must wear sterile gloves, provide sterile ultrasound probe covers and use sterile ultrasound gel or state-of-the-art sterile covers that do not require gel interposition between probe and device and do not cause artifacts due to the glue on the cover adhering to the probe"	16/18 (88%)	8.60
8) What is the appropriate setting (location where injection is performed) for IA therapy? "IA therapy in athletes as in other patients should only be performed in hospitals, clinics, private surgeries, equipped medication rooms. The locker room or all those environments that do not meet the minimum hygiene requirements are not indicated"	18/18 (100%)	8.93
9) What are the indications to the use of ozone in the IA therapy of the athletes? "There is insufficient data in the literature regarding the validity of the ozone therapy, the treatment is permitted by the WADA via IA but not systemically"	18/18 (100%)	9.40
10) What are the indications to the use of collagen in the IA therapy of the athletes? "We have no data about the indications for the use of collagen in athletes; however, the substance is permitted by the WADA for IA use"	15/18 (83%)	8.93
11) What are the indications to the use of polynucleotides in the IA therapy of the athletes? "We have no data about the use of Polynucleotides in IA therapy for athletes, but they are used in OA, and they are permitted by the WADA"	18/18 (100%)	9.07
12) What are the indications to the use of prolotherapy in the IA therapy of the athletes? "We have no data about the use of prolotherapy in the IA therapy of the athletes, but it is used in OA, and it is permitted by the WADA"	17/18 (94%)	8.93
13) What are the indications to the use of Chitosan in the IA therapy of athletes? "We have no published data about the use of chitosan in the IA therapy of Athletes, but it is used in patellofemoral OA, and it is permitted by the WADA"	18/18 (100%)	8.87
14) What are the indications to use of Multicomponent Arnica based agents? "We have no data about the use of multicomponent arnica based agents in the IA therapy of the athletes. It is under investigation in OA"	17/18 (94%)	7.93
15) What are the indications of the combination of HA plus one or more products? "We have no data in literature about the combination of HA with one or more products in athletes"	14/18 (77%)	8.33
16) Is it advisable for the athletes to practice competitive activity immediately after intra-articular treatment? "Time of return to competition after IA treatment depends on clinical and instrumental targets. However, there are no contraindications to return to activity immediately afterwards IA treatment, if there is no lesion and/or discomfort (especially for antigravitaris sports)"	14/18 (77%)	8.87

Continues

Table 2. Continues

Questions & statements	Agreement	Strength
17) What are the indications to the use of Mesenchymal Stem Cells (MSCs)? "We have no data in literature about the use of MSCs in athletes"	16/18 (88%)	9.00
18) Intra-articular therapy in minors: indications and precautions "Indications and precautions are the same used for adults, in minors practicing an activity at a competitive level. An age of 14-15 can be taken as cut-point to start with IA therapy"	18/18 (100%)	9.20
Section of peritendinous injection		
19) Which type of PRP is optimal for peri-tendon therapy in athletes? "Data from literature are not homogeneous about the use of a type of PRP over the others"	17/18 (94%)	9.07
20) Which type of HA is optimal for peri-tendon therapy in athletes? "Products of HA having specific indication for peri-tendon use"	17/18 (94%)	9.27
21) Use of peri-articular, peri-tendinous collagen: indications "We have no data about the use of intra- and peri-articular collagen in athletes, but commonly it's used especially for tendinopathies (patellar or shoulder tendinopathies)"	15/18 (83%)	8.33
22) Which modalities of peri-articular, peri-tendinous hyaluronic injections are appropriate in athletes? "Ultrasound guide is always strongly recommended for peri-articular and peri-tendinous HA injection"	17/18 (94%)	9.40
23) Are there any EBM on the Use of peri-articular collagen? "There are no data about the use of peri-articular collagen in athletes"	16/18 (88%)	8.93
24) Which type of collagen is the most useful to use in peri-tendon therapy in athletes? "Comparative data about the use of different collagen products in peri-tendon therapy are not available in athletes."	17/18 (94%)	9.07
25) Which are the main medical devices used for tendon diseases? "There are no data in literature that make to prefer the effectiveness of a device, as optimum, over the others"	18/18 (100%)	9.40
26) In which state of tendon's disease (pain, tendinopathy, tendinitis, partial lesion) there are more EBM in using injection therapy? "Local injections are commonly performed to control pain, and to treat tendinopathies and partial injury"	18/18 (100%)	9.27

The choice should be made by comparing the diagnostic assessment, clinical scientific data and product characteristics as well as the timing of the athlete's sporting commitments. In clinical practice, low-medium-high MW, cross-linked or mobile reticulum HA products are used. Considering that the joint damage of athletes is most often purely mechanical, HA with higher rheological properties could be employed. Other authors believe that visco-induction action obtained by low/medium MW HA products could also be useful in athletes.

