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Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis. A Delphi method consensus initiative among experts in Italy

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Abstract

Objective. The aim of the study was to identify the main aspects involved in patient selection, the choice of therapeutic agents and the safety profile, as well as the medico-legal and organizational aspects of intra-articular injection therapies for osteoarthritis.

Methods. A committee of 10 experts from Italian universities, public hospitals, territorial services, research institutes and patient associations was set up. Fifty-two clinicians from a large number of Italian medical centers specialized in intra-articular injection therapy took part in a Delphi process aimed at obtaining consensus statements among the participants.

Results. Large consensus was obtained for statements grouped under the following main themes: treatment indications; drug/medical device choice; treatment efficacy; and appropriate setting.

Conclusions. The consensus statements developed by a large number of experts may be used as a practical reference tool to help physicians treat osteoarthritis patients by means of intra-articular injection therapies.

Key words

- intra-articular injections
- osteoarthritis
- Delphi studies
- consensus development

INTRODUCTION

Osteoarthritis (OA) is among the most common causes of pain and disability in European countries [1]. Its estimated prevalence is 35% among people aged 50-59 years, and 55% for people over 70 years of age [2], while the lifetime risk for knee and hip OA is 45% [3] and 25% [4], respectively.

Although the impact of OA on health status and work productivity is similar across a number of countries, there are marked variations in the pharmacotherapy adopted to treat this disease [1]. Intra-articular (IA) injections are one type of therapy that is widely used in the management of OA to deliver the therapeutic agent directly into the joint space. IA injection therapies have a good safety profile and several products can be used [5], including steroids [6-9], hyaluronic acid (HA) [10, 11], platelet-

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rich plasma (PRP) [12] and polymerized collagen [13], all of which are commercially available in Italy.

Interestingly, recommendations made in different international guidelines for the non-surgical management of OA are not always concordant with regard to the role of IA injection therapies [14]. IA steroids injections are recommended for hip and knee OA by the American College of Rheumatology and the Royal College of Physicians [15, 16], though not by the American Academy of Orthopedic Surgeons (AAOS) [17] or the European League Against Rheumatism (EULAR) [18]. Intra-articular HA injections receive low strength recommendations from the OARSI [19] and the EULAR [20], but should not be used according to the Royal College of Physicians [16] and the AAOS [17]. Intra-articular PRP injections were only considered by the AAOS, though evidence was considered to be insufficient to make a recommendation [17]. It should be borne in mind, however, that the results and recommendations made by the various organs are often biased by significant conflicts of interest, as pointed out by Printz *et al.* [21]. Moreover, the therapeutic products used for OA are generally considered as a class, rather than as single products. For example, none of the guidelines makes any clear distinction between the different formulations of HA, thereby possibly reducing the perceived impact of these products on the management of OA. Lastly, information on the optimal setting for IA injections is rarely provided in current guidelines for the management of OA.

For all these reasons, it is crucial that the clinical issues and management of IA injections used to treat OA be defined on the basis of experiences shared by clinicians who have a high level of expertise in the use of such injections.

The Delphi method is a process designed to reach a consensus and develop group decisions in health research [22]. The basic principles of the Delphi method are anonymity (experts work independently of each other), controlled feedback (experts are asked to judge the opinion expressed in previous rounds, presented in statistical form) and a statistical group response leading to a collective view expressed in statistical form [23, 24].

To the best of our knowledge, a consensus method between experts has not previously been applied to the clinical aspects and management of IA injection therapy for OA in daily practice.

The aim of the present study was, therefore, to gather, by using the Delphi method, the opinions of a group of Italian clinicians who represent different scientific societies, are involved in the management of OA patients and have a high level of expertise in IA injection therapies. Our goal was to identify the main aspects involved in patient selection, the choice of therapeutic agents and the safety profile, as well as the medico-legal and organizational aspects of IA injection therapies for OA, to obtain opinion-based recommendations to be used in daily clinical practice.

