Received: 1 January 2024 | Accepted: 24 January 2024

DOI: 10.1002/ksa.12077

The use of injectable orthobiologics for knee osteoarthritis: A European ESSKA-ORBIT consensus. Part 1—Blood-derived products (platelet-rich plasma)

Lior Laver[1,2,3] | Giuseppe Filardo[4,5,6] | Mikel Sanchez[7,8] | Jeremy Magalon[9,10,11] | Thomas Tischer[12] | Ferran Abat[13] | Ricardo Bastos[14,15] | Ramon Cugat[16,17] | Micahel Iosifidis[18,19] | Baris Kocaoglu[20] | Elizaveta Kon[21,22] | Rodica Marinescu[23] | Marko Ostojic[24,25] | Philippe Beaufils[26] | Laura de Girolamo[27] | ESSKA-ORBIT Group

Correspondence
Lior Laver, Hillel Yaffe Medical Center, Hadera, Israel.
Email: laver17@gmail.com

Funding information
European Society for Sports Traumatology, Knee Surgery and Arthroscopy

Abstract

Purpose: The aim of this European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) consensus is to provide recommendations based on evidence and expert opinion to improve indications, decision-making and administration-related aspects when using blood-derived orthobiologics (for simplicity indicated as PRP—platelet-rich plasma—with PRP being the most common product) for the management of knee osteoarthritis (OA).

Methods: Leading European expert clinicians and scientists were divided into a steering group, a rating group and a peer review group. The steering group prepared 28 question—statement sets divided into three sections: PRP rationale and indications, PRP preparation and characterisation and PRP protocol. The quality of the statements received grades of recommendation ranging from A (high-level scientific support) to B (scientific presumption), C (low-level scientific support) or D (expert opinion). The question–statement sets were then evaluated by the rating group, and the statements scored from 1 to 9 based on their degree of agreement with the statements produced by the steering group. Once a general consensus was reached between the steering and rating groups, the document was submitted to the peer review group who evaluated the geographic adaptability and approved the document. A final combined meeting of all the members of the consensus was held to produce the official document.

Results: The literature review on the use of blood-derived products for knee OA revealed that 9 of 28 questions/statements had the support of high-level

For author affiliations refer to page 795.

Abbreviations: A2M, alpha-2-macroglobulin; ACS, autologous conditioned serum; CS, corticosteroid; HA, hyaluronic acid; IA, intra-articular; KL, Kellgren–Lawrence—KL is a 5-point scale ranging from 0 (patients with no chondral lesions or OA signs) to 4 (severe OA with large osteophytes, marked joint space narrowing and well-defined bone deformity); MR, magnetic resonance; NS, normal saline; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PRP, platelet-rich plasma; RCT, randomised controlled trial; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

scientific literature, while the other 19 were supported by a medium-low scientific quality. Three of the 28 recommendations were grade A recommendations: (1) There is enough preclinical and clinical evidence to support the use of PRP in knee OA. This recommendation was considered appropriate with a strong agreement (mean: 8). (2) Clinical evidence has shown the effectiveness of PRP in patients for mild to moderate degrees of knee OA (KL ≤ 3). This recommendation was considered appropriate with a strong agreement (mean: 8.1). (3) PRP injections have been shown to provide a longer effect in comparison to the short-term effect of CS injections. They also seem to provide a safer use profile with less potential related complications. This recommendation was considered appropriate with a very strong agreement (mean: 8.7). Six statements were grade B recommendations, 7 were grade C and 12 were grade D. The mean rating score was 8.2 ± 0.3.

Conclusions: The consensus group reached a high level of agreement on all the questions/statements despite the lack of clear evidence for some questions. According to the results from this consensus group, given the large body of existing literature and expert opinions, PRP was regarded as a valid treatment option for knee OA and as a possible first-line injectable treatment option for nonoperative management of knee OA, mainly for KL grades 1–3.

Level of Evidence: Level II.

KEYWORDS

Delphi consensus, knee, injections, orthobiologics, osteoarthritis, platelet-rich plasma

INTRODUCTION

Osteoarthritis (OA) is reported to affect more than 500 million people worldwide with a constant annual increase of cases due to the aging of the population and an average annual cost per patient of about 0.7–10K Euro [23]. The knee is the most common joint to be affected by OA [19], whose treatment is still a matter of debate. In fact, while the treatment of late-stage OA usually results in knee replacement, various conservative management options are available for earlier stages, although not always providing consistent or long-term outcomes [2]. In this context, the field of orthobiologics has emerged as a result of growing interest in biologic treatments for tissue healing in a variety of musculoskeletal conditions, among which knee OA, both as conservative injection treatment and in combination with surgical procedures. Injectable orthobiologic treatment options for knee OA have undoubtedly become a major player in the field of nonoperative management of this pathology. Nevertheless, the lack of unanimous opinion by professionals in terms of patients' indications, administration protocols and even more in the choice of the available options/devices need to be addressed.

The most commonly used orthobiologic treatment to address knee OA is currently platelet-rich plasma (PRP) injection. Preclinical studies have shown favourable disease-modifying actions of PRP in animal models [7] in terms of cartilage damage progression, reduction of synovial inflammation and changes in biomarker levels. On humans, a few studies demonstrated disease-modifying effects. Among them, a recent randomised controlled trial (RCT) analysed the synovial fluid from mild-moderate OA knees treated with PRP or saline. The results showed significant changes for the biomarker A2M, the expression of cellular markers and gene expression profiles in mesenchymal stem cells for matrix metalloproteinases and inflammatory markers in favour of the PRP-treated group [33].

Despite a wide variety with regards to PRP formulations, protocols and control groups used in clinical studies, at the at the time of the conclusion of the consensus process, 48 RCTs on the use of PRP for the management of knee OA written in English language were retrieved in Medline, with the majority (38, of which 24 of level of evidence I and 14 of level II) showing superiority of PRP treatment compared to other injectable options such as corticosteroids (CSs) and hyaluronic acid (HA) as well as saline. The remaining 10 showed similar results of PRP injections to either CS, HA, bone marrow aspirate concentrates or even saline. However, although most of the RCTs report superiority of PRP versus saline in treating knee OA [9, 17, 22, 26, 27, 34], a few studies showed that in patients with symptomatic mild to moderate knee OA,

intra-articular injection of PRP did not result in a significant difference in symptoms or joint structure at 12 months compared with injection of saline [6, 18, 20]. This has been suggested to be related to the wide heterogeneity of PRP products, variability in patient populations, the multifactoriability of knee OA and various potential biases. In any case, the fact that some studies have shown lack of such superiority still warrants some caution when assessing the efficacy of orthobiologic treatments and could explain why additional assessment and quality measures are required when evaluating the full potential of these treatments.

It is undisputable that some conflicting evidence is still found in the literature. However, in the last few years, there has been an increase of more consistent and homogeneous reports about the effect of platelet concentrates showing that PRP injections provide satisfactory results in the treatment of knee OA. Recent meta-analyses showed that patients undergoing treatment for knee OA with PRP can be expected to experience improved clinical outcomes when compared to saline [15] or to HA at 12-month follow up [5, 15, 31], with a comparable safety profile of both treatment options.

As Europe's largest association of musculoskeletal specialists, the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA), beyond playing a fundamental role in education of young orthopaedic surgeons and other professionals of the field [11, 28], it has felt the responsibility to provide its members and in general the orthopaedic community with practical sources of reference and guidance. Therefore, the ESSKA established the ORthoBIologics InitiaTive (ORBIT) to assemble a pan-European collaboration to create a common language and a uniform and reliable voice in the field of orthobiologics as well as driving good standard of care in this field.

