The use of injectable Orthobiologics for knee osteoarthritis: a formal ESSKA consensus

Part 1 - Blood-derived Products (PRP)

Introduction

The field of Orthobiologics has emerged in recent years as a result of the growing interest in biologic approaches for tissue healing for a variety of musculoskeletal (MSK) conditions and pathologies. They have been used in a plethora of musculoskeletal conditions affecting bone, cartilage, tendons/ligaments and muscles, both as conservative injection treatment and in combination with surgical procedures. The results of these treatments are inconclusive because of 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. Moreover, therapy developers and providers must address hurdles from regulatory issues, through reimbursement considerations and to commercial challenges before successful orthobiologic procedures are available to patients. All of this risks to devalue the potential and the use of these treatments, with a potential loss of valid care opportunities.

As Europe's largest association of musculoskeletal specialists, ESSKA felt it had a responsibility to advance the quality of care in the orthobiologics field in a fully transparent and scientific manner. Therefore, ESSKA has established the ORthoBIologics InitiaTive (ORBIT) in order to establish and assemble a pan-European/International collaboration to create a common language and a uniform and responsible voice in the field of orthobiologics as well as driving good standard of care in this field.

ORBIT's focus includes orthobiologic treatment options and strategies for variable musculoskeletal conditions/pathologies. Since injectable orthobiologic options are the most widely used, ORBIT's consensus will initially address these treatment options, further divided into non transfusional hemo-components or blood-derived products (including but not limited to Platelet Rich Plasma, Part 1), and Cell-based therapy (sometimes referred, although improperly to as "stem cell therapy", Part 2).

Mission/scope of the Orthobiologics Initiative (ORBIT)

The ORBIT leadership has highlighted and prioritized the importance of adopting an evidence-based and systematic approach to evaluating the effectiveness of existing and emerging orthobiologic treatments. Such an approach is necessary to improve and optimize the objective evaluation of orthobiologics use, and to properly lay the groundwork for their use by clinicians, equipping them to make informed decisions regarding orthobiologic treatment options and allow improved and meaningful patient-informed decision-making.

The Initiative's main mission is to promote the responsible use of orthobiologics in clinical practice, address regulatory issues across Europe, while developing improved standards and defining clear indications as well as improved assessment and monitoring guidelines.

The ESSKA Formal Consensus

Since one of the aim of the ORBIT group to assist clinicians in decision making for the non-operative management of patients using orthobiologics, an ESSKA Formal Consensus was carried on. The goal was to propose recommendations rather than strict guidelines.

While Orthobiologics can be used to treat a variety of conditions, osteoarthritis and in particular knee osteoarthritis is the most commonly addressed pathology. Therefore, the aim of this first ESSKA Formal Consensus on orthobiologics is to provide a combination of evidence based and expert opinions regarding the non-operative management of patients affected by knee osteoarthritis with Orthobiologics.

When considering the use of blood-derived products for knee OA, one of the main challenges is to identify the ideal patient. Profiling the ideal knee OA patient for PRP/Blood derived products use is complex and multi-factorial. Treatment decision is often not based on isolated factors and it is the understanding of where in the arthritic process the clinician meets the patient, integrating variable factors, objective and subjective, including the clinician's personal experience. Therefore the scope of this consensus is not to provide an 'a-la-carte' menu in order to profile the ideal patient/candidate, but rather to provide recommendations which address commonly encountered scenarios when considering blood-derived therapy for knee OA and which could aid in decision making when managing this population of patients.

Definitions

Blood derived products

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 Platelet Rich Plasma (PRP), Platelet Rich Fibrin (PRF), Platelet Rich Growth Factors (PRGF), Autologous Conditioned Plasma (ACP), Autologous Protein Solution (APS), all based on platelet concentration, as well as other products such as Autologous Conditioned Serum (ACS), Alpha-2-Macroglobulin (A2M).

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. Therefore for the sake of simplicity, being PRP (Platelet Rich Plasma) the most common term to refer to this wide product category, 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 non-platelet concentration based products such as ACS or A2M, which will be briefly discussed separately).

More specific information about the characteristics of the different systems/techniques can be found in literature.

Also, it is important to remember that knee OA is often multifactorial and mechanical malalignment may play a significant role in certain cases (i.e tibio-femoral malalignment, 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.

Methodology

The ESSKA'S "Formal Consensus Methodology" derived from the Delphi methodology was used. For the Delphi process the core group comprised a Steering Group of 14 experts that was equally divided into a question and a literature group. The question group proposed a series of relevant questions which were ranked according to clinical importance, answerability and scientific importance by a decision-making software (1000minds.com) that was used for the first time in an ESSKA Consensus. The ranked list was then narrowed down and refined by the entire Steering Group. Following completion of the literature reviews by the Literature Group for each of the chosen questions, the Steering Group produced respective statements/recommendations based on the existing literature (screened from 2000 - today) as well as the entire Steering Group's expert opinion.

Foe each statement, the following grading system was used:

Grade A: high scientific level
Grade B: scientific presumption
Grade C: low scientific level
Grade D: expert opinion

A Rating Group composed by an independent panel of 20 experienced clinicians was asked to review the statements produced by the steering group. The rating phase was composed by two rounds, during which the panel evaluated and ranked each answer according to a discrete numerical scale (Likert scale from 1 to 9, 1 lowest grade of agreement, 9 highest grade of agreement). Appropriateness and agreement will then be assessed. When needed, after the first round the text was modified by the steering group, taking into account the rating group's comments and a second round to the rating group was carried on. After this, a combined meeting of the steering and rating groups was organized to validate the draft and finalize the following text.

For each statement, in addition to the grade, the mean rating score has been indicated.

In the final step the finalized text was then circulating among a Peer Review group (about 40 people) to assess the geographic adaptability and acceptance among Europe. Peer review group was set up by nominating delegates from the ESSKA Affiliated National Societies.

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ESSKA Consensus projects advisor

Philippe Beaufils (*France*)

Steering group members

Abat Ferran (*Spain*)
Bastos Ricardo (*Portugal*)
Cugat Ramon (*Spain*)
Filardo Giuseppe (*Italy*)
Iosifidis Michael (*Greece*)
Kocaoglu Baris (*Turkey*)
Kon Elizaveta (*Italy*)
Magalon Jeremy (*France*)
Marinescu Rodica (*Romania*)
Ostojic Marko (*Bosnia-Erzegovina*)
Sanchez Mikel (*Spain*)
Tischer Thomas (*Germany*)

Rating group members

Andia Isabel (*Spain*)
Blønd Lars (*Denmark*)
Bøe Berte (*Norway*)
Cengic Tomislav (*Croatia*)
Dallo Ignacio (*Italy*/*Argentina*)
Heuberer Philippe (*Austria*)
Izadpanah Kaywan (*Germany*)
Kovacic Ladislav (*Slovenia*)
Lagae Koen Carl (*Belgium*)
Mangiavini Laura (*Italy*)
Menetrey Jacques (*Switzerland*)
Mogos Stefan (*Romania*)
Papakostas Emmanuel (*Greece*/*Qatar*)
Pengas Yiannis (*UK/Cyprus*)
Pereira Helder (*Portugal*)
Spalding Tim (*UK*)
Piontek Tomasz (*Poland*)
Thoreux Patricia (*France*)
Totlis Trifon (*Greece*)
Ulku Kerem Tekin (*Turkey*)
Yonai Yaniv (*Israel*)
Zaffagnini Stefano (*Italy*)

Peer-review group members

Arriaza Rafael (*Spain*), Athanasios Liantsis (*Greece*), Audebert Stéphane (*France*), Bąkowski Paweł (*Poland*), Bellaiche Laurence (*France*), Bernáldez Domínguez Pedro (*Spain*), Bode Gerrit (*Germany*), Bukach Dzmitry (*Belarus*), Çetinkaya Engin (*Turkey*), Charousset Christophe (*France*), Chavigny Eric (*France*), Custers Roel (*The Netherlands*), de Graeff Jan Jaap (*The Netherlands*), Di Matteo Berardo (*Italy*), Frey Alain (*France*), Gremeaux Vincent (*France*), Kaux Jean Francois (*Belgium*), Kocabaş Atilla (*Turkey*), Lamo de Espinosa José Mª (*Spain*), López-Vidriero Emilio (*Spain*), Mahiroğullari Mahir (*Turkey*), Malovrh Tomaz (*Slovenia*), Mardna Mihkel (*Estonia*), Marmotti Antongiulio (*Italy*), Nehrer Stefan (*Austria*), Oliva Francesco (*Italy*), Pereira Ruiz Maite (*Italy*), Peretti Giuseppe (*Italy*), Pioger Charles (*Luxembourg*), Ribeiro de Oliveira Paulo (*Portugal*), Salzmann Gian (*Switzerland*), Szwedowski Dawid (*Poland*), Vannini Francesca (*Italy*), Vieira da Silva Manuel (*Portugal*), Zellner Johannes (*Germany*)

Other contributors

Delgado Diego (*Spain*), Laiz Patricia (*Spain*), Garcia Montserrat (*Spain*)

ESSKA Office

Hansen Anna (Luxembourg/Poland)

The Chairs of the ESSKA Consensus Project on Injectable Orthobiologics

Laura de Girolamo

Lior Laver

Luxembourg, 20 April 2022

QUESTIONS AND STATEMENTS COLLECTION

The use of injectable Orthobiologics for knee osteoarthritis: an ESSKA consensus

Part 1 - Blood-derived Products (PRP)

(for the sake of simplicity the term PRP is used to indicate any generic autologous product based on platelet concentration by minimal blood manipulation)

The questions are divided into 3 (three) sections:
Section 1: PRP Rationale/Indications (Question 1-14)
Section 2: PRP Preparation/Characterization (Question 15-18)
Section 3: PRP Protocol (Question 19-28)

Grading system:
Grade A = high scientific level
Grade B = scientific presumption
Grade C = low scientific level
Grade D = expert opinion

Mean Rating Score (herein reported as mean score):
1 = minimum score
9 = maximum score

Abbreviations:
A2M (Alpha-2-Macroglobulin)
ACS (Autologous Conditioned Serum)
CS (Corticosteroids)
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)
MSCs (Mesenchymal Stem Cells)
NS (normal saline)
NSAIDs (non steroidal anti-inflammatory drugs)
OA (Osteoarthritis)
PRP (Platelet Rich Plasma)
RCT (Randomized Controlled Trial)
VAS (Visual Analog Scale)
WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index
WORMS (Whole-Organ Magnetic Resonance Imaging Score)

SECTION 1
PRP RATIONALE/INDICATIONS

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

Statement

Clinical evidence confirms the efficacy of PRP in the treatment of knee osteoarthritis (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 hyaluronic acid or corticosteroids (CS). 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 conclude 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

Mean score: 8.0

Literature summary (Best evidence: 5 Meta-analyses, 1 Systematic review, 4 RCTs)

Several current level I and II studies exist to support the use of PRP for knee OA, but also some level IV articles target interesting and key points.