In a recent review on OA treatment, Manjoo reported that HMW IA-HAs shows greater efficacy compared to the alternative of LMW products, while avian-derived and cross-linked products potentially cause more inflammatory events, compared with non-avian-derived, non-cross-linked Has³.

About safety and efficacy of IA HA preparations, high-quality studies are required, because efficacy varies widely across preparations, as reported in a Webner meta-analysis of 129 articles⁴.

4. *What would you choose between achieving a biological or mechanical effect through hyaluronic acid injections?*

"In athletes, both biological and mechanical effects must be the target in intra-articular therapy, to solve pain, to raise a faster recovery and to permit a complete return to sport".

However, safety for the athletes, the degree of the lesion, the level of pain or infection risk have to be always the main focus in IA therapy.

Chu Wen Tang's study on the effects of IA HA injection on muscular activity in patients with knee OA, shows that the muscle activities of quadriceps, hamstrings, tibialis anterior, and medial gastrocnemius muscles recovered to a pattern similar to the control group after the completion of IA HA injections in knee OA patients, while, normally, in these patients, during the stance phase of gait cycle, these muscles had longer muscle contraction duration compared with the control group. Moreover, the H/Q ratio (maximum concentric force of the Hamstrings/maximum concentric force of the quadriceps) improved significantly after

the IA HA injections, and also lasted up to a period of six months ($p < 0.01$). The authors suggest that IA HA is an available treatment option to reduce co-contraction and to improve motor activity of the lower extremity muscles in knee OA, to a period up to six months⁵.

The study of Chu-Wen Tang et al. in 2015 revealed that IAHA injections can provide significant pain relief and improvement in activity of daily living function for patients with knee OA, last up to 6 months. This can cause excessive load on the knee joints, which can further accelerate the process of osteocartilaginous degeneration of the knee. Therefore, we need a longer study time to determine the correlation between the kinetic results obtained and the osteocartilaginous damage of the knee⁶.

5. *Which type of PRP is optimal for IA therapy in athletes?*

“At the moment, there are no data in the literature that privilege the use of one PRP over another”.

There are different types of PRP preparation and activation: pure PRP, PRP rich in leukocytes, pure PRP rich in fibrin, PRP rich in leukocytes and fibrin. The first two, are characterized by a liquid formulation and need to be activated in gel form by the addition of calcium or thrombin. They possess greater biological activity and a lower mechanical performance. The PRP rich in leukocytes and fibrin have an already in active gel/solid composition possessing lower biological activity but better mechanical action⁷.

A recent meta-analysis including 24 RCTs comprising 1344 patients knee OA (KOA), hip OA (HOA), ankle OA (AOA), and temporomandibular joint OA (TMJOA) shows that PRP injection therapy is effective and safe in improving functional activity in patients with OA and produce positive analgesic effects in patients with KOA, TMJOA, and AOA. There are no significant effects in reduction of pain symptoms in patients with HOA. Moreover, comparing leukocyte-poor (LP) PRP group, with Leukocyte-rich (LR) PRP group, the first one seems to be more effective in improving pain symptoms in patients with OA⁸.

6. *When is ultrasonography (US) guidance necessary and beneficial for IA injection?*

“It is essential to use US guidance to inject deep joints such as the hip, as well as imaging guidance in the vertebral area, in all peritendinous injections and when using complex and/or expensive products. The use of US guidance in all other joints is recommended to ensure proper product placement and distribution at IA level”.

Using US during IA injection, we can achieve important benefits, as: excellent soft tissue resolution, IA injection accuracy, low cost, ease of access, portability, absence of ionizing radiation and the ability to perform guided procedures with real-time images. Furthermore, studies on corpses and clinical studies show a greater accuracy of US compared with the use of anatomical landmarks, especially in the following joints: glenohumeral, acromioclavicular, elbow, wrist, hand, hip, knee and foot as well as in biceps, wrist, hip, knee and ankle tendons.