MATERIALS AND METHODS

The Delphi method was used to conduct this consensus initiative. A committee of 10 experts from Italian universities, public hospitals, territorial services, research institutes and patient associations was set up. A panel composed of a university physiatrist (VS), a physiatrist representing the Italian Society of Physical Medicine and Rehabilitation (SIMFER) (SB), an orthopedist representing the Italian Society of Orthopedics and Traumatology (FC), a radiologist representing the Italian Society of Medical Radiology (Alb Bel), a general practitioner representing the Italian Society of General Medicine (OB), a pharmacologist representing the Italian Society of Pharmacology (APC), a geriatrician (MF), an expert in pharmacoeconomics (LM), a rheumatologist representing the Italian Society of Rheumatology (AM) and a representative of a patient association (UV) formed the Consensus Board. The Consensus Board reviewed the literature and, on the basis of the drugs/medical devices currently available in Italy for IA injection therapy, developed the first-round questionnaire (Q1). Technical support regarding the questionnaire design, data analysis and interpretation of the results was provided by two public health researchers and two university researchers in Physical Medicine and Rehabilitation who attended the meetings held by the Consensus Board.

Q1 was submitted to a group of IA injection therapy experts, comprising orthopedics, physiatrists, rheumatologists and general practitioners, who were selected from among the largest Italian medical centers specialized in IA injection therapy, by means of a non-probability sampling method. The experts received an email in which the rationale and the aims of the research were explained. The email sent to each physician contained a strictly personal link to Q1 that allowed the questionnaire to be filled in online. Three reminder emails were sent to each expert in the 30-day period within which the Q1 had to be returned.

The Q1 was composed of 34 questions and was divided in three parts: characteristics of the center in which the experts work, professional skills and expertise (part I); clinical and organizational aspects of treatment of OA patients (part II); supplementary treatments other than intra-articular injections (results not presented in this paper) (part III). The Delphi method was only applied to questions in part II, in which a 9-point Likert scale, graded "1" (strongly disagree) to "9" (completely agree), was used to assess the extent to which the experts agreed or disagreed. In order to determine the consensus level, the answers to each question were grouped into three tertiles according to the Likert-scale scores (1-2-3: disagreement; 4-5-6: neutral; 7-8-9: agreement). For the purposes of this study, we considered the consensus level as good (a recommendation can be made), for both "agreement" and "disagreement", when 66% of the experts agreed or disagreed. When the neutral answers were ≥ 66%, the Consensus Board deemed it impossible to make a specific recommendation on that item. When the consensus level was low (*i.e.* none of the tertiles attained 50% of answers), the expert opinions were considered to be too dissimilar and a shared recommendation was not made. All the items in which consensus was weak (*i.e.* 50-65% of answers) were included again in a second-round question-