PRP is a safe and efficient therapeutic option for treatment of knee osteoarthritis. It was demonstrated to be significantly better than hyaluronic acid. Also, the efficacy of PRP increases after multiple injections[1]. Also, it is stated with high quality systematic reviews that patients undergoing treatment for knee OA with PRP can be expected to experience improved clinical outcomes when compared to a control treatment group of hyaluronic acid (HA).[2] For the nonsurgical treatment of KOA, compared with HA, intraarticular injection of PRP could significantly reduce patients' early pain and improve function. PRP was more effective than HA in the treatment of KOA, and the safety of both treatment options was comparable[3].

A systematic review and meta-analysis suggest that PRP is superior to HA for symptomatic knee pain at 6 and 12 months. However, there were no advantages of PRP over HA for clinical outcomes at both 6 and 12 months[4]. To be considered that the preclinical literature shows an overall support toward the PRP application. An intraarticular injection does not just target cartilage; instead, PRP might influence the entire joint environment, leading to a short-term clinical improvement[5]. PRP has the potential to improve symptoms starting from 2 months for up to 12 months[6], and showed better results in improving pain, stiffness, and function at 3-, 6- and 9-months post-intervention. At 6-months, PRP allowed greater return to sport than patients treated with corticosteroid.[7]

Three very recent RCTs have highlighted both the fact that while the majority of studies have shown the superiority of PRP treatment over other injectable agents including placebo, not all have shown consistent results which could be explained by the variability which still exists in study methodologies, as well as product and protocol variability, and is a matter for further investigation and research. The recent RESTORE study, for example, has highlighted this, reporting no superiority of PRP treatment over placebo,[8] while two other recent RCTs have once again shown the superiority of PRP treatment over placebo,[9,10] one being a four arms study also comparing 1 *vs*. 3 injections of both placebo (saline) and PRP.[10]

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➢ QUESTION 2

For which degrees of knee OA is PRP best indicated?

Statement

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

Mean score: 8.1

➢ QUESTION 3

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

Statement

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

Mean score: 8.1

Literature summary (for question 2 & 3): (Best evidence: 6 RCTs)

6 level I studies, 2 level II studies and 5 level IV studies were examined regarding the effect of PRP treatment on different degrees of knee osteoarthritis (OA). Based on the available literature, PRP treatment is effective in reducing pain and increasing function in patients with low (Kellgren-Lawrence grade 0-2), moderate (Kellgren – Lawrence grade 3) and severe (Kellgren-Lawrence grade 4) knee OA. However, the magnitude of the improvements is inversely proportional to the degree of OA, being lower in knees with severe OA and higher in knees with low-moderate OA.

Several studies have evaluated the efficacy of PRP administration in patients with knee OA[1–11]. All of them used the Kellgren – Lawrence (KL) score to define the degree of knee OA of the patients involved. The vast majority of studies reported significant improvements after the treatment with PRP. They also described higher improvements in patients with lower grades of knee OA. However, only 5 articles included patients with severe OA (KL grade 4).[6,7,9–11] Filardo et al.[6] reported positive effects in knee function after three weekly PRP injections in all patients. However, patients with severe OA reported significantly lower improvements than patients with low and moderate knee OA. Similar results were obtained by other authors,[7,9,11] suggesting that patients with higher degrees of knee OA, despite presenting significant improvements in knee pain and function, were less likely to improve than patients with lower OA grades.

Positive effects of PRP have been proven in patients with knee OA regardless of the grade of degeneration. However, the magnitude of the improvements has been associated with OA grade, being significantly higher in lower OA grades compared to severe OA. Despite the lower magnitude of the improvements described in patients with severe knee OA, PRP injections are effective in improving pain and function regardless of the degree of knee OA.

The clinical results of a randomized, double-blind, placebo-controlled trial indicate that IA PRP and HA treatment is suggested for all stages of knee OA.[7] Further, for patients with late-stage knee OA older than 67 years, an intra-articular injection of PRP provided similar results to a corticosteroid injection[13].

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QUESTION 4

Is PRP indicated for the treatment of Patellofemoral OA (PFOA)?

Statement
Despite current literature on the effect of PRP for patellofemoral OA 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

Mean score: 7.6

Literature summary (Best evidence: 2 RCTs)
The limitation to answering this question is the relatively low amount of clinical studies conducted on PFOA treatments in general, and on PRP treatment for PFOA in particular.
A prospective study by Pintat et al.,[1] published in 2017, examined the effect of IA injection of MSC and PRP for PFOA in 19 patients, using WOMAC score and MR analysis, with a follow-up period of 12 months. PRP, with a final volume of 3ml injected, contained a controlled platelet number (700,000/mm^3 ± 25,000) and a controlled leukocyte number (200/mm^3 ± 35). For the MSCs, adipose tissue was harvested and processed into stromal vascular fraction (SVF), with a medium cellular rendering estimation was 3.70×10^7 MSCs per gram of lipoaspirate (6ml injected). At 6- and 12-months post injection there was a significant improvement in WOMAC score versus baseline. However, no significant improvement in MR analysis were observed. Authors concluded that a combined injection of MSCs and PRP improve clinical symptoms in patients with early PFOA, without significant objective improvements at MR.
A more recent retrospective study by Cobianchi Bellisari et al.[2] compared two groups of patients (cohort of 34 in each group) suffering from patellofemoral chondropathy, with a mean follow-up of 6.4 ± 1.9 months for both groups. One group was treated with 3 IA PRP injections while the control group underwent standard non-operative treatment with a mean follow-up of 6.4 ± 1.9 months (range 4-12m). Each PRP injection had a volume of 5ml, containing 9000–11,000 leukocytes/µL, and the platelet count was measured to average 128×10^5/µl. Both groups underwent imaging evaluations using 3 T MR with cartilage analysis with T2 mapping sequences for cartilage analysis before and after treatment and were assessed by WORMS, WOMAC and VAS. In the treatment group, all the scores significantly improved at the final follow-up point, while no significant improvement was achieved by the control group at the follow-up. Authors concluded that PRP treatment in patients affected with patellofemoral chondropathy has a positive clinical effect.
The following three studies did not examine the effect of PRP on isolated PFOA. Conversely, they examined the clinical and MR response of the patellofemoral joint (PFJ) to PRP treatment in the setting of knee osteoarthritis (KOA), K/L score 1-3, in all studies. In a prospective study, Jang et al.[3] reported that the presence of PFJ degeneration produced a worse clinical outcome in a cohort of 65 patients (90 knees) treated with a single PRP injection with 12m follow-up. They reported 60% of knees in their study had PFOA (54 knees), which resulted in pain relapse at 7.9 months on average, compared to an average of 10.2 months, if PFOA was not present. In a recent level I, randomized control study Yurtbay et al.[4] compared between four different treatments to patients diagnosed with Knee OA – a single injection of normal saline (NS), three doses of NS, a single injection of PRP and three doses of PRP. The PFJ clinical response was assessed using the Kujala Patellofemoral Score (KPS). The KPS score was significantly improved at all time periods after 6 months (24 months follow-up) in the PRP groups versus the NS groups, with no significant advantage of multiple PRP injections versus single PRP injection. In a double blind randomized controlled clinical trial by Raeissadat et al.[5] 46 patients were randomly selected for either a treatment group (PRP, two

injections at 4weeks interval) or a control group with a 32 weeks follow up. Patellofemoral cartilage volume and synovitis was reported to be significantly improved in the PRP group versus controls.

Despite the scarcity of the literature regarding the direct effect of PRP on PFOA, current evidence suggests it may have positive radiological and clinical effects, especially in early-stage disease. However, the magnitude and the longevity of these improvements remains uncertain.

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➢ QUESTION 5

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

Statement

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 co-existent 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 4 main groups):
  - Infections

  Besides the well-known reasons not to perform a knee injection in a patient with active systemic infections, systemic infections also affects 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 tumor proliferation, either locally or remotely. However, due to the theoretical risk that PRP and growth factors may contribute to tumor growth promotion in situations where either a benign or malignant tumor 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 tumors 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…) 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 pro-inflammatory molecules that may lead to lower results.
  - Blood and quantitative and qualitative platelet disorders

  Problems such as thrombocytopenia, thrombocytosis or coagulopathies can also alter platelets number and their functionality.
  - The use of antiplatelet therapy should be considered a relative contraindications to PRP. This is related mainly with 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

Mean score: 8.0

Literature summary (Best evidence: 2 RCTs, 2 Systematic reviews)

The contraindications for the use of PRP for knee OA is registered as exclusion criteria for patient eligibility for the studies[1]. Systemic disorders, such as diabetes, rheumatoid arthritis, major axial deviation, hematological diseases (coagulopathies), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants–antiaggregants, patients with Hb values of<11 and platelets values of <150,000/mmc, use of NSAIDs in the 5 days before blood donation[2,3,4] or one week before[5]. It is also considered as potentially contraindication systemic metabolic diseases, immunodeficiency, hepatitis B or C,

HIV-positive status, infection and septicemia and local infection[6-9]. It is reported history of tumor or active tumor or hematologic malignant disease as exclusion criteria for PRP injections for OA[10-13].
Randomized, double-blinded and placebo controlled clinical trial have as exclusion criteria significant (.10°) valgus or varus deformities as evidenced by standard-of-care radiograph, inflammatory diseases including Rheumatoid arthritis[14-15], gout and history of infection or current infection at the affected joint[6].
It seemed that PRP therapy is not suggested in case of chronic, unstoppable antiplatelet therapy. The reason is that antiaggregant drugs impair platelets' granules secretion and, therefore, the in situ release of GFs and other bioactive molecules.[16] But a report suggests that PRP could be effective also in patients with chronic anti-platelet therapy for this treatment.[17]

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➢ QUESTION 6

For what age range is PRP recommended?