US-guided knee procedures have advantageous in particular patients as obese patients, severe OA, athletes with hypertrophic muscle mass and in case of arthrocentesis. For these reasons in some joints (knee, ankle, shoulder and elbow, wrist) the use of US guidance is strictly recommended, although this procedure is not mandatory. About the IA injection of facet joints, a recent review has shown that there are no significant differences in effectiveness on pain and joint function between US, CT or fluoroscopic guidance techniques. For periarticular injection, US guidance is strictly recommended too⁹⁻²⁰.

7. *What precautions must be adopted to ensure an aseptic procedure?*

“Careful skin disinfection is necessary and the skin region where the injection is given should be free from any type of injury. The operator must wear sterile gloves, provide sterile US probe covers and use sterile US gel or state-of-the-art sterile covers that do not require gel interposition between probe and device and do not cause artefacts due to the glue on the cover adhering to the probe”.

It's mandatory to use all means for a completely sterile injection's execution. In addition, it's very important before injection to exclude state of debilitation or immunosuppressive pathologies, or uncontrolled diabetes, that may facilitate the onset of infection. Before injection, patients don't need antibiotic prophylaxis.

8. *What is the appropriate setting (location where Injection is performed) for IA therapy?*

“IA therapy in athletes as in other patients should only be performed in hospitals, clinics, private surgeries, equipped medication rooms. The locker room or all those environments that do not meet the minimum hygiene requirements are not indicated”.

IA therapy, which is always invasive, should only be carried out by the physician and only in appropriate medical environments that guarantee cleanliness and hygiene, and possible help in case of allergic reaction or vagal crisis.

9. *What are the indications to the use of ozone in the IA therapy of the athletes?*

“There is insufficient data in the literature regarding the validity of the ozone therapy, the treatment is permitted by the WADA via IA but not systemically” (1*).

Sconza et al. review on Oxygen-Ozone therapy (OOT) for the treatment of OA, shows that OOT can be a safe approach with good effects in pain control and functional recovery; but there are several prejudices that limiting the possibility to compare OOT with other treatments.

Moreover, both Li et al. and De Sire et al. meta-analysis in patients with Knee OA, show that treatment with OOT reduce pain less than HA injection; however based on the current evidence available, more RCTs are needed for further investigation²¹⁻³⁰.

10. *What are the indications to the use of collagen in the IA therapy of the athletes?*

“We have no data about the indications for the use of collagen in athletes; however, the substance is permitted by the WADA for IA use.” (1*).

In literature we have data about the use of collagen with IA injection in patients with OA. These studies show that the IA administration of collagen may stimulate chondrocytes to produce hyaline cartilage and hinder the normal inflammatory response leading to fibrous tissue formation, reducing symptoms, and improving functionality. The use of type-I collagen as an IA treatment for knee OA was found not only to be effective, but also safe with negligible side effects³¹.

Borja-Flores et al. cohort study on the long-term effectiveness of polymerized-type I collagen IA injections in patients with symptomatic KOA, shows that the use of polymerized-collagen, increases the time to TKR (total knee replacement surgery) by at least 60 months, improving functional disability and decreasing pain³². Moreover, Martin Martin et al. in a double blind randomized active-controlled clinical trial on the IA use of Collagen Md-Knee versus HA in patients with KOA, showed that both preparations have similar effects considering the outcome measures (Lequesne Knee Index and pain VAS)³³. Recently Damjanov N showed that the US guided IA hip injections of porcine collagen resulted in significant improvement in VAS pain and WOMAC scores compared to treatment with oral NSAIDs in forty-four patients with Kellgren-Lawrence grade I or II hip OA. However further studies are necessary³⁴.

11. *What are the indications to the use of polynucleotides in the IA therapy of the athletes?*

“We have no data about the use of Polynucleotides (PN) in IA therapy for athletes, but they

are used in OA, and they are permitted by the WADA” (1*).

Studies in patients with KOA, showed that the use of PN, can be considered an alternative to the use of HA in the treatment of OA, in term of pain reduction, quickly response and no adverse effects³⁵.