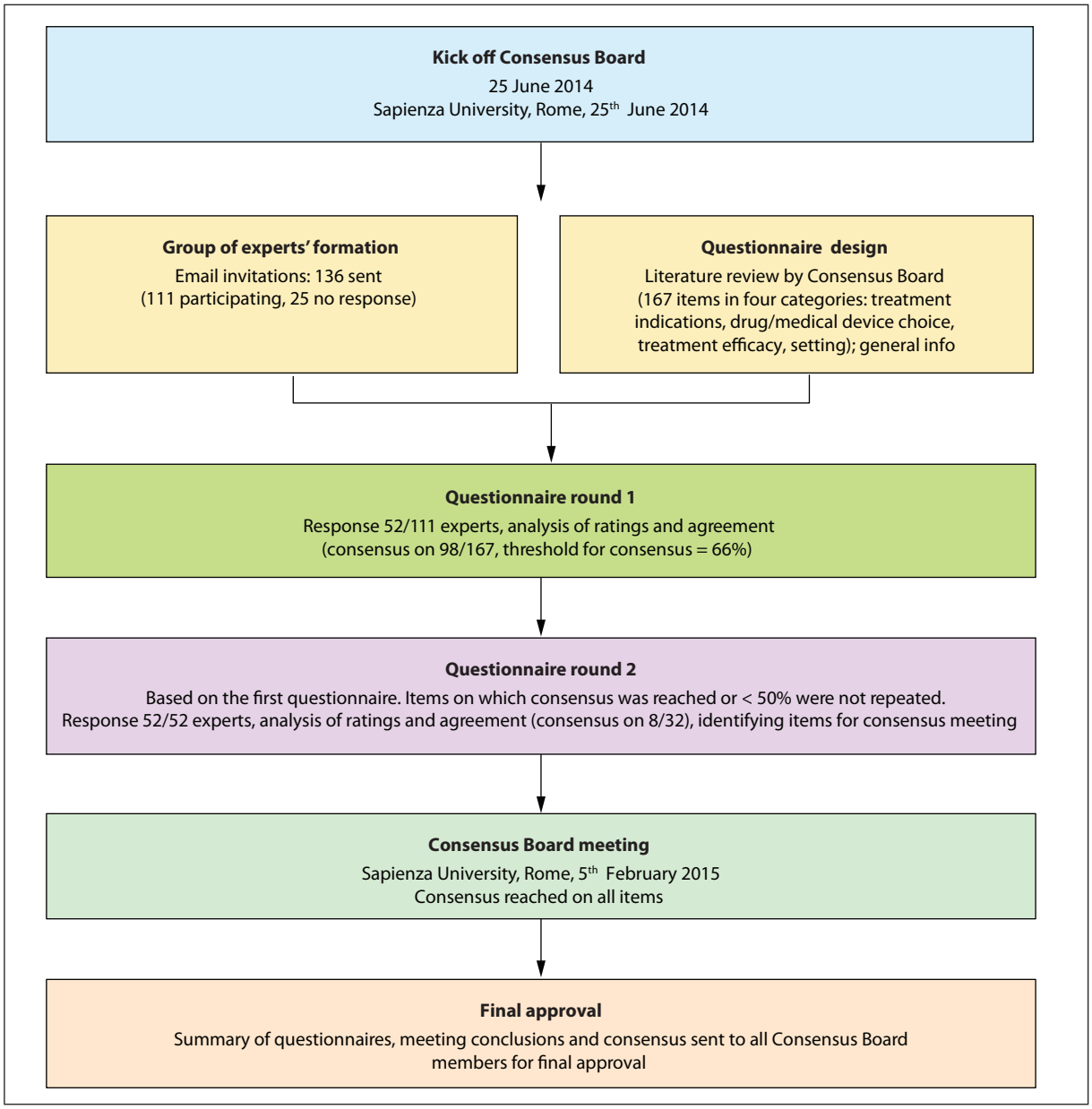

Figure 1
Flow chart of the consensus process.

naire (Q2) to those physicians who completed Q1. The results yielded by Q2 were analyzed in the same way as those yielded by Q1. The final analysis was followed by a board meeting held to discuss the results and to announce the final recommendations by the Consensus Board *(Figure 1)*.

RESULTS

Q1 was sent to 136 experts, 111 of whom returned the questionnaire. Fifty-two of these experts completed both parts of Q1 (Q1 response rate: 45.8%), with the exception of the question on the region of residence (answered by 32/52 experts). Both the descriptive and the Delphi analyses were, therefore, conducted on 52 complete questionnaires. Q2 was sent to the 52 responders of the first round. All the Q2 questionnaires were filled in and returned (Q2 response rate: 100%).

The 52 experts who responded to both Q1 and Q2 comprised 25 (48%) orthopedists, 14 (26.9%) physiatrists, 5 (9.6%) rheumatologists, 6 (11.5%) with more than one post-graduate qualification and 2 (3.8%) who did not list any post-graduate qualification. Thirty-five (67.3%) experts had more than 10 years of experience in OA treatment, with 22 (22/35: 62.8%) stating that they directly followed at least 21 OA patients each month. More than half of the responders reported that in 2013 they had treated a mean of 400 OA patients, more than 150 of whom had been specifically treated with IA injections.

By analyzing data from both questionnaires, the

Table 1
Summary of recommendations in which a consensus was reached for agreement