The specific focus of this manuscript is on blood-derived products (including but not limited to PRP). Following previous successful collaborative experiences conducted under the ESSKA formal consensus process on other topics [3, 10, 21, 32], the results of the current consensus provide recommendations based on evidence and expert opinion to improve indications, decision-making and administration-related aspects when using blood-derived orthobiologics for the non-operative management of knee OA.

MATERIALS AND METHODS

Terminology

The term ‘blood-derived products' refers to a wide variety of products that are obtained by processing peripheral blood with different systems/techniques, resulting in blood fractions enriched in therapeutic molecules. Among them, the most known and used are PRP, platelet-rich fibrin, platelet-rich growth factors, autologous conditioned plasma and autologous protein solution, all based on platelet concentration, as well as other products such as autologous conditioned serum (ACS) and alpha-2-macroglobulin (A2M). For the sake of simplicity, PRP being the most common product, it will be generically used to refer to any autologous blood-derived product based on platelet concentration by minimal blood manipulation (not including in this term nonplatelet concentration-based products such as ACS or A2M, which were addressed in specific questions-statement briefly discussed separately).

While the authors recognise that there is great variability among different products, the aim of this consensus is not to provide information about any specific technique or commercial system available but to provide general recommendations about the use of blood-derived products for the treatment of knee OA.

Consensus methodology

The process of this consensus project was similar to previously published ESSKA formal consensus projects [3, 21, 32] and followed the ESSKA ‘formal consensus process' derived from the Delphi methodology as described by the French National Healthcare Institution Haute Autorité de Santé HAS [4, 29] (Figure 1). All the group meetings for the current consensus were performed online due to COVID-19 restrictions. The consensus process included three groups of experienced orthopaedic surgeons and scientists: steering group, including literature group, $n = 14$; rating group, $n = 22$; and peer review group, $n = 35$. The steering group, which included 14 expert orthopaedic surgeons and scientists under the leadership of two specialists with a particular interest in orthobiologics (LL and LdG) and under the guidance of the ESSKA consensus projects advisor (PB), was equally divided into a question and a literature group. The former group did a series of relevant questions that were drafted with the aim of addressing areas of interest, daily practice and current controversies with regard to the use of PRP for the management of knee OA. The questions underwent prioritisation based on their clinical significance, answerability and scientific importance facilitated by a piece of decision-making software (1000minds.com). This software repeatedly presented the group members with pairs of research questions and asked them to choose one according to either clinical importance, answerability or scientific/research importance. Repeated comparisons, across all group members, led to an ordered list of research questions which was then narrowed down and refined by the steering group, resulting in 28 questions.

The questions were divided into three main topics which would represent the three sections of the question list: PRP rationale and indications (questions 1–14), PRP preparation and characterisation (questions 15–18) and PRP protocol (questions 19–28).

For each question, a targeted literature search was independently performed by the literature group to determine the current knowledge status. The literature search was performed between June 2021 and November 2021 on PubMed, according to keywords relevant to each specific question. References in the identified studies were also examined to provide additional evidence-based information. Relevant papers published whilst conducting the consensus study were also included. The title and abstract of all references were examined, and any relevant article was then obtained in full for the steering group and summarised as a brief report. Only papers published in English between 2000 and 2022 were considered, for a total of 275 citations corresponding to 217 manuscripts (mean citations per question = 10).

Following completion of the literature reviews by the literature group for each of the questions, the members of the steering group, except those who were in charge of the literature search, produced respective statements/recommendations based on the literature found as well as the entire steering group's expert opinion. For each statement, a grading system was used to determine its scientific level. The ratings, based on the level of evidence (LOE) of existing studies, indicate whether the literature provides sufficient and clear evidence to produce a clear answer to each question and whether the literature is in accordance with the consensus expert's experience.

Grade A (When at least three LOE1 papers were present).

Grade B (When at least three LOE2 papers were present).

Grade C (Cohort series/comparative studies, with concordant conclusions. Or high-level studies but with contradictory or nonconclusive results).

Grade D (Literature is very poor or absent = expert opinion of the group).

The assignment of the grade was based on the LOE of the literature existing on the topic related to the question following international guidelines with slight modifications [16].

All question-statement sets were thoroughly discussed, and a consensus was achieved by the steering group according to the scientific grading. After a general agreement was achieved within the steering group, the questions-statements were then submitted to the rating group, composed by an independent panel of 22 experienced clinicians who were asked to score all the statements. The rating phase was composed of two rounds, in which the panel evaluated and ranked each statement according to a discrete numerical scale (Likert scale from 1—lowest grade of agreement/totally inappropriate to 9—highest grade of agreement/totally appropriate). A value of '5' would indicate uncertainty, and therefore, any value below this threshold would be considered unappropriated. Following the first rating round, the text was modified by the steering group, taking into account the rating group's comments, and a second rating round by the rating group was carried out. Following this stage, a combined meeting of the steering and rating groups was organised to validate the draft and finalise the text statements.

It should be noted that the LOE (resulting in grade of recommendation) and agreement are not related. Agreement is a specificity of a consensus, which means the raters found a common agreement on a given question-statement. Obviously, if there is a high LOE in the literature, a high agreement will be theoretically easy to achieve among raters. But even in case of low LOE (i.e., grade C) or absence of literature (i.e., grade D), it is possible to achieve a high agreement (i.e., 8 and 8.5), provided the statement is well written.

In the final step, the finalised text was then circulated among the peer review group composed by delegates chosen by the ESSKA-affiliated societies across Europe to assess the clarity, geographic adaptability and acceptance of the statements across Europe. In total, 18 affiliated societies (16 European countries) participated to the peer review of the document. A final meeting of the entire steering group was then conducted to finalise the whole text.

RESULTS

The complete consensus document which included the used references can be found both on ESSKA and ESSKA Academy websites (http://www.esska.org/page/projects and https://academy.esska.org), as well as available as Supporting Information: File 1.

Following the second rating round, recommendations were rated with an average of 8.2 ± 0.3 points out of maximum 9 points. The mean agreement scores for each question/statement ranged from 7.5 to 8.8. Only six of the 28 statements received a rating of less than 8, with three receiving a score of 7.9, one of 7.8 and one question divided into 2 statements received a score of 8.0 for the first part and 7.5 for the other one. All the other questions achieved an agreement of above 8.0 points. All the statements were, thus, considered as appropriate. Three questions/statements were evaluated as grade A, six as grade B, seven as grade C and 12 as grade D (Table 1).