Statement

The majority of studies included patients with a mean age between 55 and 65 years of age. The consensus group agrees that a specific age range cannot be recommended, though recognizes 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

Mean score: 8.4

Literature summary (Best evidence: 3 Meta-analyses, 2 RCTs)

Platelet rich plasma (PRP) has recently increased the conservative treatment options for patients affected by cartilage degeneration and osteoarthritis, although when it comes to establishing an age limit, a consensus seems to be missing.

Current medical literature tends to emphasize the positive effects that PRP has on younger patients with lower degrees of cartilage degeneration and an active lifestyle. The beneficial impact on such patients could be explained by the mechanism of action hypothesized for PRP treatment: younger and less damaged knees have a higher percentage of living and vital cells and therefore a higher response potential to the growth factors present when compared to older and more degenerated joints.[1]

Most of the studies on the topic included only patients above 18 years old and excluded patients over the age of 75/80, therefore precluding the estimation of upper and lower age boundaries outside which PRP treatments are ineffective.

A recent metanalysis from 2021 published by Belk et al.[2]collected all the RCTs on the use of PRP vs Hyaluronic acid. Among the 18 studies included, the weighted average for age of the patients injected with PRP was 57,6 years. Another metanalysis from 2020 by Filardo et al.[3] included 34 RCTs comparing the use of PRP vs other injective treatments. The patients' age from the PRP group ranged from 49,8 to 65,5 years.

Several studies[4–6] agreed that 50 years is the age limit before which PRP shows better results when compared to viscosupplementation in the treatment for degenerative knee pathologies. It seems that this clinical response is not only dependent on the cartilage status, but seems to be highly relevant the donor age itself. A study conducted by O'Donnell et al.[7] compared the response of *in vitro* chondrocytes and macrophages to PRP obtained from both young healthy patients and older OA patients (older than 62 years). The study, even if conducted on 19 patients, demonstrated how the age of the donor could influence gene expression, shifting to an inflammatory response when the PRP from the older group was obtained. Other preclinical studies also showed that the composition of PRP can depend on the age of the donor. PRP from older donors had a more pro-inflammatory composition and was less active than PRP from younger donors.[8,9]

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Controlled Animal Study

➢ **QUESTION 7**

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

Statement

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.

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

Mean score: 7.9

Literature summary (Best evidence: 3RCTs, 4 controlled laboratory studies)

Various experimental and clinical studies conducted to date have used either multiple injections or single injections and were able to demonstrate the positive effect of PRP on structural modulation and anti-inflammatory effects in the knee joint. Progress has been made in understanding the effectiveness of PRP on intra-articular homeostasis[1]. Treatment with PRP for patients with knee osteoarthritis presented beneficial effects in regulating inflammatory factors and alleviating joint inflammation[2]. On the other hand**,** in a level I study a non-statistical tendence was observed between time and group (HA vs PRP) effects in proinflammatory and anti-inflammatory cytokines.[3]

Treatment consisting of HA along with PRP decreased inflammatory potential of infrapatellar fat pad adipocytes through the inhibition of cytokines and adipokines[4]. A case series study revealed a decreased volume and concentration of proteins associated with inflammation such as apolipoprotein A-I, haptoglobin, immunoglobulin kappa chain, transferrin, and matrix metalloproteinase (a 2-fold decrease) in patients with moderate knee OA combined with supra-patellar bursitis after 3 monthly PRP injections for 3 months[5].

Some basic science research reported that PRP had anti-inflammatory activity in an IL-1β-induced inflammatory model and anti-inflammatory actions through nuclear factor kB (NF-κB) signaling pathway[6]. In a murine OA model, multiple PRP injections reduced pain and synovial thickness, possibly through modulation of macrophage subtypes. PRP injections in early OA or shortly after joint trauma can reduce pain and synovial inflammation and may inhibit OA development in patients[7].

To note that in contrast with the evidence reported by “in vitro” studies[8,9], where a cellular pro-inflammatory response appears to be induced by the presence of leukocytes, the results of a RCT study suggest that the presence leukocyte-rich PRP doesn’t induce a relevant in vivo up regulation of pro-inflammatory mediators[10].

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Level of evidence: Level IV, Study type: Narrative review

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Level of evidence: Level I, Study type: RCT

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Level of evidence: Level I, Study type: RCT
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Level of evidence: n/a, Study type: Controlled laboratory study
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Level of evidence: Level I, Study type: RCT

➢ **QUESTION 8:**

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

Statement:

While current evidence regarding repeated cycles of PRP treatment for knee OA is limited, it has been suggested 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

Mean score: 8.4

Literature summary (Best evidence: 3RCTs, 1 prospective randomized study)

Clinical studies suggest that intraarticular injections of PRP for all stages of knee OA is a useful treatment. For patients with early OA, multiple (3) PRP injections are more useful in achieving better clinical results than a single injection or other treatments[1,2]. It is stated in randomized controlled trials that the efficacy of PRP increases after multiple injections[3]. The anti-inflammatory effects on the synovium in the short term are similar in singular and multiple injections. However, this effect is sustained in the long term only for multiple injections[4].

When comparing PRP maintenance injection, some studies suggest that there is a significant reduction in pain and improvement in function after 12 months, which can be further improved at 18 months by annual repetition of the PRP treatment. The patients with two cycles consisting of 3 injections each one showed higher mean values for all the scores compared to patients with only one cycle[5]. Another study claimed that patients with two cycle-treatment did not show a significantly higher pain reduction compared with one cycle treatment but showed significant improvement in WOMAC stiffness, LEQUESNE MCD, LEQUESNE ADV and LEQUESNE global subscales. Therefore, patients treated with two cycles present an improvement in quality of life[6]. A retrospective analysis of patients undergoing total knee replacement suggested that repeating PRP cycles over the time could delay the prosthesis placement[7].

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Level of evidence: Level IV, Study type: Retrospective study

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Level of evidence: Level I, Study type: Double blind RCT

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Level of evidence: Level I, Study type: RCT

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Level of evidence: Level IV, Study type: Experimental Study

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Level of evidence: Level II, Study type: Prospective randomized study

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Level of evidence: Level IV, Study type: Retrospective study

➢ **QUESTION 9:**

Is there rationale in injecting PRP in asymptomatic early knee OA? (Prevention?)

Statement

Currently, there are not enough clinical studies addressing this question, and therefore it cannot be stated that the application of PRP in asymptomatic osteoarthritis 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

Mean score: 8.7

Literature summary (Best evidence: 3 systematic reviews, 2 Controlled laboratory study)

Level II and IV studies have observed benefits in the preclinical application of PRP in knee OA.

In a level IV study with rat model, the authors observed higher chondrocyte count and cartilage thickness in the PRP treatment group compared to the non-treated group[1]. These results agree with the level II systematic review from Filardo et al.[2] and Boffa et al.[3] that describe the effects of PRP injections in preclinical studies, including chondrocyte cell proliferation, inhibition of chondrogenic marker expression, increased cartilage repair effect of MDSCs, improved histologic appearance, higher number of cells producing type II collagen and an improvement in the degree of lameness and joint effusion.

Several in vitro studies have also confirmed those results, by showing significant improvements in chondrocyte proliferation, decreased apoptosis and relieved inflammatory stress in chondrocytes.[4,5]

On the other hand, in a level II systematic review from 2014, Gallagher et al. did not find evidence in the literature to support or refute the use of PRP for chondroprotection.[6]

There is no agreement on the chondroprotection effect of PRP in patients with asymptomatic and early stages of OA. Preclinical and in vitro studies have found significant improvements in histologic scores, chondral proliferation, and cell apoptosis after the application of PRP. However, more clinical studies are needed to support the use of PRP for chondroprotection in human asymptomatic patients.

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Controlled animal study

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Systematic review

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Systematic review

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Controlled laboratory study

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Controlled laboratory study

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Systematic review

QUESTION 10:

Are there advantages of PRP use in comparison to Corticosteroids for treating knee OA?

Statement

While corticosteroids 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 shorter 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, non-chondro-toxic and more effective treatment option, with longer term clinical improvements compared to CS injections.

Grade A

Mean score: 8.7

Literature summary (Best evidence: 6 Meta-analyses, 2 Systematic reviews, 1 RCT)

Several meta-analysis and systematic reviews have been recently published (2020 and 2021) comparing several nonoperative treatment options for knee osteoarthritis (OA)[1-8]. Among these different therapies, platelet-rich plasma (PRP) and corticosteroids (CS) have been compared to identify which therapy is better for the management of knee OA. When crossing all data, 11 studies focused on PRP versus CS, including 371 and 350 patients, respectively.

When comparing VAS and WOMAC total scores, 3 out of 5 reported a significant overall improvement for PRP, especially concerning pain relief and knee joint function. One meta-analysis did not perform subgroup analysis and only provided positive outcome for PRP compared to other injectable solutions[3].

Among them, one meta-analysis was focused exclusively on the comparison between PRP and CS[1] with significant positive results in favor of PRP injections on pain and function between 3 and 9 months after injection. One year after injection, WOMAC and VAS scores remain lower in PRP group compared to CS without reaching statistically significant result. This may be explained by the fact that only one study provides data until 12 months.