Recommendations	(%)
IA injection therapy is useful in patients with hip OA	69.2
IA injection therapy is useful in patients with knee OA	100.0
IA injection therapy is useful in patients with shoulder OA*	69.2
IA injection therapy is useful in patients with ankle OA*	71.2
IA injection therapy is useful in patients with mild to moderate OA	88.5
The choice of drug/medical device to be used is influenced by their safety profile	90.4
The choice of drug/medical device to be used is influenced by their rapid action on symptom relief	74.5
The choice of drug/medical device to be used is influenced by the long-term maintenance of results	90.4
The choice of drug/medical device to be used is influenced by their interaction with other therapies	82.7
The choice of drug/medical device to be used is influenced by their scientific evidences	86.5
High molecular weight HA is adequate for IA injection therapy in patients with hip OA	82.0
Mobile Reticulum HA is adequate for IA injection therapy in patients with hip OA	68.0
Medium molecular weight HA is adequate for IA injection therapy in patients with knee OA	69.2
High molecular weight HA is adequate for IA injection therapy in patients with knee OA	80.8
Cross-linked HA is adequate for IA injection therapy in patients with knee OA	70.6
Mobile Reticulum HA is adequate for IA injection therapy in patients with knee OA	78.0
5 IA injections (1/week) of Low molecular weight HA are useful for early/mild stages of OA*	67.3
1 to 5 IA injections (1/week) of Medium molecular weight HA are useful for early/mild stages of OA	68.0
2 to 3 IA injections (1/week) of High molecular weight HA are useful for early/mild stages of OA*	69.2
1 to 2 IA injections (1/week) of Mobile Reticulum HA are useful for early/mild stages of OA	68.0
Costs determine the lack of use of adequate drugs/medical devices for IA injection therapy of OA	70.0
Minor adverse events are rare (≥1/10.000 a <1/1.000)*	69.2
Major adverse events are rare (≥1/10.000 a <1/1.000)	82.0
IA injection therapy is useful in management of OA	96.0
IA injection therapy with steroids is effective on symptoms relief in patients with OA*	78.8
IA injection therapy with HA is effective on symptoms relief in patients with OA	80.0
IA injection therapy with HA is effective to control objective signs in patients with OA	78.0
IA injection therapy with high molecular weight HA help to delay/avoid joint prosthetic implants	68.0
IA injection therapy with Mobile Reticulum HA help to delay/avoid joint prosthetic implants	67.3
IA injection therapy with high molecular weight HA help to reduce systemic NSAIDs/analgesics consumption	80.0
IA injection therapy with cross-linked HA help to reduce systemic NSAIDs/analgesic drugs consumption	67.3
IA injection therapy with Mobile Reticulum HA help to reduce systemic NSAIDs/analgesics consumption	75.0
Private medical surgery is an appropriate setting to practice IA injection therapies	81.6
Ambulatory is an appropriate setting to practice IA injection therapies	91.8
Hospitals are appropriate settings to practice IA injection therapies	81.6
Ultrasound/ radiologic guide is useful to perform hip IA injections	100.0

IA: intra-articular; OA: osteoarthritis; HA: hyaluronic acid; NSAIDs: non-steroidal anti-inflammatory drugs.
*Recommendations derived from Q2.

Board identified those statements that attained a wide consensus (more than 66%), which led to the definition of the recommendations *(Tables 1 and 2)*.

DISCUSSION

Intra-articular injections are widely used in the treatment of OA [25]. Several drugs, as well as various drug administration systems, are available for IA use [26]. However, differences in the use of IA injections has led to discordant recommendations being made in international guidelines [15-17, 19, 27]. Moreover, daily practice in the non-surgical management of OA appears to vary markedly between specialists in different European countries [1]. For these reasons, we decided to use this Delphi survey to investigate the level of knowledge and agreement regarding the role of IA injection therapy in the management of OA in a group of Italian specialists.

Table 2
Summary of recommendations in which a consensus was reached for disagreement

Recommendations	(%)
IA injection therapy is useful in patients with cervical spine OA	78.8
IA injection therapy is useful in patients with lumbar spine OA	71.2
Low molecular weight HA is adequate for IA injection therapy in patients with hip OA*	71.2
Polymerized collagen is adequate for IA injection therapy in patients with knee OA*	67.3
Homotoxicology products are adequate for IA injection therapy in patients with hip OA	70.0
Homotoxicology products are adequate for IA injection therapy in patients with knee OA	72.5
5 to 10 IA injections (1/week) Homotoxicology products are useful for early/mild stages of OA	66.0
Minor adverse events are very common (≥1/10)	88.0
Minor adverse events are common (≥1/100 a <1/10)	75.5
Major adverse events are very common (≥1/10)	95.8
Major adverse events are common (≥1/100 a <1/10)	95.8
Pain after IA injection is one of the most frequent minor adverse event	75.0
Sepsis after IA injection is one of the most frequent major adverse event	72.9
Thromboembolism after IA injection is one of the most frequent major adverse event	83.3
IA injection therapy with homotoxicology products is effective on symptoms relief in patients with OA	69.9
IA injection therapy with homotoxicology products is effective to control objective signs in patients with OA	79.6
IA injection therapy with homotoxicology products help to delay/avoid joint prosthetic implants	73.3
IA injection therapy with homotoxicology products help to reduce systemic NSAIDs/analgesics consumption	71.4
Antibiotic prophylaxis is necessary in case of IA injection therapy	96.0
For IA injection therapy is appropriate to use sterile medical gloves	73.5
Ultrasound/radiologic guide is useful to perform knee IA injections	77.4