COMPLETE LIST OF QUESTIONS AND STATEMENTS

Section 1: PRP rationale/indications

1. Does current clinical evidence support the use of PRP for knee OA?

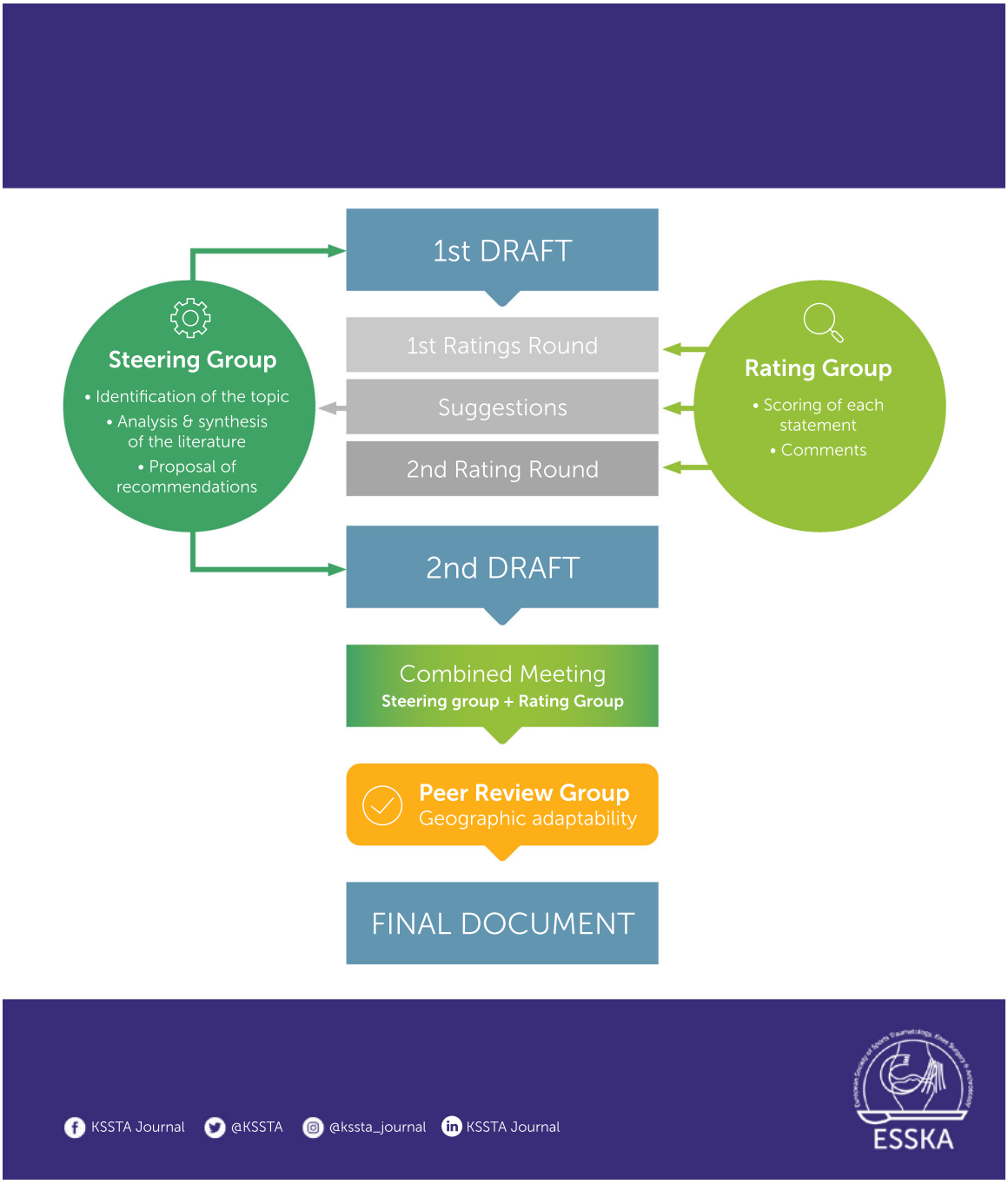

FIGURE 1 Flowchart of the procedure used to determine the ESSKA consensus on the use of injectable orthobiologics for knee osteoarthritis. ESSKA, European Society of Sports Traumatology, Knee Surgery and Arthroscopy.

Clinical evidence confirms the efficacy of PRP in the treatment of knee OA. Level I and II clinical studies, as well as additional prospective studies, support the safety and clinical benefit of PRP for knee OA, which was shown in comparison to both placebo (saline) and control treatments such as HA or CSs. The efficacy of PRP in the treatment of knee OA has been also supported by meta-analyses and confirms the findings of preclinical research.

The consensus group therefore concluded that there is enough preclinical and clinical evidence to support the use of PRP in knee OA (see following questions addressing PRP specifications and indications).

(Grade A, Agreement: 8.0)

2. **For which degrees of knee OA is PRP best indicated?**

Clinical evidence has shown the effectiveness of PRP in patients for both mild to moderate degrees of knee OA (KL ≤ 3). The consensus group concludes

that PRP can be indicated mainly in mild and moderate cases of knee OA.

(Grade A, Agreement: 8.1)

3. **Can PRP be used in severe knee OA (KL4)?**

The consensus group agrees that PRP treatment could be considered in selected severe knee OA cases (KL4), for example, in patients who decline or are not suitable for surgery due to comorbidities, although lower results could be expected and physicians should provide cautious expectations when discussing or suggesting this approach.

(Grade C, Agreement: 8.1)

4. **Is PRP indicated for the treatment of patellofemoral OA (PFOA)?**

Despite current literature on the effect of PRP for PFOA being limited, evidence suggests it may have positive effects, especially in early-stage disease. The consensus group does not consider the presence of PFOA a contraindication or a limiting factor when considering PRP as an injectable option for knee OA. In addition, as PRP has been shown to affect the knee environment in general, the consensus group considers PRP as an option in the presence of PFOA.

(Grade C, Agreement: 7.6)

5. **Are there specific contraindications for the use of PRP for knee OA?**

Besides the generally accepted contraindications for any knee injections, other specific contraindications have been identified for PRP injections for the treatment of knee OA. While the majority of suggested contraindications have not been thoroughly or sufficiently studied, the consensus group chose to recommend caution in the presence of coexistent malignancies or systemic conditions due to possibility of unknown interactions.

- Contraindications due to local problems in the injection area: any contraindication for knee injections, such as infection, skin problems, others.
- Contraindications due to systemic problems (they can be grouped in four main groups):

- Infections

Besides the well-known reasons not to perform a knee injection in a patient with active systemic infections, systemic infections also affect negatively the PRP performances/functionalities because in addition to the immune and inflammatory process they generate at the systemic level, platelets are modified in these processes and may be more hyper-reactive, altering their functionality.

- Cancer

Specific contraindications exist for the use of PRP in patients with active malignancies.

In terms of malignancies, current literature has not demonstrated a clear link between PRP contents and the risk of tumour proliferation, either locally or remotely. However, due to the theoretical risk that PRP and growth factors may contribute to tumour growth promotion in situations where either a benign or malignant tumour exists in the knee joint, the consensus group considers these conditions a contraindication for injecting PRP. Due to similar concerns and until further evidence is available, the consensus group recommends this recommendation should also apply to tumours with or without metastasis located in other locations, outside/even remote from the knee, although consultation should be made with the managing oncologist/physician in specific cases.

- Inflammatory diseases

The presence of local or systemic inflammatory diseases (rheumatoid arthritis, Chron's disease and or other autoimmune diseases) does not prevent the possibility of injecting PRP in the knee. However, the nature of these diseases can lead to a plasma with a high content of proinflammatory molecules that may lead to lower results.

- Blood and quantitative and qualitative platelet disorders

Problems such as thrombocytopenia, thrombocytosis or coagulopathies can also alter platelet numbers and their functionality.

The use of antiplatelet therapy should be considered a relative contraindication to PRP. This is mainly related to patients unable to perform surgery or other types of more invasive treatment, without many alternatives in the search of temporary symptomatic relief. However, information regarding expected lower outcome should be mandatory.