Choi et al. investigated the effect of a combination of PN and HA in patients with KOA, showing that PNHA has anti-inflammatory effects in OA and improved locomotor activity regardless of the OARSI grade³⁶. This anti-inflammatory effect is confirmed in an in vitro cell-based OA model by Kuppa et al. that show as PN suppress inflammation and stimulate matrix synthesis, and for this reason can potentially serve as treatment for OA³⁷. Kim et al. study comparing efficacy and safety between IA PN and HA for KOA treatment, shows as PN treatment has comparable efficacy and safety to IA HMWHA at 3 times injection with an interval of 1 week, and for this reason it could be used as alternative to HA injection for the treatment of KOA. Further studies are necessary and also in comparison with PRP³⁸.

12. *What are the indications to the use of prolotherapy in the IA therapy of the athletes?*

“We have no data about the use of prolotherapy in the IA therapy of the athletes, but it is used in OA, and it is permitted by the WADA” (1*).

In literature, studies about the use of prolotherapy (hypertonic dextrose) in patients with KOA are available. These studies show that the effect of hypertonic dextrose in patient with KOA is as effective as HA, ozone or radio-frequency, in term of pain reduction, with no side effects or serious adverse reactions³⁹. In a comparative analysis, Öztürk and Baygutalp show that in patients with KOA, groups treated with dextrose prolotherapy (expecial 20% dextrose concentration) have a greater improvement, compared with control group (home exercise)⁴⁰. Waluyo et al. review shows that prolotherapy has potential benefits in term of pain and functional outcomes; however further studies are needed⁴¹.

In a narrative review, Hsu et al. show how prolotherapy is used with benefits in a variety of different musculoskeletal conditions, including: lateral epicondylitis, rotator cuff tendinopathy, plantar fasciitis, Achilles tendinopathy, OA, low back pain, sacroiliac joint pain, and TMJ laxity⁴².

13. *What are the indications to the use of chitosan in the IA therapy of athletes?*

“We have no published data about the use of Chitosan in the IA therapy of athletes, but it is

used in patellofemoral OA, and it is permitted by the WADA" (1*).

Chitosan has been the subject of intense research on its use in various medical applications for the past 2-3 decades^{1,2}. Recently a new product class for IA injection in OA, based on non-animal carboxymethyl-chitosan (Kiomedine CM-Chitosan), was introduced in Europe. Clinical studies conducted to date have demonstrated the safety and efficacy of this CM-Chitosan liquid implant in knee OA³⁻⁶, including in refractory knee OA patients with predictive factors of non-response to HA7, such as patellofemoral OA^{8,43-50}.

14. *What are the indications to use of multicomponent arnica based agents?*

"We have no data about the use of multicomponent arnica based agents in the IA therapy of the athletes. It is under investigation in OA".

This kind of multicomponent has been used in KOA (Iozada)⁵¹. Smita recently found that Tr14 (Traumeel) acts primarily on the late phase of acute inflammation (during resolution) compared to diclofenac, which suppresses acute inflammation immediately after injury. This result provides new insights how network pharmacology of multicomponent drugs may support resolution phase in inflammatory conditions. This property could be potentially useful in sport injury^{52,53}.

15. *What are the indications of the combination of HA plus one or more products?*

"We have no data in literature about the combination of HA with one or more products in athletes".

There are examples of combinations used in OA (association with mannitol, sorbitol or clodronate), so it's necessary to study them in athletes, with the target to improve performance and quickness in recovery. All the combination with CS is prohibited by the WADA (in competition).

In patients with KOA, a meta-analysis that compares PRP+HA therapy, with PRP-alone therapy, doesn't show significant differences in pain relief and function improvement for patients with KOA in the two groups; but combined PRP with HA injections was generally safer than PRP injections alone, by assessing the incidence of adverse events⁵⁴.

16. *Is it advisable for the athletes to practice competitive activity immediately after intra-articular treatment?*

"Time of return to competition after IA treatment depends on clinical and instrumental targets. However, there are no contraindications to return to activity immediately af-

terwards IA treatment, if there is no permanent lesion and/or discomfort (Especially for anti-gravity sports)".

It has been suggested that the resumption of physical and sporting activity could be recommended after the complete resolution of the pain symptomatology and the full recovery of the sport-specific athletic action. But it is also true that the resumption of physical activity may be functional to sports recovery (for example, resumption of quadriceps training or sports action in the presence of iatrogenic inhibition or immobilization hypotrophy). In addition IA injection therapy is not always able to resolve pain and therefore this parameter should not be considered as an absolute indication in allowing a return to activity.

A study conducted by Bradley et al. show that in National football League players with grade 2 Hamstring injuries, PRP injection allows a faster return to play (1 game sooner)⁵⁵.