Remaining meta-analyses included different intra-articular modalities for knee OA[2-5], from which two of them[2,4] performed subgroups analysis with positive results for PRP against CS 6 months after the injection. Long-term benefit of PRP against CS were reported[3] as PRP provided continued pain relief up to one year post injection whereas CS lacked this longevity . A meta-analysis concluded that PRP currently has insufficient evidence to make a conclusive recommendation for or against its use, while hyaluronic acid (HA) or CS are favored for different needed responses and can be utilized within the knee OA treatment[6].

Only one meta-analysis[5] reported that CS was associated to better outcomes than PRP in knee OA. However, this paper was strongly criticized by other Authors because of incongruences and methodological flaws[9]. Conversely, CS injections are associated with radiological cartilage degeneration at > 12 months[7]. Similarly, multiple IA CS injections were no better than placebo for OA pain while showing a detrimental effect on structural OA progression,[8,10] even associated with an increased risk of knee arthroplasty in patients with, or at risk of developing, symptomatic OA of the knee.[11]

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Level of evidence: Level II, Study type: Meta-analysis

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Level of evidence: Level I, Study type: RCT
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Level of evidence: Level III, Study type: Observational study

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

Statements
Several high level studies as well as multiple meta-analyses exist comparing the effectiveness of PRP compared to HA for knee OA, with the majority favoring PRP in terms of overall clinical improvement and a longer-lasting effect.
Based on current available evidence, the consensus group supports the use of PRP over HA for knee OA due to overall clinical improvement and expected longer-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

Mean score: 8.1

Literature summary (Best evidence: 10 Meta-analyses)
In addition to a large number of studies, ten meta-analyses[1-10] have been recently published (2020 and 2021) comparing several non-operative treatment options for knee osteoarthritis (OA) and including at least PRP and HA to identify which therapy is better for the management of knee OA. When gathering and crossing data from these meta-analyses, 37 studies provided the analysis on the effect of PRP versus HA, for a total of 1684 and 1636 patients, respectively.
When comparing VAS and WOMAC total scores, 8 out of 10 reported a significant overall improvement in favor of PRP, especially concerning pain relief and knee joint function. One meta-analysis did not perform subgroup analysis and only provided a positive outcome for PRP compared to other injectable solutions[8].
Among them, five meta-analyses were focused exclusively on the comparison between PRP and HA[1,2,4,5,7] with positive results in favor of PRP injections. Interestingly, 4 out of 5 meta-analyses[1,2,4,7] concluded toward a significant superiority of PRP against HA in terms of pain and function both at short and long term (minimum 12 months of follow-up) whereas the last one[5] did not provide conclusions after 6 months. These data were also confirmed by others[8], concluding that PRP injections provide continued pain relief up to one year post injection whereas HA lack this longevity.
Remaining meta-analyses included different intra-articular modalities for knee OA treatment[3,6,9,10] from which two of them[3,9] performed subgroups analysis with positive results for PRP against HA. One[6] moderated these positive conclusions over HA due to the important heterogeneity among trials, such as posology, PRP type, weight of HA, follow-up time, patient age and weight, or grade of OA for example.
Finally, only one meta-analysis[10] determined that HA was associated to better outcomes than PRP in knee OA.

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Level of evidence: Level Ia, Study type: meta-analysis

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Level of evidence: Level I (assigned by the journal), Study type: meta-analysis

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Level of evidence: Level II, Study type: meta-analysis

➢ **QUESTION 12**

Does PRP induce disease-modifying effects in knee OA?

Statement

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 recognizes that current clinical evidence regarding the disease modifying effects of PRP in knee OA in humans is insufficient.

Grade C

Mean score: 8.3

Literature summary (Best evidence: 8 RCTs, 1 Systematic review)

Due to practical and ethical limitations, the evaluation of PRP potential in counteracting OA progression largely relies on animal models, which play a crucial role in the understanding the pathogenesis of the disease as well as structural effects of novel therapeutic interventions. Accordingly, a recent systematic review of the ORBIT ESSKA initiative focused on evaluating if PRP injections induce disease-modifying effects in the treatment of osteoarthritis in animal models. All selected studies reported on the use of PRP with a control group or the combined use of PRP with another product to analyze the specific contribution of PRP treatment[1].

Forty-four articles were included, for a total of 1251 animals. PRP injections showed clinical effects in 80% of the studies, which is of relevance due to the lack of placebo in the animal setting where thus improvements are more likely related to the effects of PRP to the diseased tissues. More important, these studies performed the analysis of tissue-related changes at different levels. Overall, disease-modifying effects were documented in 68% of the studies. More in detail, 61% of the studies investigating the disease-modifying effects on cartilage tissue reported positive results. Animals treated with PRP were reported to sustain a marked reduction in the severity of cartilage destruction and surface loss, as well as less fibrillation and irregularity, with better cellularity and cartilage matrix compared to control groups. Positive disease-modifying effects of PRP on the synovial membrane were documented after PRP injection in 75% of the studies, with thinner synovial membrane, less synovial hyperplasia, reduced the inflammatory reactions with less edema, fewer synovial vascularity, fibrosis, and inflammatory cell infiltration compared to controls. Most of the studies focused on the measurement of synovial fluid or serum biomarkers related to cartilage metabolism or inflammation also showed positive effects on a wide range of molecules in favor of PRP[1].

However, the risk of bias was low in 40%, unclear in 56%, and high in 4% of items. Moreover, evidence is limited on the best PRP formulation, injection intervals, and synergistic effect with other injectables. Thus, the overall low quality of the published studies warrants further preclinical studies. Even more important, these positive preclinical findings must be confirmed in the clinical setting.

Unfortunately, the clinical evidence on the disease modifying effects of PRP in humans is based on a few reports and results are still inconclusive. In fact, most of the studies focused on the clinical outcomes at short-term follow-up, while only a few documented longer-term results at the tissue level.

At the ultrasonographic evaluation, Ahmad et al[2] reported a significantly lower synovial vascularity, synovial hypertrophy, and effusion in the PRP group compared to the hyaluronic acid group at 3 and 6 months. Bansal et al.[3]observed better magnetic resonance imaging (MRI) findings at 12 months in patients treated with PRP injections compared to hyaluronic acid, showing an unchanged cartilage thickness in 83% of the patients in the PRP group versus 62% in the hyaluronic acid group. Lisi et al.[4] found that PRP injections reduced articular cartilage damage at MRI evaluation at 6 months in 48% of patients, compared to the 8% of patients improved after hyaluronic acid injection. Kon et al.[5] described significant differences at MRI evaluation between autologous protein solution (APS) and saline in change from baseline to 12 months in bone marrow lesion size and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group, while no differences were observed in cartilage status. On the other hand, the same

authors[6] reported no significant differences (improved or worsened) at MRI evaluation comparing baseline and 24 months in the APS group. Also, Elik et al.[7] did not detect any statistically significant difference between cartilage thicknesses before and 6 months after a single or triple injections of PRP. Moreover, Buendía-López et al.[8] even documented a reduction in cartilage thickness in all tibial and femoral subregions at MRI evaluation at 12 months after PRP injection, and no significant differences were reported among PRP, hyaluronic acid, or oral nonsteroidal anti-inflammatory drugs (NSAID).
Overall, the current evidence does not allow us to respond to this question in humans, expecially in terms of improving tissues quality. Nevertheless, a few recent human trials revealed MRI changes after PRP injection in knee osteoarthritis[9,10], as well as delay in the need of TKA[11]. Further studies are however needed to demonstrate if the positive preclinical results can translate into disease-modifying effects when PRP is used in the clinical practice to treat OA.

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Level of evidence: Level III, Study type: Retrospective study

➢ **QUESTION 13**

Does current clinical evidence support the use of Autologous Conditioned Serum (ACS) for knee OA?

Compared to PRP, ACS is much less well 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 dominance 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

Mean score: 8.8

Literature summary (Best evidence: 2 RCTs, 3 Prospective cohorts)

Note: Autologous conditioned serum (ACS) was developed in the mid-1990s in an attempt to generate an injectable material enriched in endogenous IL-1Ra as a novel therapeutic for OA[1]. The medical grade glass beads contained in the ACS syringes induce the dose-dependent production of IL-1Ra by white blood cells in whole blood incubated at 37°C. ACS is therefore not based on platelet concentration.

In the OA context, interleukin 1β (IL-1β), a pro-inflammatory cytokine plays an important role in the production of collagenase and prostaglandins by releasing a cascade of inflammatory and catabolic events, resulting in a reduction in the synthesis of proteoglycans and cartilage-specific collagens[2,3]. The number of receptors for IL-1β is significantly increased in chondrocytes and synovial fibroblasts in OA[4].

Meijer et al. showed that, following the blood exposure to glass beads, a rapid increase in the synthesis of various inflammatory cytokines, including IL-1βRa, is obtained[5]. ACS is prepared by taking a blood sample and incubating it in a syringe, into which CrSO4-coated glass beads are disposed. It has been shown that the synthesis of IL-1βRa, as well as other anti-inflammatory cytokines such as IL-4, IL- 10 and IL-13[4] are stimulated through this procedure[6].

Current data suggest that the anti-inflammatory cytokine IL-1 receptor antagonist (IL-1Ra) can alter the inflammatory response and cartilage erosion present in OA[1]. Intra-articular gene expression of IL-1Ra has shown promising results in animal models to provide symptomatic improvement and minimize osteoarthritic changes[1]. Treatments with ACS have demonstrated in preclinical cell cultures a protective effect and anti-inflammatory target for cartilage injuries[5]. In a level 2 RCT, one hundred and sixty-seven patients received six intra-articular injections either with ACS or physiological saline. At the end of the study, they concluded that there was statistically significant improvement of KOOS symptom and sport parameters together with the consistently higher, though non-statistically significant, improvement of most other parameters demonstrates that ACS clearly induced a biological response different from placebo treatment. However, in that current study the primary efficacy objective was not met and, therefore, the use of ACS currently cannot yet be recommended for the treatment of OA[7].