(Grade D, Agreement: 8.0)

6. **For what age range is PRP recommended?**

The majority of studies included patients with a mean age between 55 and 65 years. The consensus group agrees that a specific age range cannot be recommended, though recognises that there is evidence of reduced response in older patients. The consensus group suggests that other factors should come into consideration and that the decision should not be based only on chronologic age.

(Grade D, Agreement: 8.4)

7. **Could PRP for knee OA be used during the inflammatory phase when joint effusion is present (following effusion aspiration)?**

Current clinical evidence is lacking regarding the injection of PRP during the inflammatory phase in knee OA, as well as with regards to effusion aspiration prior to PRP injection.

Preclinical and clinical studies have suggested anti-inflammatory properties in PRP which could

TABLE 1 Summary of the consensus results.

Question	Question title	Scientific grade	Rating score	No. of references cited (best evidence)
1	Does current clinical evidence support the use of PRP for knee OA?	A	8	10 (5 MA; 1 SR; 4 RCTs)
2	For which degrees of knee OA is PRP best indicated?	A	8.1	13 (6 RCTs)
3	Can PRP be used in severe knee OA (KL4)?	C	8.1	13 (6 RCTs)
4	Is PRP indicated for the treatment of patellofemoral OA (PFOA)?	C	7.6	5 (2 RCTs)
5	Are there specific contraindications for the use of PRP for knee OA?	D	8	17 (2 SR; 2 RCTs)
6	For what age range is PRP recommended?	D	8.4	10 (3 MA; 2 RCTs)
7	Could PRP for knee OA be used during the inflammatory phase when joint effusion is present (following effusion aspiration)?	D	7.9	10 (2 RCTs; 4 CLS)
8	Is a repeated cycle of PRP injections recommended following a previous successful PRP treatment for knee OA upon the re-emergence of symptoms?	D	8.4	7 (3 RCTs; 1 PRT)
9	Is there rationale in injecting PRP in asymptomatic early knee OA? (Prevention?)	D	8.7	6 (3 SR)
10	Are there advantages of PRP use in comparison to corticosteroids for treating knee OA?	A	8.7	11 (6 MA; 2 SR; 1 RCT)
11	Is PRP a clinically better injectable option than hyaluronic acid for the treatment of knee OA?	B	8.1	10 (10 MA)
12	Does PRP induce disease-modifying effects in knee OA?	C	8.3	11 (1 SR; 8 RCTs)
13	Does current clinical evidence support the use of autologous conditioned serum (ACS) for knee OA?	B	8.8	10 (2 RCTs; 3 PCS)
14	Does current clinical evidence support the use of alpha-2-macroglobulin (A2M) for knee OA?	D	8.7	8 (1 animal RCT; 1 PCS; 2 IVS)
15	Which PRP is preferred for knee OA: leucocyte-rich PRP (LR-PRP) or leucocyte-poor PRP (LP-PRP)?	B	8.1	7 (5 MA; 2 RCTs)
16	What is the recommended platelet number/concentration range for PRP injections in knee OA?	C	8.2	9 (1 SR; 4 RCTs)
17	PRP preparations/products for a knee OA: what should we measure in PRP/quality control?	D	8	10 (10 EOP)
18	What is the recommended volume of PRP to inject into a knee for the treatment of knee OA?	D	8.7	14 (1 MA; 2 RCT; 1 PCS, 1 Consensus Paper)
19	How many injections of PRP are recommended for the treatment of knee OA?	B	8	20 (15 RCTs)
20	When using a treatment protocol with more than one injection for knee OA, what is the recommended interval between each injection of PRP?	B	8	19 (1 SA; 11 RCTs)
21	Do syringe and needle size matter for blood harvesting and injecting PRP?	C (S1)	7.9 (S1)	2 (1 PCS; 1 OS)
		D (S2)	7.9 (S2)	
22	Are nonsteroidal anti-inflammatory drugs (NSAIDs) allowed around PRP use?	C (S1)	8.1 (S1)	9 (1 RCT; 3 PCS; 3 IVS)
		C (S2)	8.3 (S2)	

(Continues)

TABLE 1 (Continued)

Question	Question title	Scientific grade	Rating score	No. of references cited (best evidence)
23	Should intra-articular local anaesthetics be used when injecting PRP?	D	8.7	3 (3 IVS)
24	Is antibiotics administration recommended around PRP use?	D	8.6	4 (1 SR)
25	Is fasting recommended before PRP use? Any other patients's behaviour could affect the treatment?	D (S1) D (S2)	8.0 (S1) 7.5 (S2)	15 (2 RCT)
26	Can corticosteroid (CS) injections prior to PRP improve the results in knee OA?	D	8.3	13 (1 MA; 1 SR; 1 RCT; 1 PCS)
27	Does PRP and HA have a synergistic effect?	C	7.8	6 (3 MA; 1 SR; 1 RCT)
28	Is there any synergy between PRPs and cell-based therapies for knee OA?	B	8	16 (5 RCT; 4 CLS; 1 PCS)

Note: S1 and S2: statement 1 and 2, respectively, where more than a statement was produced for the given question.

Abbreviations: CLS, controlled laboratory study; EOP, expert opinion publication; IVS, in vitro study; MA, meta-analysis; OS, observational study; PCS, prospective cohort study; PRT, prospective randomised trial; RCT, randomised controlled study; SR, systematic review.

support the rationale for its use during the inflammatory phase.

While evidence is lacking with regards to the optimal timing of PRP injection for knee OA when effusion is present, the consensus group recognises that when present, effusion aspiration is likely beneficial in pain improvement and relieving functional limitations. The consensus group recommends effusion aspiration also to avoid the dilution of the PRP following injection.

(Grade D, Agreement: 7.9)

8. **Is a repeated cycle of PRP injections recommended following a previous successful PRP treatment for knee OA upon the re-emergence of symptoms?**

While current evidence regarding repeated cycles of PRP treatment for knee OA is limited, it has been suggested that this strategy may have clinical benefit. As evidence suggests a decrease in the effects of PRP for knee OA over time, the consensus group agrees that an additional cycle could be considered upon the re-emergence of symptoms.

(Grade D, Agreement: 8.4)

9. **Is there rationale for injecting PRP in asymptomatic early knee OA? (as a prevention strategy)**

Currently, there are not enough clinical studies addressing this question, and therefore, it cannot be stated that the application of PRP in asymptomatic OA prevents its progression. Although preclinical studies suggest a chondroprotective role of PRP, there is no sufficient clinical evidence on the chondroprotective effect of PRP in patients with asymptomatic early stages of OA. Therefore, the consensus group currently does not advocate the use of PRP in asymptomatic early knee OA.

(Grade D, Agreement: 8.7)

10. **Are there advantages of PRP use in comparison to corticosteroids for treating knee OA?**

While CSs are strong anti-inflammatory agents and can provide short-term relief in knee OA, they have been shown to have detrimental effects on chondrocytes and can lead to accelerated cartilage degeneration, especially with multiple/repeated injections. PRP injections have been shown to have a longer effect in comparison to the short-term effect of CS injections. They also seem to provide a safer use profile with less potential related complications. The consensus group considers PRP injections to be a safer, nonchondrotoxic and more effective treatment option, with long-term clinical improvements compared to CS injections.

(Grade A, Agreement: 8.7)

11. **Is PRP a clinically better injectable option than hyaluronic acid for the treatment of knee OA?**

Several high-level studies as well as multiple meta-analyses exist comparing the effectiveness of PRP compared to hyaluronic acid for knee OA, with the majority favouring PRP in terms of overall clinical improvement and a long-lasting effect.