17. *What are the indication to the use of Mesenchymal Stem Cells (MSCs)?*

"We have no data in the literature on the use of MSCs in athletes, a procedure not allowed by WADA, so we need further and more detailed studies on athletes".

Reporting the position statement on the non-surgical management of knee OA the Italian Orthopaedic and Traumatology Society (SIOT), the use of MSCs, is not recommended by scientific authorities because of the lack of standardization in their preparation modalities. MSCs can be used in highly specialized centers, particularly in clinical trials, while they are weakly recommended in daily clinical practice as they are still being studied⁵⁶.

18. *Intra-articular therapy in minors: indications and precautions.*

"Indications and precautions are the same used for adults, in minors practicing an activity at a competitive level. An age of 14-15 years can be taken as cut-point to start with IA therapy".

Literature is characterized by a lack of study protocols and outcome assessment measures and there is no evidence-based certainty about the effectiveness of IA injection therapies of any kind in minor athletes. Two problems requiring definition: concern the use of local anesthetic or conscious sedation during the injection procedure and the use of imaging guidance; US guidance is mandatory instead of radiology because of the absence of radiation.

Section of peritendinous injection

1. *Which type of PRP is optimal for peri-tendon therapy in athletes?*

“Data from literature are not homogenous about the use of a type of PRP over the others”.

Several types of PRP are actually available differing for preparation and activation: pure PRP, PRP rich in leukocytes, pure PRP rich in fibrin, PRP rich in leukocytes and fibrin. In treating tendinopathy PRP seems to produce both anti-inflammatory and pro-healing effects. PRP inhibits tendon cell inflammation by upregulating genes like HGF and decreasing NF- κ B signaling in macrophages and fibroblasts. PRP releases growth factors capable to enhance chemotaxis and proliferation of fibroblasts, to stimulate collagen synthesis driving tendon repair. Ibrah et al. report that US guided PRP (pure PRP) vs corticosteroid injection in patients with rotator cuff tendinopathy has good results in term of reducing of pain and improving of range of movement (ROM). US guide increases injection efficacy⁵⁷.

2. *Which type of HA is optimal for peri-tendon therapy in athletes?*

“Products of HA having specific indication for peri-tendon use”.

There is in literature evidence of efficacy and safety in the use of low to medium molecular weight by peritendinous route. In literature some studies underline as LMW HA is an option for the management of sport-related tendinopathies, with a special attention to pain reduction and functional assessment, without severe adverse effects, but further studies with a larger sample size are needed to confirm available findings⁵⁸.

3. *Use of peri-articular, peri-tendinous collagen: indications*

“We have no data about the use of intra- and peri-articular collagen in athletes, but commonly it’s used especially for tendinopathies (patellar or shoulder tendinopathies)”.

In 2019 Corrado et al. reported fifty patients suffering from lateral epicondylitis for at least 6 months, treated with a series of 5 injections of type I porcine collagen, at weekly intervals. After treatment as regards the baseline, the total score showed an average reduction of 57% (55% in terms of pain and 58% in terms of function) at 1-month follow-up and an average reduction of 66.1% (68.9% in terms of pain and 63.2% in terms of function) at 3-month follow-up. The results were statistically significant ($p < 0.05$) according to the Kruskal-Wallis test⁵⁹. In 2020 Corrado et al. again treated a patient with a partial-thickness

tear of the supraspinatus tendon by a series of four type I porcine collagen US-guided injections, at weekly intervals. At the same time the patient underwent physical therapy, consisting of motor re-education and proprioceptive exercises.

Shoulder pain and functional limitation progressively improved and they almost completely disappeared at the last follow-up. US showed a gradual healing of the partial-thickness tear and a regeneration of the tendon structure⁶⁰.

4. *Which modalities of peri-articular, peri-tendinous hyaluronic injections are appropriate in athletes?*

“US guide is always strongly recommended for peri-articular and peri-tendinous HA injection”.

The use of US guidance allows for safe and selective injection of target tissue, contributes to the selection of the appropriate drug/device and preserves nearby structures not involved in the targeting

Mezian and et al.’s work shows that in elbow tendinopathies, US-guide helps to set the final diagnosis, and guides interventions to reach precisely the target structure and to avoid vulnerable structures such as nerves or vessels⁶¹.

Silva et al. show how image-guided procedures, and particularly US guide during injections, aim to reduce pain and increase function⁶².