Vitali et al.[8] showed that VAS scales among all patients decreased by 35.8% (p = .00148), KSS functional scores improved by 38.2% (p = .00148), KSS clinical scores improved by 28.9% (p = .00236) and WOMAC scores were reduced by 19.8% (p = .00188) at 15 patients have knee osteoarthritis. Few adverse effects were observed in their sample. The most common complaint was pain and swelling in the subsequent days after performing the intra-articular injection. Only one patient reported rigidity following the injection of the ACS.

In a level 2 RCT[9], the effects of ACS were found significantly superior to HA (hyaluronic acid) and saline for all outcome measures and time points. Improvements were clinically relevant; there were no differences between the effects of HA and saline. The frequency of adverse events was comparable in the ACS and saline groups, but higher in the HA group. In another level 2 RCT[7], ACS injection considerably improves

clinical signs and symptoms of OA when compared with placebo treatment. It remains to be determined whether ACS is disease-modifying, chondroprotective, or chondroregenerative.

ACS therapy is highly effective in cases of tendinopathy, enthesopathy, osteoarthritis of the small joints of the hand and in early stages of knee osteoarthritis in Godek's study[1]. It is suggested that autologous products containing WBCs may play a role in modulating inflammation and should be further explored as a potential treatment for OA.[6-10]

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Level of evidence: Level III, Study type: **Cohort study**

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Study type: **Review article**

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Level of evidence: Level VI, Study type: **Retrospective study**

➢ **QUESTION 14**

Does current clinical evidence support the use of Alpha-2-Macroglobulin (A2M) for knee OA?

Statement

Compared to PRP, A2M is much 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

Mean score: 8.7

Literature summary (Best evidence: 1 prospective cohort, 1 Animal RCT, 2 in-vitro studies)

Note: α2-Macroglobulin (A2M) is a plasma glycoprotein obtained through concentration of autologous blood known for its ability to inhibit a broad spectrum of serine, threonine, and metalloproteases as well as inflammatory cytokines which contribute to osteoarthritis (OA).[1] Alpha-2-macroglobulin is not a platelet product, rather, A2M circulates in the plasma of the blood and it is obtained through multi-phase centrifugation and filtration.

A2M was shown to be a promising bio-inhibitor for catabolic proteases[2]; moreover, supplemental intra-articular A2M induces an anti-inflammatory mechanism and slows cartilage damage and bone resorption in a mouse CIA model[2]. α2-macroglobulins are also broad-spectrum endopeptidase inhibitors, which have to date been characterized from metazoans (vertebrates and invertebrates) and Gram-negative bacteria[3].

ADAMTS-7 and ADAMTS-12, two members of ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) family, degrade cartilage oligomeric matrix protein (COMP) *in vitro* and are significantly induced in the cartilage and synovium of arthritic patients. A2M inhibited both ADAMTS-7- and ADAMTS-12-mediated COMP degradation in a concentration (or dose)-dependent manner[4].

Most of the mouse models of osteoarthritis converge at the up-regulation of catabolic enzymes, such as MMP-13 and ADAMTS[5], suggesting that these enzymes may serve as potential therapeutic targets in regulation of the progression of OA.[6,7] The proteinases responsible for the breakdown of cartilage aggrecan include ADAMTS-4 (aggrecanase 1) and ADAMTS-5 (aggrecanase 2). Post-translational inhibition of ADAMTS-4/-5 activity may be important for maintaining normal homeostasis of aggrecan metabolism, and thus, any disruption to this inhibition could lead to accelerated aggrecan breakdown. To date TIMP-3 (tissue inhibitor of matrix metalloproteinases-3) is the only endogenous inhibitor of ADAMTS-4/-5 that has been identified. Alpha (2)-macroglobulin has been also reported as an additional endogenous inhibitor of ADAMTS-4 and ADAMTS-5.[6]

Neutrophils have a role in the inactivation of alpha 2M in the synovial fluid of patients with inflammatory joint diseases.[5] The results of several studies support the idea that the functions of α2 Macroglobulin are uniquely regulated by hypochlorite, an oxidant that is generated during inflammation, which induces the native α 2Macroglobulin tetramer to dissociate into dimers.[7] Recently, the results of a prospective randomized control trial were presented at a conference and showed the non superiority of A2M over PRP and corticosteroids, although only at 3 months-follow up.[8]

As a conclusion, although intra-articular A2M induces an anti-inflammatory mechanism and slows cartilage damage and bone resorption, the lack of clinical RCTs prevent any recommendation for the usage of A2M in the management of knee OA.

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Study type: Conference abstract

SECTION 2
PRP PREPARATION/CHARACTERIZATION

➢ QUESTION 15
Which PRP is preferred for knee OA: Leukocyte-Rich PRP (LR-PRP) or Leukocyte-Poor PRP (LP-PRP)?

Statement
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 leukocytes 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

Mean score: 8.1

Literature summary (Best evidence: 5 Meta-analyses, 2 RCTs)
Platelet-Rich Plasma (PRP) products can be divided in two main types according to the preparation leading to the presence or not of white cells. Leukocyte-poor (LP) PRP is based on plasma extraction whereas Leukocyte-Rich (LR) PRP is based on buffy-coat extraction.
There is only one head to head randomized controlled study[1] comparing injections of LR-PRP and LP-PRP formulations to HA injections. The authors concluded that LR-PRP seems to be the most effective treatment for moderate OA as this formulation reaches the highest improvement one year after the injection for both WOMAC score and pain VAS. It is important to precise that LR-PRP formulations not only presented leukocytes compared to LP-PRP but also platelets at a 2.5 higher concentration.
Five different meta-analyses were published and investigated the impact on efficacy of leukocytes presence in PRP in knee OA[2-6]. This represents 43 studies from which 759 patients received LP-PRP and 1130 received LR-PRP.
The injection of LP-PRP resulted in significantly better WOMAC scores in comparison with HA or placebo whereas no such difference was observed in LR PRP[2]. Similar conclusion was reported by others[3] with significant improvement of WOMAC score when using LP-PRP in comparison with HA or placebo. No differences on WOMAC score and pain VAS were found between the two formulations, whereas LP-PRP provided higher improvement in the IKDC score[4].
Conversely, another paper[5] reported both PRP modalities were able to demonstrate significant and prolonged improvement compared to other injectable solution. LR-PRP is also the only injection that after one year of follow-up continues to show improvement on WOMAC scores, unlike the other injection types which have regressed. However, the lowest VAS pain scores at the longest follow-up was achieved with LP-PRP.
A very recent RCT showed no differences between LP- and LR-PRP[6]
The last meta-analysis[7] reported no significant difference in the efficacy of either on WOMAC or VAS scores and that larger, randomized high-quality studies are needed to compare the effects of LP-PRP and LR-PRP.
Such heterogeneous results can be explained by the method used for assessing the type of PRP, which is variable between meta-analysis, besides we observed inconsistencies concerning three publications that have been reported either LR or LP-PRP given the meta-analysis performed.

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Level of evidence: Level I (journal), Study type: **meta-analysis**

➢ **QUESTION 16**

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

Statement

The effect of PRP is complex and multifactorial, with the 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 the 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 characterization 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

Mean score: 8.2

Literature summary (Best evidence: 4 RCTs, 1 Systematic review, 3 case series)

The limit to answer to this question is the relatively low quantity of clinical studies providing complete biological data regarding the injected PRP[1].

The technical analysis published in 2017[2] compared technical features from randomized controlled trials where PRP injections in knee OA lead to very good results (7 studies) and bad outcomes (4 studies) based on MCID. They concluded that platelets concentration should be lower than 5 times the baseline with avoidance of leukocytes. Further studies reporting bad outcomes[3-6] revealed that they all performed 3 injections with a potential cumulative platelets dose injected ranging from 9 to 19 billion in a three injection procedure.

Two other studies indicated that the more is not necessarily the better. A randomized controlled study[7] compared a single injection of PRP highly concentrated (mean of 800 G/L) and standardized to a final volume of 3 ml (mean platelets dose: 2.4 billion) using a double-spin procedure versus a single injection of hyaluronic acid (Durolane®). Characterization of released growth factors from injected PRP showed a significant correlation between TGF-b1 and PDGF-AB and the worsening of the WOMAC score. These two growths factors were correlated with the dose of injected platelets although this latter was not directly correlated with a poorer clinical issue. Another study[8] reported a series of 75 patients treated with a single injection of PRP and analyzed/compared the characteristics from patients described as responders (n=34) or impaired (n=11). The dose of injected platelets was significantly higher in the impaired group patients (3.28 billion vs 2.60 billion) and was identified as a factor of bad response associated with the fact that MRI revealed that these patients have 3 compartments altered and among other biological parameters (IL1-Ra, VEGF, EGF).

In this context, it is important to highlight a recent study[9] that managed to completely standardize the PRP formulation to obtain a final product containing 10.45 ± 0.46 billion of platelets without leukocytes in 8 ml which corresponds to a concentration even higher that the concentration described as detrimental before in this statement. Interestingly, the findings of the study showed a superiority of such a high-platelet count PRP over HA, with more stable results up to 1 year follow-up. Increase in cartilage thickness was not observed on MRI in either group, but in the PRP group, it remained unchanged in 53 (82.8%) patients at one year as compared to 42 (61.7%) patients in control ($P < 0.05$).

These conflicting results suggest that concentration/dose are parameters among others that could influence PRP efficacy. However, they should never be interpreted without information about the volume and other variables. To conclude, the existing difficulty to standardize PRP preparations have resulted in the fact that no classical dose study comparing different doses in a final fixed volume has never been performed in the field.

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➢ QUESTION 17

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

Statement

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 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. Therefore, the consensus group suggests that recording the baseline whole blood cellular and platelet composition, as well as 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

Mean score: 8.0

Literature summary (Best evidence: 10 Expert opinion publications)

Performing biological characterization in the context of PRP injections is in line with the consensus recommendations recently edited by the American Academy of Orthopedic Surgeons[1] and the Minimum Information to provide for studies evaluating Biologics in the Orthopedics field also called MIBO[2]. This was also highlighted and diffused in a broader way by the guidance from the scientific and standardization committee on platelet physiology from the International Society on Thombosis and Hemostasis (ISTH)[3].