Based on current available evidence, the consensus group supports the use of PRP over hyaluronic acid for knee OA due to overall clinical improvement and expected long-lasting effects, whilst acknowledging that there are different formulations of the products that may introduce some bias in the conclusions of meta-analyses. *(Grade B, Agreement: 8.1)*

12. **Does PRP induce disease-modifying effects in knee OA?**

Preclinical studies (animal models) suggest some disease-modifying effects, with positive changes on cartilage tissue and on the synovial membrane. Although few clinical studies have suggested disease-modifying potential of PRP on degenerative cartilage, the consensus group recognises that current clinical evidence regarding the disease-modifying effects of PRP in knee OA in humans is insufficient.

(Grade C, Agreement: 8.3)

13. **Does current clinical evidence support the use of autologous conditioned serum (ACS) for knee OA?**

Compared to PRP, ACS is less investigated. There is no clear evidence with regards to the role of ACS in OA management. While it may have a role as a possible inflammation-modulating agent due to the presence of IL-1 receptor antagonists in this product, results on the clinical efficacy of this approach are inconsistent. Currently, no recommendations can be provided given due to the lack of sufficient evidence.

(Grade B, Agreement: 8.8)

14. **Does current clinical evidence support the use of alpha-2-macroglobulin (A2M) for knee OA?**

Compared to PRP, A2M is less investigated. Preclinical studies showed that intra-articular A2M administration induces an anti-inflammatory mechanism and slows down cartilage damage and bone resorption. However, since there are no clinical RCT studies regarding the use of A2M for knee OA, currently no recommendations can be provided.

(Grade D, Agreement: 8.7)

Section 2: PRP preparation/characterisation

15. **Which PRP is preferred for knee OA: leucocyte-rich PRP (LR-PRP) or leucocyte-poor PRP (LP-PRP)?**

Several meta-analyses and network meta-analyses have compared the effectiveness of LP-PRP compared to LR-PRP for knee OA with overall inconclusive results.

The consensus group acknowledges that the effectiveness of PRP is likely multifactorial and therefore the dependence on the presence of leucocytes alone might be overestimated as other factors may also have a contribution. Therefore, the consensus group currently does not support one type of PRP over the other and considers both LP-PRP and LR-PRP valid options for the management of knee OA when PRP is considered.

(Grade B, Agreement: 8.1)

16. **What is the recommended platelet number/concentration range for PRP injections in knee OA?**

The effect of PRP is complex and multifactorial, with numerous growth factors released playing an important role, as well as pro- and anti-inflammatory cytokines released following platelet activation. However, a clear correlation between the number of platelets in PRP and clinical response has not been well established. There is no doubt that platelets are the central player in PRP products; however, the consensus group concludes that the optimal characterisation of PRP for knee OA is complex and includes many variables, and therefore, currently optimal platelet ranges for the treatment of knee OA cannot be defined.

(Grade C, Agreement: 8.2)

17. **PRP preparations/products for knee OA: what should we measure in PRP/quality control?**

PRP preparations and products vary in terms of platelet number and concentration, specific growth factors levels, white blood cells content and volume, as well as they are influenced by baseline blood parameters (i.e., baseline platelet count). Therefore, PRP preparations using commercial kits may vary in content and could still produce inconsistent preparations. For these reasons, the consensus group suggests that recording the baseline whole blood cellular and platelet composition, as well as those of the produced PRP preparation as a minimum, would improve the understanding of the efficacy of PRP for knee OA and should be recommended as quality control measures in clinical research setups, with the aim to encourage using such quality control measures routinely in clinical setups in the future. Collecting these parameters would enable incorporating data into one of the currently available PRP classification, further allowing comparisons between products and a deeper analysis of quality control.

(Grade D, Agreement: 8.0)

18. **What is the recommended volume of PRP to inject into a knee for the treatment of knee OA?**

While the total volume of PRP injected may play a role, currently there is no evidence in the literature for the optimal volume to be injected,

with volumes ranging from 2 to 12 mL.

The consensus group cannot provide any recommendation on the volume even if the group suggests that the knee size could be taken into consideration.

(Grade D, Agreement: 8.7)

Section 3: PRP protocol

19. **How many injections of PRP are recommended for the treatment of knee OA?**

While the literature is not conclusive with regards to the optimal number of injections per PRP treatment cycle for knee OA, the majority of articles reports that protocols with more than one injection provide better clinical improvement, at least with early OA.

The consensus group realises that factors such as injection volume and platelet concentration may largely differ between available PRP products and may influence the effect of each injection. The consensus group recommends a range of two to four injections.

(Grade B, Agreement: 8.0)

20. **When using a treatment protocol with more than one injection for knee OA, what is the recommended interval between each injection of PRP?**

While the literature is not conclusive on the optimal interval between injections when using a multiple PRP injection protocol (>1 injection per treatment cycle) for knee OA, intervals ranging from 1 to 4 weeks have been reported.

As the main period of released growth factor activity takes place within the first 3 weeks from injection, the consensus group suggests that interval ranges of 1–3 weeks may be more appropriate.

(Grade B, Agreement: 8.0)

21. **Do syringe and needle size matter for blood harvesting and injecting PRP?**

Current evidence does not suggest needle size being a factor influencing platelet integrity. The consensus group recommends that needle size should not matter neither for injection of PRP nor for blood collection for PRP preparations for musculoskeletal disorders.

(Grade C, Agreement: 7.9)

Caution should be applied to the flow rate during blood aspiration when using large size syringes in a manual technique to avoid blood haemolysis.

(Grade D, Agreement: 7.9)

22. **Are nonsteroidal anti-inflammatory drugs (NSAIDs) allowed around PRP use?**

With regards to NSAIDs use around PRP injections, while current evidence is inconclusive, the potential effects of NSAIDs on platelets and in vivo growth factors release still warrants caution. The consensus group therefore recommends to avoid the use of NSAIDs for 2 weeks prior to PRP administration.

(Grade C, Agreement: 8.1)

For pain management after PRP injections, since NSAIDs may affect growth factor release even after the injection, the consensus group recommends to avoid NSAIDS for the first week postinjection and if necessary use nonanti-inflammatory pain medications (i.e., paracetamol, dipyrone and tramadol).

(Grade C, Agreement: 8.3)

23. **Should intra-articular local anaesthetics be used when injecting PRP?**

Currently no high-level clinical studies exist regarding the effect of local anaesthetics on PRP; however, in vitro studies have shown that local anaesthetics interfere with platelet integrity and functionality as well as diminish the positive effects of PRP on cell proliferation. Therefore, the consensus group currently does not recommend the use of intra-articular local anaesthetics when injecting PRP.

The consensus group does, however, agree that local anaesthetics can be administered subcutaneously, without penetrating the capsule.

(Grade D, Agreement: 8.7)

24. **Is antibiotics administration recommended around PRP use?**

Current clinical evidence does not support the use of antibiotics around PRP use. Therefore, the consensus group does not recommend the use of antibiotics around PRP administration.

(Grade D, Agreement: 8.6)

25. **Is fasting recommended before PRP use? Any other patients' behaviour could affect the treatment?**

Data regarding the direct impact of fasting on the therapeutic effects of PRP is lacking. However, since there is evidence on the effect of various foods and high-fat and high-cholesterol diets on platelet behaviour, both in number and function, as well as on platelet activation, the consensus group recommends patients to avoid high-fat foods for at least 24 h prior to blood harvest.