Masiello highlight et al. the relevance of US-guide in tendinopathies treatment with PRP (lateral epicondylitis, plantar fasciitis, Achilles tendinopathy, rotator cuff tendinopathy, patellar tendinopathy, carpal tunnel syndrome), in term of pain reduction and functional improvement⁶³.

5. *Which type of collagen is the most useful to use in peri-tendon therapy in athletes?*

“Comparative data about the use of different collagen products in peri-tendon therapy are not available in athletes”.

We have clinical experiences on the use of collagen in peritendon therapy in subjects who do not practice high level sports, so it is necessary to study them more thoroughly on athletes.

6. *Which are the main medical devices used for tendon diseases?*

“There are no data in literature that make to prefer the effectiveness of a device, as optimum, over the others”.

Suresh et al.’s treating patients with medial epicondylitis shows that a combination of dry needling and autologous blood injection under US guidance, can have positive effects in term of pain and function⁶⁴.

7. *In which state of tendon's disease (pain, tendinopathy, reactive tendinopathy, partial tear) there are more EBM in using injection therapy?*

“Local injections are commonly performed to control pain, and to treat tendinopathies and partial tear”.

Giannini et al. showed the safety and the potential effectiveness of peritendinous injections of PRP and HA in reducing the recovery time after muscle-tendinous injury in not professional soccer player affected by adductor longus and brevis lesion⁶⁵.

The same first author reports that US -guided infiltration with a multi fractionated HA combined with dry needling allowed to treat the junctional and tendon injury by restoring tendon continuity and function, reducing time to return to play^{65,66} in not professional marathon runner suffering from high-grade posterior tibial tendon injury.

Comment on the questions where no agreement was reached

No agreement was reached on two common issues in clinical practice. The first concerns the need of performing an imaging investigation before IA injection in athletes. There is no clear literature data to express an EBM based opinion in this class of subjects. Usually, an X-Ray examination is performed in clinical practice to confirm the suspected diagnosis and consequently the right indication to IA injection of patients suffering from OA or inflammatory arthritis. The experts require further studies to provide clear evidence to specialists in the field of sport medicine⁶⁷⁻⁷⁸.

The second question that had not reached an agreement, is about the clinical and laboratories parameters that could be useful to evaluate before indicating IA treatment. In this case too, there are no clear data in the EBM. Some markers as CBC with formula, coagulation tests, ESR, CRP, uricemia and blood sugar should be analyzed before injection to exclude inflammatory or blood diseases, but further studies are needed to reach evidence and agreement.

Discussion and conclusions

This paper is an attempt to produce international IA therapy guidelines in sports medicine. It is the first initiative that has been taken to review EBM and to collect experts' opinion with the aim to clarify issues related to infiltration therapy in the clinical practice of sports medicine. Firstly, issues have been targeted with the commitment to provide an EBM response. Analysis of the literature on the topics covered by our questions produced only a modest response, due to the paucity of trials performed. The experience of

Consensus members, composed by specialists with expertise in different fields of sport, has tried to make up for this shortcoming. The results reported are based on the Delphi method, which reflects the current opinion of a sample of doctors from countries on all five continents with a high level of expertise in the specific field of sports medicine.

While one of the strengths of the Delphi method is that the physicians involved in it bring a wide range of competency and experience to the decision-making process, the limits are that the physicians chosen should ideally include a wide range of experience relevant to the question being addressed. From this point of view, as we did not evaluate the participants' competencies in all fields of the survey (e.g. peritendinous injections, intratendinous injections, use of collagen, etc.), we cannot exclude that some disagreement may arise from the lack of specific experience. Finally, the choice of a consensus level of >66% is open to debate as the use of a higher or lower threshold could have led to different results. However, this threshold value is present in the literature and, as it represents two thirds of the responses, it can be reasonably considered acceptable for the recommendations. In practice, specific IA therapy recommendations have been formulated for the first time for sports medicine that can support and guide clinicians in the treatment of competitive and non-competitive athletes. For those topics that have not found a sufficient consensus to draft a recommendation, we need to encourage and conduct scientific work that will bring more precise indications as regards the unresolved topics and confirm the experience-based propositions of currently formulated recommendations. In addition, it will be important to stimulate research on new promising products for IA use in athletes.

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1*) <https://www.wada-ama.org/en/news/wadas-2024-prohibited-list-now-force>

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