Since 2008, the limits associated to the absence of biological characterization of PRP have given rise to seven different PRP classification[3-9] systems but none has been widely adopted. Analysis of these classifications showed that 13 different biological parameters have been used to describe PRP preparations (6 related to platelets, 4 related to leukocytes and 3 related to red blood cells). Six from 7 of these classifications necessitate to perform a cell count both on whole blood and PRP to get the necessary data to calculate the described parameters. One classification suggests to provide the polynuclear neutrophils concentration within PRP.

As there is not enough evidence to select a classification (and the associated parameters) or another, it could be recommended to perform a systematic cell count on whole blood and PRP with detailed leukocytes formula for LR PRP formulations (increase factor in leukocytes > 1). These counts associated to the volume of harvested blood and injected PRP will be sufficient to classify the PRP in most of the above-mentioned classifications that should be selected by users/authors.

Finally, we should control not only what we inject, but also how we should do it (how to sample your blood and PRP, which analyzer is validated). Regarding this specific point, a publication already provided technical tools to realize the cell counts on blood and PRP within the frame of PRP injections[10].

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Level of evidence: Level V, Study type: Expert *Opinion*

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Level of evidence: Level V, Study type: *Expert Opinion*

➢ QUESTION 18

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

Statement

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

Mean score: 8.7

Literature summary (Best evidence: 1 Meta-analysis, 2 RCTs, 1 Prospective study, 1 Consensus/Expert opinion)

There are no strong evidences demonstrating that a specific volume for PRP injections is more effective compared to another. In all studies taken under analysis discussing about this topic, it emerged that rather than a specific volume, there is a range of volume that can be used for i.a PRP injections.

A recent study[1] had the objective to develop guidelines for PRP injections in knee osteoarthritis. Fifteen specialists from different French-speaking nations were selected for their experience in the fields of PRP and osteoarthritis. In relation to the correct volume for PRP injection in knee osteoarthritis, they concluded with strong agreement that the PRP volume should be between 4–8 mL. The efficiency of IA PRP injections might possibly be modified by the total value of injected platelets and by the rate of growth factors and cytokines included in the PRP, which rely on the amount of PRP injected[2]. In randomised studies, the average amount injected was 5 mL[3].

An uncontrolled open-label research indicated the effectiveness of a single injection of PRP with an average volume of 8.8 mL[4]. The adoption of this number was validated by the distribution volume of the knee joint space which was previously calculated at 9 mL[5]. Still the precise volume remains controversial, what has been established is the association between the amount of platelets and the quantity of growth factors produced in the injected PRP[6-10]. Experts feel that the injection of a volume of PRP of 4 to 8 mL is adequate, although it ultimately stays reliant on the equipment used for its extraction.

Another study conducted[11] showed that, if the centrifugation rate and time are increased, the platelet production drops in a proportionate manner. The findings of this study imply that a decreased centrifugation rate and duration produces better platelet yield. The likely rationale for the decline in the platelet count at greater centrifugation rate and time would be due to clumping or destruction of platelets. When such breakdown occurred prior to PRP activation, the growth factors are released in an inactive condition that may not impact the wound healing process.

Othersl[12] proved that a dosage of 10 billion platelets in 8 ml volume of PRP enhances functional results and preserves the articular cartilage from additional damage in patients with knee OA. Direct comparison is challenging because of variances in PRP preparation, the dosage (amount and concentration of platelets), and no uniform structural effectiveness criteria. They found that injecting 8 ml PRP in joint space using supra lateral route does not generate any distension or oedema and is safe since knee joint has high volume and surface area[13]

PRP preparation for OA knee injection should, consider the articular capacity of the knee in order to improve PRP dispersion throughout the joint[4]. Also, the volume should be adjusted to distend the joint properly while avoiding extra-articular extravasation[14].

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SECTION 3
PRP PROTOCOL

➢ QUESTION 19
How many injections of PRP are recommended for the treatment of knee OA?

Statement:
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 >1 injection provide better clinical improvement, at least with early OA.
The consensus group realizes 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 2-4 injections.

Grade B

Mean score: 8.0

Literature summary (Best evidence: 15 RCTs)
The evidence in several RCT trials suggests multiple injections to be superior to single injections.[1-9].
A systematic review published in 2016[1]reported a number of injections between 1 and 4 for a favorable outcome. A study published in 2012[10] obtained significant effect after 4 PRP injections; the effect was obtaining shortly after the fourth injection and continually improved up to 24 weeks. Similarly, other studies[2,11] provided data to sustain the effectiveness of PRP in treating OA, showing significantly improvement of all the scores after 3 PRP usage; the effect was maintained at 12 months follow-up. The same number of injections-3- with an interval between administrations of 1 week was reported by another paper[3] or the treatment of knee OA with higher benefits, maintained for longer time, in terms of pain, physical functions and stiffness comparing to HA. The same results were found by other authors who demonstrated statistically significant improvement in treating mild OA with the usage of 3 intraarticular PRP injections, at a week-time interval[4]. The study also suggested that anti-inflammatory properties of PRP contribute to improvement of OA signs but has no data to recommend a certain number of injection for optimal results. Although other studies reported the same positive results with a 3-injecton protocol[12], however, no recommendations regarding proper number of injections needed was addressed. A study published in 2016 concluded that 2 injections of PRP provided better effects in OA treatments comparing to ozone and HA and this effects last for at least 12 months. However, the number of injections was based more on manufacturer recommendations than on evidence based data[13].
Conversely, 1 injection of PRP was shown to be as effective as 2 in terms of improving symptoms in early OA;[14] however, this study used a PRP in concentrations of 10 times the normal amount and this may affect the number of injections needed.
A few studies compared directly the effect of single or multiple injections. Among them, a RCT study from 2017 comparing documented better clinical results for multiple usage in early OA while no difference between one or multiple injections was noted in patients with advanced stage of disease[15]. Similarly, to a previously mentioned study,[14] this study recommended only single PRP dose for advanced cases. This is in line with other authors who pointed out that anti-inflammatory effect of PRP can be demonstrated in multiple usage and not in single one, implying that reparative cartilage repair may not be documented in single use[16].
Taking into account the previous mentioned papers, a study published in 2019[17] starts from the idea that multiple PRP doses may be effective in cases with severe inflammation. The study proves that for obtaining

in 50% of patient's satisfaction and symptoms relief, a number of minimum 4 injections is needed. This study came is in agreement with another one published in 2018 that recommended 4, 5 or 6 injections to obtain maximal relief in advanced OA cases[18].

Finally, in a recent 4-arm double-blinded placebo controlled RCT with a 2 year follow-up, 237 patients diagnosed with OA were randomized to receive either a single dose of PRP (n: 62), single dose of sodium saline (NS) (n: 59), three doses of PRP (n: 63), or three doses of NS (n: 53). Authors reported patients treated with PRP maintained better scores at 3, 6 and 12 months compared to the NS groups, and that multiple doses of PRP were shown to be more effective than single-dose PRP at 6 and 12 months. These effects seemed to deteriorate at the end of the 24 months period, at which point there was no significant clinical difference between all the groups.[19]

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RCT

➢ QUESTION 20

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

Statement

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-week to 4-week 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 interval ranges of 1-3 weeks may be more appropriate.

Grade B

Mean score: 8.0

Literature summary (Best evidence: 1 systematic review, 11 RCTs)
Initial studies/protocols used three injections at weekly interval without any specific rational, probably in an attempt to compare with HA which was used similarly.
Ten studies (8 of level I and 2 of level II) published between 2012 and 2019, offering information about the recommended interval between each PRP injection, were selected from a total of 32 studies (level I to V) with time interval documented. Overall, in all 32 selected studies the 1-week interval was favored in 17.
A RCT study from 2012 reported a 1-week interval between injection and this protocol results in better results comparing to HA been injected at the same interval; a significant PRP effect was obtained after the last injection and effect continue to improve up to 24 weeks from the last injection[1]. Similarly, the same 1-week interval was recommended in other level I studies as reported in a recent review[2]; the effects obtained were good both in clinical and functional scores. The same review analyzed the preparation techniques providing the PRP and brings into discussion the lack of standardization, the differences in quantity and quality of the products used in clinical practice[2].
An interval of 2 weeks between injections was recommended in 2 RCT[3,4] and in a prospective comparative study from 2011[5].
In another systematic review from 2016 a flexible interval of 2 to 4 weeks between injections was recommended, based on included studies, which documented good clinical and functional outcome in knee OA[6]. An Expert opinion from 2020[7] did not find enough data to sustain a time interval between PRP injections.
In a RCT from 2013 it was pointed out that 3 weeks is the interval for benefits from PRP to be installed and that results are better in early OA.[8] The 3 – week interval is related to the release of growth factors from PRP, which occurs immediately, lasts for around three weeks[9] and the clinical effect tends to wane down by the end of one year of follow-up. Several other studies support similar protocols.[10,11]
A 4- week selected interval between PRP injections was used in a therapeutic study published in 2016[12], in a prospective RCT from 2019[13] and 2021.[14]
The single PRP injection protocol has several documentations; PRP was used at yearly interval and still proved the clinical efficacy[15]. A lot more research in this direction needs to be carried out as to how long we can prolong the pain-free status with multiple yearly injections. At the other side of the spectrum, others have chosen a complex protocol with a total of nine injections within a year.[16]
PRP at monthly intervals for six months (six injections) were used in several studies, reporting significant improvement in knee stiffness, IKDC scores and VAS scores compared to baseline.[17,18]

In a Meta- analysis from 2019 the authors concluded that a single injection was as effective as multiple PRP injections in pain improvement; however, multiple injections seemed more effective in joint functionality than a single injection at 6 months.[19]

In summary, the most frequently studied interval is 1-week, with 41% of studies using this interval being level I or II studies. Another 3 studies suggesting a 2-week interval as well as another 3 suggested a 4-week interval. Two level I papers documented a variable time interval, between 1 and 4 weeks.