(Grade D, Agreement: 8.0)

Eliminating alcohol for at least 48 h prior to PRP preparation may allow platelets to re-establish their normal factor content and aggregation properties, and therefore, the consensus group considers it as a safe suggestion.

(Grade D, Agreement: 7.5)

26. **Can corticosteroid (CS) injections prior to PRP improve the results in knee OA?**

The consensus group recommends to avoid using PRP in close proximity to CS. However, the consensus group recognises that patients may

have had recent CS injections, and, in this scenario, the consensus group suggests a minimum interval of 6 weeks from a recent CS injection.

(Grade D, Agreement: 8.3)

27. **Do PRP and hyaluronic acid (HA) have a synergistic effect?**

While current preclinical and clinical literature suggest some potential benefits of combining these two products, evidence of clear benefits of combining these treatments is still lacking. Therefore, the consensus group recognises that more data are required before recommending the combination of PRP and HA over PRP alone for knee OA.

(Grade C, Agreement: 7.8)

28. **Is there any synergy between PRP and cell-based therapies for knee OA?**

While current preclinical and clinical literature suggest some potential benefits of combining PRP and cell-based therapy, with the majority of studies focusing on culture-expanded cells, evidence is still lacking regarding the clear benefits of using these products in combination over using them on their own. Therefore, based on current evidence, the consensus group does not suggest the combination of PRP and cell-based therapy over PRP or cell-based therapy alone for knee OA.

(Grade B, Agreement: 8.0)

DISCUSSION

The ESSKA-ORBIT consensus group produced a consensus document on the use of blood-derived orthobiologic products for the nonoperative management of knee OA, where the main finding is that, based on the current evidence, there is an agreement within the consensus group to support the use of PRP as a valid nonoperative treatment option for KL grades 1–3 knee OA, which could be considered as a first-line injectable treatment option in these patients (Figure 2).

Even though the documented clinical outcomes are affected by the variability in indications, preparations protocols, administration protocols and product characteristic, the consensus group was able to reach a high level of agreement in all the questions/statements. Nevertheless, it should not be neglected that controversies still exist in relation to its full effectiveness. However, these discrepancies have been progressively reduced over time, with more and more consistent results showing significant and durable clinical outcomes when PRP is used for the conservative treatment of knee OA.

Looking at the competitor treatments, although HA could be still considered the most common first-line conservative treatment for practical reasons, PRP is shown to be superior to HA, with more than 25 level I randomised controlled studies published between 2011 and 2019 consistently supporting this evidence [1, 8, 12, 13, 22]. Interestingly, no differences have been seen after 1 month from injection between the two treatments, whereas PRP scored clinically better at 3-, 6- and 12-month follow-ups, confirming the longer durability of the results over other treatments [15, 24, 25, 31]. Compared to CSs, PRP was also shown to be superior by multiple meta-analysis including level I [25] or level I and II studies [24], beyond being reported to be safer and without side effects when compared to CSs.

The consensus was aimed to answer and provide recommendations on the key issues clinicians may encounter when considering orthobiologics use for knee OA. Therefore, for practical reasons, the document was divided into three main sections addressing the appropriateness of this approach and relevant indications, aspects regarding product variability and characteristics of different available products, as well as common administration, safety and peri-administration-related aspects. Also, the document discusses the role of PRP in comparison to other injectable agents.

Assembling a leading group of experts in a specific field is crucial to generate a high-quality consensus. Another key factor to successfully conduct and complete a consensus project is the strict adherence to a well-defined and validated methodology [4, 29, 30] that includes an iterative process that is necessary to ensure increasing agreement and aids in achieving a high consensus level.

An additional strong point of the current consensus is its pan-European geographical representation: the consensus project involved 75 clinicians and scientists from a total of 23 European countries. The consensus document should therefore be considered as a reliable depiction of the European position on this topic, making it wider than those already published by national groups on the same topic, even if of a good quality [14]. Moreover, this consensus group focused on aspects such as the comparison with other injective treatments, the difference with blood-derived products not based on platelet concentration, the possible disease-modifying effect of PRP treatment, as well as the possible influence of patients' behaviour on the clinical efficacy of PRP which were not addressed in previous consensus work [14].

Given the active participation of 18 European national orthopaedic societies, it would be important to spread the consensus results in their respective communities to create a homogenous continental approach. However, it is also important to acknowledge that healthcare systems are different among different countries and they may influence the daily practice

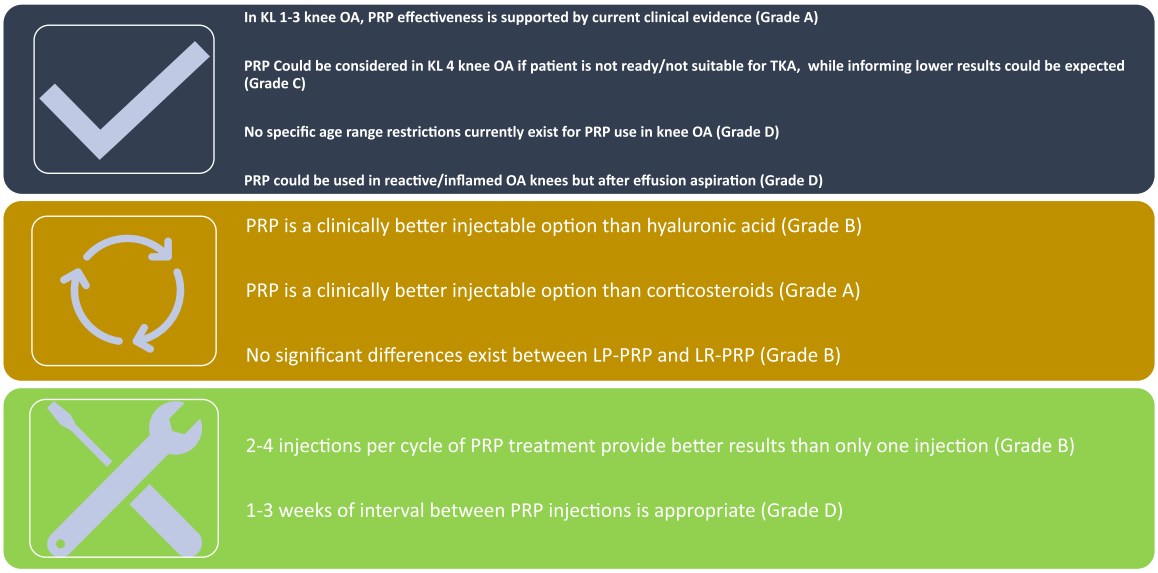

FIGURE 2 A summary of the main messages of the ESSKA consensus on the use of injectable orthobiologics for knee osteoarthritis. ESSKA, European Society of Sports Traumatology, Knee Surgery and Arthroscopy.

clinical decision-making and may not always be in line with the scientific data. Thus, the statements and recommendations provided in this consensus do not represent absolute values or standalone parameters, rather they should be interpreted in a critical manner for each individual patient and used in combination with clinical evaluation and other objective assessments to develop an adequate preoperative planning on a case-by-case basis.

The document includes some limitations too. First, a consensus typically includes aspects with high-level and other with low-level scientific evidence. In the latter cases, expert opinion has been used to give the best available recommendation. However, while high-level systematic reviews include only high scientific evidence, often they are not able to answer the questions asked by the daily practitioners. This is the scope of a consensus: even if for some questions the grade of recommendation is low, still the document provides the best practical help available to practitioners.