IA: intra-articular; OA: osteoarthritis; HA: hyaluronic acid; NSAIDs: non-steroidal anti-inflammatory drugs.
*Recommendations derived from Q2

Treatment indications

In order to obtain an optimal response to a given treatment, the indications for that treatment need to be clearly defined. If they are not, poor results may result from the inappropriate use of IA injections, which may not be suited to the patient's OA phenotype [28]. According to our results, IA injections are useful for mild to moderate OA of the hip, knee, ankle and shoulder. By contrast, the panel of experts agreed that IA injections are not useful in cervical and lumbar spine OA patients. A consensus was not reached, both for agreement nor disagreement in other sites, usually treated with IA injection therapies, like trapeziometacarpal joint [29]. To assess the grade of OA, in our question we referred to the Kellgren and Lawrence classification [30], which is a widely used classification system based on X-ray images. Our experts found that IA injections are suitable for grade II/III OA as diagnosed according to the Kellgren and Lawrence classification (*i.e.* grade II = definite osteophytes and possible joint space narrowing on radiograph; grade III = multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity). This finding further supports the role of non-surgical management in lower grades of OA, particularly in view of the fact that patients with Kellgren and Lawrence grades ≤ III usually have poorer outcomes following surgery [31, 32]. Although it was not possible to reach an agreement on the use of IA injections in low grade OA (grade 0-I), it is noteworthy that the percentage of responders in favor of this approach was very high in both Q1 and Q2 (63.5%). This may reflect a tendency to perform IA injections earlier in the clinical course of OA. Future studies are needed to specifically address the role of IA injection therapies in the initial stages of OA.

Drug/medical device choice

To select the most appropriate therapeutic product for IA injection therapy, the main variables taken into account by the experts in this survey were the safety profile, rapid symptom relief, long-term effect, interaction with other therapies and scientific evidence of efficacy. Interestingly, the cost of therapy is not considered among the factors that determine the choice of the drug/medical device. However, a subsequent question shows that the main reason for not always using the most suitable product for treatment is its cost. This is particularly relevant to Italy, where some drugs are either free or subsidized, while others are not covered by the national health system and have to be paid in full. The conflicting evidence regarding the cost effectiveness of IA treatments in OA patients [32, 33] and the lack of cost-effectiveness analyses conducted on all the products available suggests that studies designed to address the economic burden of IA injection therapies in Italy are needed.

The choice of the product to be injected was found to be influenced by the location of the OA process. In hip OA, experts believe that high-molecular weight HA (the distinction between high-, medium- and low-molecular weight HA was based on the product manufacturers' indications) and mobile reticulum (a partially hydrophobized derivative of HA stabilized by side-chain hydrophobic interactions) [34] HA are considered to be the most appropriate products. By contrast, homotoxicological products and low-molecular weight HA are considered as inappropriate. In knee OA, high- and medium-molecular weight HA, and mobile reticulum and cross-linked (a network of HA chains, which have been covalently linked by chemical processing) HA are the most appropriate products according to the experts in our survey, whereas homotoxicological products and collagen medical devices are considered as inappropriate.

As regards the posology for the various products, the experts generally follow the product manufacturers' indications, both as regards the dosage and the frequency of injections.

It is noteworthy that there is no consensus on therapies that are used extensively in everyday clinical practice, such as IA injection therapy with corticosteroids, polymerized collagen and PRP. Consequently, no recommendations could be made regarding their use. By contrast, it is generally agreed that homotoxicological products are inappropriate for IA injection therapy in OA. This finding may be due to the fact that physicians that perform IA injection therapies tend to know relatively little about the principles of homotoxicology and homoeopathy, and are consequently less likely to use such products, as well as to a general distrust of homeopathy by physicians who practice "conventional" medicine. Interestingly, patients with musculoskeletal disorders who consult primary care physicians who prescribe homeopathy and complementary medicines tended to differ from those who consulted physicians who prescribe "conventional" therapies [35]. This appears to indicate that there is little overlap between these two approaches. Any choice of therapy should clearly be based on strong evidence of efficacy [36], which appears to be one of the most important factors involved in the choice of the product to be used for IA injection therapy in OA. Once again, further researches aimed at clarifying aspects regarding the usage of IA corticosteroids, polymerized collagen and homotoxicological products are needed.