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Systematic review

➢ QUESTION 21

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

Statement 1

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

Mean score: 7.9

Statement 2

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

Grade D

Mean score: 7.9

Literature summary (Best evidence: 1 prospective clinical study, 1 Observational study)

The narrowest commercialized needle (30G) had no significant influence on the count and the quality of platelets in a highly concentrated PRP. After passage through the smallest needle, platelets were not aggregated[1]. Previous studies of the extraction of whole blood from the vein with different sizes needles (21G compared to smaller sizes – 23 and 25G) showed no significant difference in coagulation testing. There was a slight difference in platelet count in favor of larger size needle.[2]

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Level of evidence: Level III, Study type: observational study

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Level of evidence: Level IV, Study type: prospective observational study

➢ QUESTION 22

Are non steroidal anti-inflammatory drugs (NSAIDs) allowed around PRP use?

Statement 1

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 two weeks prior to PRP administration.

Grade C

Mean score: 8.1

Statement 2

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

Grade C

Mean score: 8.3

Literature summary (Best evidence: 1 RCT, 2 Clinical studies, 3 in-vitro studies)

Aspirin and other COX inhibitors are capable of inhibiting the synthesis of other prostaglandins and TxA2 that activate platelets. NSAID medications found to negatively affect growth factor production although they differ in reversibility and COX isomer selectivity[1,2].

Interesting observation, in vitro, tendon and cartilage cells showed increased cell viability after an exposure to allogeneic PRP and ketorolac tromethamine[3]. Also experimental, the association of PRP and ketorolac reduced cellular inflammation markers (E-selectin, vascular cell adhesion molecule, and human leukocyte antigen DR) compared with controls[4]. Another experimental study suggested that there is no need to withhold a COX-2 inhibitor before PRP preparation, particularly if thrombin is going to be used to activate the PRP.[5]

However, a more recent study in healthy subjects showed that daily use of naproxen significantly decreased the amount of certain growth factors such as PDGF AA and AB until one week after discontinuing naproxen.[6] In a recent systematic review, the majority of studies reported on the use of nonsteroidal anti-inflammatory drugs as antiplatelet therapy - most of them were in vitro analyses of growth factors, inflammatory cytokines, or cell viability, whereas only 1 study examined clinical outcomes in an animal model. None of the studies investigated clinical outcomes in humans. All of the studies showed no effect or mixed effects of antiplatelet therapies on PRPP efficacy. One study showed PRP recovery to baseline function after a 1-week washout period.[7]

There is a well-known pharmacodynamic interaction between NSAIDs, especially in some of the current clinical practices. Naproxen and flurbiprofen have significant antiplatelet effects at plasma concentrations seen with usual doses and interfere with the antiplatelet effect of aspirin when added before the latter.[8]

Some reduction in growth factor release, recognized to daily use of low-dose aspirin or other COX inhibitors can be diminished when PRP samples are activated with thrombin.

In a recent systematic review which included 15 studies: 8 of 15 studies found a decrease in growth factors or mitogenesis. 7 studies detected no significant decrease in growth factors or mitogenesis, whereas 6 detected a decrease with antiplatelet agents, 1 detected mixed results with an antiplatelet agent, and 1 reported mixed results with the use of an antiplatelet agent. [9] In terms of PRP activation, all 3 studies

assessing collagen, the 2 studies analyzing adenosine diphosphate alone, and the 1 study investigating arachidonic acid found a decrease in growth factor concentration. Authors concluded antiplatelet medications may decrease the growth factor release profile in a cyclooxygenase 1– and cyclooxygenase 2–dependent manner. Clinical studies are needed to determine whether activation before PRP injection is needed in all applications where ASA is in use and to what extent ASA may inhibit growth factor release in vivo at the site of injury.[9]

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Study type: **Clinical study**

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Review

➢ QUESTION 23

Should intra-articular local anesthetics be used when injecting PRP?

Currently no high-level clinical studies exist regarding the effect of local anesthetics on PRP, however, In vitro studies have shown that local anesthetics interfere with platelets 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 anesthetics when injecting PRP.
The consensus group does, however, agree that local anesthetics can be administered subcutaneously, without penetrating the capsule.

Grade D

Mean score: 8.7

Literature summary (Best evidence: 3 in-vitro studies)
No high-level studies done *in vivo* exist that give us exact data on combining local anesthetics and orthobiological treatment.
A study examined effects of local anesthetics on two different concentrations of PRP, measuring its ability for enhancing tenocyte proliferation. PRP was mixed with 1% lidocaine and 0.5% bupivacaine and added to the culture of tenocytes. It was compared to group with PRP only, as well as a control group. Local anesthetics decreased tenocyte proliferation and cell viability when added to both PRP group and control group. Both bupivacaine and lidocaine seem to diminish the positive effects of PRP on cell proliferation. Result on tenocytes can have a possible translation on the effect on intraarticular ligaments[1]. A study examined the effects of PRP to ameliorate the negative effects of local anesthetic. The results obtained showed that both lidocaine and bupivacaine, when mixed with PRP and culture of chondrocytes, had worse results compared to PRP alone, without significant difference between them, showing negative effects of local anesthetics to PRP.[2]
The weakness of this study was that cells culture and blood for PRP were from different donor, thus PRP may had acted differently. There is a study that examined effect of local anesthetics directly on platelets. Highly concentrated PRP sample mixed with lidocaine and ropivacaine reported lower aggregation of the platelets compared to PRP alone. The capacity of platelets to release growth factors was intact. [3]

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Level of evidence: Level III, laboratory study
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Level of evidence: Level III, Study type: laboratory study

➢ QUESTION 24
Is Antibiotics administration recommended around PRP use?

Statement
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

Mean score: 8.6

Literature Summary (Best evidence: 1 Systematic review)

It is not yet possible to identify comprehensive evidence in the literature to demonstrate that the use of antibiotics around PRP applications in orthopedics is recommended and under what conditions. There are no published studies investigating this aspect, so there are no official guidelines to follow.
However, rare adverse reactions have been reported following the administration of biological therapies for cartilage injuries, osteoarthritis, and tendon or ligament ruptures consisting mainly of infections, sterile inflammatory reactions, or a combination of both.[1,2] Depending on the type of biological therapy used, the risk of adverse reactions encountered is different, with a higher incidence of infections following, for example, the administration of umbilical cord blood cell-based therapy.[2] Therefore, it may be appropriate to systematically investigate this aspect by considering all the different variables involved in order to propose recommendations for future applications.
PRP itself is known to have an antibacterial effect, due to the presence of antimicrobial peptides and leukocytes[3], which makes it promising in a context of bone infection.[4]

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Review

➢ QUESTION 25

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

Statement 1:
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 behavior, 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 hours prior to blood harvest.

Grade D:

Mean score: 8.0

Statement 2:
Eliminating alcohol for at least 48 hours prior 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

Mean score: 7.5

Literature summary
Diet can significantly alter platelets properties, especially when diets high in saturated fats, excessive sugar, or simple carbohydrates, by inducing and increasing platelet aggregation.[1]
Diets containing caffeine, common in coffee, tea, sodas, cola drinks, "energy" drinks, and chocolate - cocoa-related products, however, have platelet-inhibiting effects when consumed in moderate amounts.[2-4]
Quercetin, a flavonoid present in high levels in onions, apples, tea, and wine - reduces platelet activation. [5]
Isoflavones, present in legumes, such as soybeans and chick peas - reduce platelet activation.[6]
No significant difference was found in the quality parameters between donors who smoked and those who consumed alcohol in small quantity.[7]
Alcohol consumption in excess is inversely associated with both platelet activation and aggregation, particularly in men.[8] Alcohol, at physiologically relevant doses, below those investigated in most previous human studies, has a dose-dependent inhibitory effect on platelet aggregation.[9] In platelet-rich plasma, after consumption of 0.5 ml/kg ethanol, aggregation (measured as maximum change in optical density) in response to 1.25 µg/ml collagen was significantly inhibited ($p < 0.05$). [10-11]
Limited smoking (three cigarettes/day) increases platelet aggregation[12] for limited a period of time.
Platelet counts of individuals who perform regular physical exercise were significantly higher than those of individuals who did not perform regular physical exercise.[8]
Clinical data suggest that platelet activation in vivo, including the formation of monocyte platelet aggregates (MPAs) is influenced by physical activity (the absence of regular exercise increases platelet aggregation in vivo with more activation and pro inflammatory mediators released). [13]
Other studies found that platelet reactivity to high shear stress was increased in a control group (like young active men).[14, 15]
Both extremes probably, as sedentary or highly active, induce modifications in platelet functions, depleting and potentially modifying the effects of PRP therapy.
Concluding, the literature reports that diet can significantly modify platelet behavior, both in number and function; the effects on platelet activation are also clinically demonstrated. Due to lack of clinical trials

studying the impact of fasting or diet on the therapeutic effects of platelet concentrates, no recommendations can be made. Therefore, reducing or eliminating alcohol and tobacco consumption prior to preparing PRP may allow platelets to re-establish their normal factor content and aggregation properties and it's a safe suggestion. Both strenuous activity (like high intensity training) or sedentary (long term) are discouraged before PRP therapy.

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➢ QUESTION 26

Can Corticosteroid (CS) injections prior to PRP improve the results in knee OA?

Statement:

The consensus group recommends to avoid using PRP in close proximity to CS. However, the consensus group recognizes 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

Mean score: 8.3

Literature Summary (Best evidence: 1 Meta-analysis, 1 RCT, 1 Systematic review, 1 Prospective, 2 Pilot studies)

Inflammatory phenotype of OA, characterized by synovitis, joint swelling and effusion, are more likely to respond to CS, so, the same protocol applies to use of CS before PRP.[1,2] For the patients who underwent previous steroid injections, some studies showed significantly higher failure rate of platelet-rich plasma treatment, even if the injection is delayed for a few months[3] thus raising the question of efficiency.