Second, this consensus reports recommendations at a specific time point, but as the knowledge will evolve in time, the management of knee OA may evolve and develop accordingly. An important acknowledgement when interpreting these recommendations is that profiling the ideal knee OA patient for PRP/blood-derived products use is complex and multifactorial. Treatment decision is often not based on isolated factors, and it is the understanding of where in the OA process the clinician meets the patient, integrating variable factors, objective and subjective, including the clinician's personal experience. Also, it is important to remember that knee OA is often multifactorial, and mechanical malalignment may play a significant role in certain cases (tibio-femoral and patello-femoral malalignment), which could be addressed surgically when relevant. While the consensus cannot address each and every specific scenario, when discussing orthobiologic injections for knee OA, we do not refer to gross mechanical malalignment scenarios which may require surgical intervention, although decisions should be made on a case-by-case basis. Third, since it would have been impossible to run a consensus process for each different type of blood-derived product, the consensus document gathers information and results deriving from several types of products with different characteristics. The consensus findings are therefore applicable to those products that are accompanied by a good level of clinical evidence.

Therefore, the scope of this consensus was not to provide an 'a-la-carte' menu in order to profile the ideal patient/candidate but rather to provide recommendations that address commonly encountered scenarios when considering blood-derived therapy for knee OA.

All potential conflicts of interest of all those involved in the drafting of the consensus (steering and rating group) are reported in the full consensus document available in Supporting Information: file 1 and on the ESSKA and ESSKA Academy websites (http://www.esska.org/page/projects and https://academy.esska.org).

Since the consensus steering and evaluation groups were composed of experts active in the fields, some of the references included in the consensus document obviously involved these members. However, the percentage of references which include steering and/or rating group members as authors (in first, last or middle position) is just 15% (33 out of 217 papers cited, with an

average of less than one paper per member, being the total number of steering and rating group members equal to 36). This adds to the fairness of the process and the impartiality of the analysis, which is further supported by the high number of clinicians and scientists involved in the process (75 in total).

CONCLUSIONS

The management of knee OA is complex, and the use of orthobiologics is ever growing in this medical field. A European ESSKA-ORBIT consensus has been developed to aid in and improve decision-making when considering the use of blood-derived products for the management of knee OA. According to the results from this consensus group, given the large body of existing literature and expert opinions, PRP was regarded as a valid treatment option for knee OA and as a possible first-line injectable treatment option for nonoperative management of knee OA, mainly for KL grades 1–3.

This project should be considered more as a 'framework' rather than 'strict guidelines' which aims to provide a reference frame for the use of blood-derived products for the management of knee OA, based on prevailing current scientific literature and expert viewpoint.

AFFILIATIONS

[1]Department of Orthopaedics, Hillel Yaffe Medical Center (HYMC), Hadera, Israel

[2]Rappaport Faculty of Medicine, Technion University Hospital (Israel Institute of Technology), Haifa, Israel

[3]Arthrosport Clinic, Tel-Aviv, Israel

[4]Service of Orthopaedics and Traumatology, Department of Surgery, EOC, Lugano, Switzerland

[5]Faculty of Biomedical Sciences, Università Della Svizzera Italiana, Lugano, Switzerland

[6]Applied and Translational Research Center, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[7]Arthroscopic Surgery Unit, Hospital Vithas Vitoria, Vitoria-Gasteiz, Spain

[8]Advanced Biological Therapy Unit, Hospital Vithas Vitoria, Vitoria-Gasteiz, Spain

[9]Cell Therapy Laboratory, Hôpital de la Conception, AP-HM, Marseille, France

[10]INSERM, INRA, C2VN, Aix Marseille Univ, Marseille, France

[11]SAS Remedex, Marseille, France

[12]Department of Orthopaedic Surgery, University of Rostock, Rostock, Germany

[13]Department of Sports Orthopaedic, ReSport Clinic, Universitat Autònoma Barcelona, Barcelona, Spain

[14]Clínica do Dragão, Espregueira-Mendes Sports Centre - FIFA Medical Centre of Excellence and Dom Henrique Research Centre, Porto, Portugal

[15]Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

[16]Instituto Cugat, Hospital Quironsalud Barcelona, Barcelona, Spain

[17]Fundación García Cugat, Mutualidad de Futbolistas Españoles-Delegació Catalana, Barcelona, Spain

[18]OrthoBiology Surgery Center, Thessaloniki, Greece

[19]3rd Orthopaedic Department, European Interbalkan Medical Center, Thessaloniki, Greece

[20]Acibadem Altunizade Sports Therapy and Health Unit, Department of Orthopedics and Traumatology, Acibadem MAA University Faculty of Medicine, Istanbul, Turkey

[21]IRCCS Humanitas Research Hospital, Rozzano, Italy

[22]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

[23]Department of Orthopaedics, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[24]Department of Orthopaedics, University Hospital Mostar, Mostar, Bosnia and Herzegovina

[25]Osteon Clinic, Mostar, Bosnia and Herzegovina

[26]ESSKA Consensus Projects Advisor, Versailles, France

[27]Orthopaedic Biotechnology Laboratory, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milano, Italy

ESSKA-ORBIT Group

The ESSKA-ORBIT Study Group is composed of: Laura de Girolamo, Lior Laver, Giuseppe Filardo, Ferran Abat, Ricardo Bastos, Ramon Cugat, Michael Iosifidis, Baris Kocaoglu, Elizaveta Kon, Jeremy Magalon, Rodica Marinescu, Marko Ostojic, Mikel Sanchez, Thomas Tischer, Diego Delgado, Patricia Laiz, Yosef Sourougeon and Montserrat García-Balletbó.

AUTHOR CONTRIBUTION

Not applicable.

ACKNOWLEDGEMENTS

The acknowledgement goes to the members of the rating group: Eduard Alentorn-Geli, Isabel Andia, Lars Blønd, Berte Bøe, Tomislav Cengic, Ignacio Dallo, Philipp Heuberer, Kaiwan Izadpanah, Ladislav Kovacic, Koen Carl Lagae, Laura Mangiavini, Jacques Menetrey, Stefan Mogos, Emmanuel Papakostas, Yiannis Pengas, Helder Pereira, Tim Spalding, Tomasz Piontek, Patricia Thoreux, Trifon Totlis, Kerem Tekin Ulku, Yaniv Yonai, Stefano Zaffagnini, as well as the peer reviewers of the affiliated national societies (AEA, AGA, BAKAST, BKS, EASTS, GOTS, HAA, LIROMS, NVA, PTA, SETRADE, SFA, SFTS, SIAGASCOT, SPAT, SPOT, SSASST and TUSYAD) for their peer review. Special thanks to the ESSKA Board and in particular to Jacques Menetrey, Roland Becker and Joan Carlos Monnlau for their support and leadership, as well as to the ESSKA office, in particular to Anna Hansen, for the administrative help. Thanks to João Espregueira-Mendes for his and his team's support of this project as well. The consensus project was endorsed and promoted by the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA).

CONFLICT OF INTEREST STATEMENT

Conflicts of interests of the consensus steering group participants: Laura de Girolamo: Honoraria or Consultation Fees: Lipogems International (IT) Grants/

research supports: Fidia (IT). Elizaveta Kon: Honoraria or Consultation Fees: Cartiheal (IL), Green Bone (IT), Geistlich (CH) Grants/research supports: Zimmer Biomet (USA), Mastelli (IT), Fidia (IT), Cartiheal (IL) Company speaker honorarium: Zimmer Biomet (USA), Fidia (IT) Stock shareholder: CARTIHEAL (IL). Jeremy Magalon: Educational support: Fidia (IT), Horiba (JP), Malopharma (FR), Arthrex (USA), Horus (FR) Co-founder of Remedex (FR). All the other steering group members declare no conflicts of interest.