The experts did not reach any consensus on the possible exclusion criteria for IA injection therapy. It may be speculated, therefore, that the decision to exclude or not to exclude a patient from IA injection therapy needs to be evaluated on an individual basis. This hypothesis is confirmed by the agreement expressed by the experts regarding the low likelihood of minor or major adverse events following IA injections, which is in line with the good safety profile reported for these treatment modalities [37, 38].

Treatment efficacy

The results of the present survey indicate that Italian experts are generally satisfied with the IA injection therapies currently available for the management of OA, which need to be combined with other general recommendations such as weight loss, life-style changes and use of analgesic drugs [39]. In particular, both corticosteroids and HA IA injections are considered to relieve the patients' symptoms. In this regard, high-molecular weight, mobile reticulum and cross-linked HAs are, according to our experts, the products that most effectively reduce the systemic use of analgesic or anti-inflammatory drugs. While IA injections of homotoxicological products are not considered to relieve symptoms, no consensus emerged on the role of IA PRP and polymerized collagen in relation to symptom relief. Furthermore, IA injections of HA are considered to be valid as a means of controlling the objective manifestations of OA. This finding is supported by the experts' opinion of high-molecular weight and mobile reticulum HA, which are considered to be able to delay or avoid a joint prosthetic implant [40].

Setting

The experts interviewed for our survey agree that IA injection therapies can be performed not only in hospitals, but also in clinics, polyclinics or private medical surgeries. It is worth noting that the possibility of effectively treating OA patients in an outpatient setting might represent an economic advantage as it obviates the need for hospitalizations and additional costs [41]. Indeed, studies specifically designed to investigate the burden of IA injection therapies on the public health system are needed.

The panel of experts did not consider either antibiotic prophylaxis before IA injections or the use of sterile gloves during IA injections mandatory. These findings indicate that precautions adopted by medical staff to avoid iatrogenous infectious complications when performing IA injections vary considerably [42], there being a general trend towards minimal use of antiseptic techniques [42]. It should be borne in mind, however, that it has been recently demonstrated that some additional practices, such as the use of ultrasound probes and transmission gel during ultrasound-guided procedures, result in greater skin contamination during simulated IA injections [43]. Consequently, every precaution should be taken reduce the risk of contamination at the injection sites and physicians should be encouraged to use of the best way to protect patients from possible septic event.

Lastly, radiographic or ultrasound guidance for IA injections is considered to be necessary for hip IA injections, though not for knee IA injections. Although there is as yet no widespread consensus in the literature regarding the need for guidance when performing IA injections, as opposed to unguided procedures, guided IA injections are reported to be more accurate and safer. Indeed, they have been found to result in a better clinical outcome in terms of joint function improvement and in a decreased risk of damage due to needle misplacement [44]. Moreover, it should be borne in mind that imaging techniques used for IA injection guidance may be extremely important in the management of patients, particularly if a differential diagnosis is needed or appropriate.

Limits

The present results are based on a Delphi method-based survey, and thus reflect the current opinion of a sample of doctors with a high level of expertise who work in the field of IA injection therapy for OA in Italy. The use of the Delphi method was justified in this case because of the discrepancies that have emerged from the most important international guidelines drawn up for IA injection therapies in the management of OA [14]. A major strength of the Delphi method is that the people taking part bring a wide range of expertise and experience to the decision-making process. One of the challenges is, however, the choice of an appropriate panel of physicians, which should ideally include a wide range of experiences relevant to the question being addressed [45]. From this point of view, as we did not assess the expertise of the participants in all the fields of the survey (*e.g.* homotoxicology/ homeopathy; use of collagen-based products; use of PRP), we cannot exclude that some disagreement may have resulted from lack of specific knowledge/ experience. Lastly, as we decided to set the consensus level at > 66%, it is arguable that the use of a higher threshold could determine different results. However, similar values have been already used in literature [24] and account for two thirds of responses, therefore being considered acceptable for the purposes of the present research.

In conclusion, this Delphi method-based survey has highlighted several consensus statements that may prove useful as a reference for the management of patients with OA by means of IA injection therapies.

Author's contribution statement

MP, An Ber, DC, AN: design of the study, analysis and interpretation of data, drafting the manuscript.

Alb Bel, OB, SB, APC, FC, MF, LM, AM, UV: conception and design of the study, interpretation of data, revising the manuscript. They formed together with VS the Consensus Board.

VS: conception and design of the study, analysis and interpretation of data, drafting and revising the manuscript. He is guarantor for the accuracy and honesty of the report and the morality of the study.

Conflict of interest statement

None.

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