Recent meta-analysis showed dose-dependent CS deleterious effects on cartilage morphology, histology, and viability in both in vitro and in vivo models.[4]

Clinically, the latest meta-analysis on the safety of CS treatment states that multiple IA CS injections are associated with worsening of joint space narrowing[5]. Also, the duration of action of intra-articular corticosteroid injections remains controversial, with various studies quoting anywhere between 1 to 24 weeks[6.7]

Taking into account the mechanisms underlying the anti-inflammatory effect of CS, it generally involves blocking antigen opsonization, leukocytic cell adhesion, and cytokine diapedesis within the capillary endothelium. Corticosteroids also attenuate the effects of IL-1, decrease leukotriene and prostaglandin release, and inhibit metalloproteases and immunoglobulin synthesis for one to three weeks inside articulations. Some of these effects (prominently on IL-1) are clearly antagonist to PRP[8,9] thus questioning a beneficial association.

There is a paucity of literature studies regarding association of CS prior to PRP. One study demonstrated that a single steroid injection followed by PRP 1 week later improved the clinical response in patients with low or moderate knee OA, compared to PRP and CS injections alone[10].

When thinking about a combined therapy, the incidence of local infectious complications following cortisone injections into the knee that ranges widely has to take into account too, and may be as high as 1 in 3000 in high-risk patients[11]. Finally, the detrimental effects of CS on other tissues are well-demonstrated too.[12,13]

Concluding, with the lack of research supporting CS combined with PRP, clinical decision to use it therapeutically is driven by other factors, including clinician experience and patient preference.

For the knee inflammatory osteoarthritis (synovitis), treatment with CS may be needed, especially in older patients. As, for the moment, the combined PRP and CS is not documented, for younger patients the treatment should be based on chondroprotective effects of PRP, until further evidence.

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Narrative Review

➢ QUESTION 27

Does PRP and HA have a synergistic effect?

Statement

While current pre-clinical 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 recognizes that more data is required before recommending the combination of PRP and HA over PRP alone for knee OA.

Grade C

Mean score: 7.8

Literature summary (Best evidence: 3 meta-analyses, 1 systematic review, 1 RCT)

In vitro studies report the positive effects derived from the combination of PRP and HA on different cell types. In particular, an in vitro controlled study showed that intra-articular the administration of PRGF (Platelet Rich Growth Factors) might be beneficial in restoring HA concentration and switching angiogenesis to a more balanced status but does not halt the effects of IL-1beta on synovial cells[1].

A meta-analysis including seven studies (5 RCTs and 2 cohort studies) was performed to explore the efficacy and safety of the intra-articular injection of PRP combined with HA compared with the intra- articular injection of PRP in the treatment of knee OA[2]. The results showed that there was no significant difference between PRP combined with HA and PRP alone for KOA at 1 month or 3 months after treatment. However, the intra-articular injection of PRP combined with HA provided better results compared with PRP alone after 6 months from the treatment, suggesting a unique advantage in the long-term relief of pain in patients with knee OA. Similarly, another meta-analysis[3] including 4 studies was focused on the comparison of PRP + HA vs HA alone. The authors concluded that symptomatic patients with knee OA who were injected with a combination of PRP and HA demonstrated greater improvement in pain and function compared with patients who received HA injections only, as assessed by 3-, 6-, and 12-month VAS scores and 12-month WOMAC physical function and stiffness scores.

Another meta-analysis including 10 studies (7 RCTs, 3 cohort studies) reported that HA + PRP resulted in better WOMAC score improvement at 3, 6 and 12 months compared to PRP alone[4].

A recent meta-analysis[5] including 8 studies (2 case series, 3 comparative, and 3 RCTs) showed that the combination therapy with PRP + HA improves the subjective clinical results and is superior to HA alone but is not superior to PRP alone.

In a recent RCT injections of HA + PRP achieved only better VAS pain reduction than a single PRP at 6 months[6]. Moreover, the results indicated a long term benefit effect of a combination of HA + PRP in a particular subset of patients with moderate knee OA but these results need to be replicated in larger trials.

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Level of evidence: n/a; Study type: Controlled laboratory study

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Level of evidence: Level 2, Study type: meta-analysis of Level I through level IV studies

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Level of evidence: Level 3, Study type: meta-analysis of Level I and II studies

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Level of evidence: Level 2, Study type: Systematic review and meta-analysis of Level I through level IV studies

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Level of evidence: Level 2, Study type: Systematic review

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Level of evidence: Level 1, Study type: RCT

QUESTION 28

Is there any synergy between PRPs and cell-based therapies for knee OA?

Statement

While current pre-clinical 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

Mean score: 8.0

Literature summary (Best evidence: 5RCTs, 1 Prospective study, 4 Controlled laboratory studies)

A rationale that PRP can be beneficial adjunct to MSCs exists because of their dissimilar biologic action. Most of the studies in this topic are not clinical and they are level II or III studies. That can lead to a certain bias, because cells *in vitro* do not mimic cells *in vivo* in entirely. Most common bias is the heterogeneity of the PRP concentrations and PRP donors, and the fact that PRP in these studies is usually allogenic and not autologous, which can lead to a possible immune effect. There was a single high-quality study that compared Bone Marrow Mesenchymal Stem Cells (MSCs) with and without PRP, which showed no benefits of adding PRP to MSCs injection.

An *in vitro* study found that adding PRP to a culture of MSCs enhances their proliferation rate[1]. Also, the numbers of factors contributing to differentiation of cells (Sox-9, RUNX2) rose significantly when PRP was added, comparing to a control group. Another *in vitro* study outlined that PRP accelerated MSCs proliferation. The effect was dose dependent and 10% PRP was sufficient to induce a marked cell proliferation.[2]. Also, an important finding was that upon treatment with 10% PRP, cells entered logarithmic growth. Removal of PRP restored the characteristic proliferation rate. That is an important finding for the in vivo translation, to avoid uncontrolled growth. One more study outlined that 10% PRP ratio brings to the ideal milieu for stem cells proliferation.[3] A systematic review of in vitro studies from 2014 draws a conclusion that adding PRP to a culture of cells increases the proliferation rate and migration of the cells, and delays the appearance of the senescence phenotype.[4] This review also stated that 10% of PRP in cultures is optimal and increasing it to 30% did not enhance proliferation, on the contrary, it lowered it, compared to the commonly used FBS (Fetal Bovine Serum). All the findings in this review were about priming the cells before implantation. The safety of possible neoplasm growth was evaluated in the study where platelet lysate was added to prime the BM MSCs. After clinical use, there were no tumors associated with use of these cells.[5] In an animal study, three concentrations of PRP (10%, 15% and 20%) were added to cultures of cells and compared. ADSCs pretreated with or without PRP were transplanted into murine models of injured articular cartilage. The results showed that there was a strong difference between 15% and 20% PRP compared to 10% PRP and FBS, but no significant difference between 15 and 20%, drawing a conclusion that 15% is an ideal ratio of PRP in the culture. Another study compared 1, 5, 10, 20, 40 and 60% PRP and the results favored the 20% PRP as the most promising for cell proliferation rate.[6] In vitro, cultures treated with PRP enhanced factors associated with chondrocyte differentiation, while in animal study, in mice, cartilage regeneration was improved with PRP primed cells.[7] Not only the cells, but the host tissue can be primed to modulate the hostile conditions. In vitro study showed that PRP can modulate cells of expressing less metalloproteinases.[8]

A clinical study involving ten knee OA patients treated with SVF and PRP showed a reduction of pain, a functional improvement at 2 years of follow-up, and an increase of cartilage thickness after 1 year in 6 out of 10 patients.[9] Narrative review from 2018 gave examples of clinical trials using different kinds of stem cells together with PRP yielding promising results, but with no comparison to control groups using only stem cells.[10] Some clinical studies from that review had comparison of PRP combined with stem cells groups

and “PRP only” groups and found superior results of the combined groups. One study showed that combining PRP with AD MSCs gave better results according to functional recovery and pain decrease than the PRP-only group.[11] A significant limitation of this study is the confounding effect of concomitant high tibial osteotomy in all patients. Other study found better results in pain score and second look arthroscopy in SVF+PRP group compared to PRP group,[12] whereas another did not find any difference between microfragmented adipose tissue alone or used in combination with PRP.[13]

A recent RCT compared BM MSCs combined with PRP to a PRP-only group. The results showed that no statistical significance between groups have been detected, but only patients being treated with BM-MSC and PRP could be considered as OA treatment responders following OARSI criteria. X-ray and MRI revealed no changes in knee joint space width or joint damage.[14]

A study compared BM MSCs with and without PRP. The results showed no statistical differences between these groups in KOOS score at 12-month end point. In both groups KOOS improved compared to the baseline.[15] The recent study from same authors compared similar groups (BM MSCs with and without PRP) to corticosteroid injection. The results at 12m month control showed significant improvement of both MSCs group compared to corticosteroid group in KOOS global score, but again no significant difference between them. Range of motion and intraarticular cytokine levels were not different in all 3 groups.[16] The possible bias of both studies was the lack of the placebo control group.

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Level of evidence: Level III, Study type: Controlled laboratory trial

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Level of evidence: n/a; Study type: Controlled laboratory study

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Level of evidence: n/a; Study type: Non-controlled laboratory study

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Level of evidence: Level II; Study type: Systematic review

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Level of evidence: n/a; Study type: Observational laboratory study

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Level of evidence: n/a, Study type: Controlled laboratory study

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Level of evidence: n/a; Study type: Comparative animal study

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Level of evidence: n/a, Study type: Controlled laboratory study

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Level of evidence: Level II; Study type: Non-randomized not controlled clinical trial

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Level of evidence: Level III, Study type: Narrative review

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Level of evidence: Level III, Study type: Randomized controlled case control study

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Level of evidence: Level II, Study type: Double blind RCT