ETHICS STATEMENT

Irrelevant.

ORCID

Lior Laver https://orcid.org/0000-0001-6616-1702

REFERENCES

1. Ahmad HS, Farrag SE, Okasha AE, Kadry AO, Ata TB, Monir AA, et al. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. Int J Rheumatic Dis. 2018;21(5):960–6.
2. Allaeys C, Arnout N, Van Onsem S, Govaers K, Victor J. Conservative treatment of knee osteoarthritis. Acta Orthop Belg. 2020;86(3):412–21.
3. Beaufils P, Becker R, Kopf S, Englund M, Verdonk R, Ollivier M, et al. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. Knee Surg Sports Traumatol Arthrosc. 2017;25(2):335–46.
4. Beaufils P, Dejour D, Filardo G, Monllau JC, Menetrey J, Seil R, et al. ESSKA consensus initiative: why, when and how? J Exp Orthop. 2023;10(1):101. https://doi.org/10.1186/s40634-023-00664-2
5. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Am J Sports Med. 2021;49(1):249–60.
6. Bennell KL, Paterson KL, Metcalf BR, Duong V, Eyles J, Kasza J, et al. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: the RESTORE Randomized Clinical Trial. JAMA. 2021;326(20):2021–30.
7. Boffa A, Salerno M, Merli G, de Girolamo L, Laver L, Magalon J, et al. Platelet-rich plasma injections induce disease-modifying effects in the treatment of osteoarthritis in animal models. Knee Surg Sports Traumatol Arthrosc. 2021;29(12):4100–21.
8. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín MÁ. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J Orthop Traumatol. 2018;19(1):3. https://doi.org/10.1186/s10195-018-0501-3
9. Chu J, Duan W, Yu Z, Tao T, Xu J, Ma Q, et al. Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2022;30(12):4063–71.
10. Dawson MJ, Ollivier M, Menetrey J, Beaufils P. Osteotomy around the painful degenerative varus knee: a 2022 ESSKA formal consensus. Knee Surg Sports Traumatol Arthrosc. 2022;31:3041–3. https://doi.org/10.1007/s00167-022-07024-0
11. de Girolamo L, Dejour D, Lind M, Karlsson J, Seil R. Surgical competence, research and evidence-based medicine (EBM) in orthopaedic surgery: what the ESSKA is doing to bring it all together. Knee Surg Sports Traumatol Arthrosc. 2020;28(2):335–8.
12. Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenacchi A, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med. 2019;47(2):347–54.
13. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. 2017;25(2):485–92.
14. Eymard F, Ornetti P, Maillet J, Noel É, Adam P, Legré-Boyer V, et al. Intra-articular injections of platelet-rich plasma in symptomatic knee osteoarthritis: a consensus statement from French-speaking experts. Knee Surg Sports Traumatol Arthrosc. 2021;29(10):3195–210.
15. Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A, et al. PRP injections for the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Cartilage. 2021;13(1_suppl):364–75.
16. Gabriel A, Maxwell GP. Reading between the lines: a plastic surgeon's guide to evaluating the quality of evidence in research publications. Plastic Reconstr Surg Global Open. 2019;7(6):e2311. https://doi.org/10.1097/GOX.0000000000002311
17. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017;25(3):958–65.
18. Han SB, Seo IW, Shin YS. Intra-articular injections of hyaluronic acid or steroids associated with better outcomes than platelet-rich plasma, adipose mesenchymal stromal cells, or placebo in knee osteoarthritis: a network meta-analysis. Arthrosc J Arthrosc Related Surg. 2021;37(1):292–306.
19. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393:1745–59.
20. Kon E, Engebretsen L, Verdonk P, Nehrer S, Filardo G. Clinical outcomes of knee osteoarthritis treated with an autologous protein solution injection: a 1-year pilot double-blinded randomized controlled trial. Am J Sports Med. 2018;46(1):171–80.
21. Kopf S, Beaufils P, Hirschmann MT, Rotigliano N, Ollivier M, Pereira H, et al. Management of traumatic meniscus tears: the 2019 ESSKA meniscus consensus. Knee Surg Sports Traumatol Arthrosc. 2020;28(4):1177–94.
22. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthrosc J Arthrosc Related Surg. 2019;35(1_suppl):106–17.
23. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the global burden of disease study 2019. Arthritis Rheum. 2022;74(7):1172–83.
24. McLarnon M, Heron N. Intra-articular platelet-rich plasma injections versus intra-articular corticosteroid injections for symptomatic management of knee osteoarthritis: systematic review and meta-analysis. BMC Musculoskelet Disord. 2021;22(1):550. https://doi.org/10.1186/s12891-021-04308-3
25. Nie L, Zhao K, Ruan J, Xue J. Effectiveness of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled clinical trials. Orthop J Sports Med. 2021;9(3):232596712097328.

26. Nunes-Tamashiro JC, Natour J, Ramuth FM, Toffolo SR, Mendes JG, Rosenfeld A, et al. Intra-articular injection with platelet-rich plasma compared to triamcinolone hexacetonide or saline solution in knee osteoarthritis: a double blinded randomized controlled trial with one year follow-up. Clin Rehabil. 2022;36(7):900–15.
27. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013;41(2):356–64.
28. Prill R, Królikowska A, de Girolamo L, Becker R, Karlsson J. Checklists, risk of bias tools, and reporting guidelines for research in orthopedics, sports medicine, and rehabilitation. Knee Surg Sports Traumatol Arthrosc. 2023;31(8):3029–33.
29. HAS Santé. "Formal consensus" method; 2011. https://www.has-sante.fr/jcms/c_272505/en/-formal-consensus-method. Accessed 24 Apr 2023.
30. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ. 1999;318(7183):593–6.
31. Tan J, Chen H, Zhao L, Huang W. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis of 26 randomized controlled trials. Arthrosc J Arthrosc Related Surg. 2021;37(1):309–25.
32. Tischer T, Beaufilis P, Becker R, Ahmad SS, Bonomo M, Dejour D, et al. Management of anterior cruciate ligament revision in adults: the 2022 ESSKA consensus. Part I—diagnostics and preoperative planning. Knee Surg Sports Traumatol Arthrosc. 2023;31(11):4642–51.
33. Tucker JD, Goetz LL, Duncan MB, Gilman JB, Elmore LW, Sell SA, et al. Randomized, placebo-controlled analysis of the knee synovial environment following platelet-rich plasma treatment for knee osteoarthritis. PM R. 2021;13(7):707–19.
34. Yurtbay A, Say F, Çinka H, Ersoy A. Multiple platelet-rich plasma injections are superior to single PRP injections or saline in osteoarthritis of the knee: the 2-year results of a randomized, double-blind, placebo-controlled clinical trial. Arch Orthop Trauma Surg. 2021;142(10):2755–68.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Laver L, Filardo G, Sanchez M, Magalon J, Tischer T, Abat F, et al. The use of injectable orthobiologics for knee osteoarthritis: a European ESSKA-ORBIT consensus. Part 1—Blood-derived products (platelet-rich plasma). Knee Surg Sports Traumatol Arthrosc. 2024;32:783–97. https://doi.org/10.1002/ksa.12077